EPA/600/R-06/123

September 2006

Peer Review Workshop Report on

"Draft Framework for Assessing Health Risks of Environmental Exposures to Children"

Prepared for:

National Center for Environmental Assessment
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Washington, DC 20460

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July 18, 2006

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EXECUTIVE SUMMARY

ERG, under contract to the U.S. Environmental Protection Agency (EPA), organized and implemented a peer review of EPA's external review draft document *A Framework for Assessing Health Risks of Environmental Exposures to Children* (referred to as the "Framework Document"). Six experts conducted an independent peer review of the document in a meeting open to the public on June 6–7, 2006, in Washington, DC. The peer reviewers were asked to address specific charge questions. This report summarizes the results of the peer review.

The peer reviewers agreed that EPA is to be commended for developing the Framework Document. The document, if implemented and subsequently enhanced with the development of case studies and guidance, will result in an important and appropriate shift in the Agency's approach to risk assessment by putting the child at the center of the evaluations when data indicate that susceptibility could be greater at the younger ages.

Key Responses to Charge Question 1

The purposes of the Framework Document are clearly stated. However, the peer reviewers thought that the first purpose—to provide a central resource for information on the assessment of health risks to children as a result of exposures to environmental agents—was not attained because the document is not a comprehensive compendium of the state-of-the science. Instead, they concluded that the second purpose—to provide the framework for conducting child-oriented health risk assessments—more accurately describes what the document accomplishes.

Most of the peer reviewers considered the graphic presentations and prompting questions to be helpful in understanding the basic components of the risk assessment process and the key considerations for a life stage-specific analysis. However, a few reviewers commented that the graphics were overly complicated. They also noted that the legends for some of the figures provided a better description than the text. They recommended that the legends be shortened and the details from the legend be incorporated into the text. The peer reviewers provided several improvements to specific figures and recommended additional prompting questions.

Key Responses to Charge Question 2

Overall, the Framework Document is consistent with existing risk assessment guidance and provides a strong scientific basis for the EPA to improve its risk assessment by addressing hazards and exposures at various life stages. The peer reviewers noted one exception that appeared to imply that only clinically apparent adverse outcomes need to be assessed (see page 79, lines 12–15).

The peer reviewers identified three additional issues that should be addressed when EPA develops guidance for implementing the framework:

- A strategy for streamlining the process to make the life stage-specific assessment more manageable.
- A decision tree indicating where decisions that will be triggered through the scoping process for exposure assessment and dose-response analysis need to be made.

- An approach for addressing and dealing with data gaps.

Key Responses to Charge Question 3

The peer reviewers agreed that the Framework Document provides adequate flexibility. However, they were concerned that the sheer volume of information limits the document's usefulness for risk assessors, who may suffer from "analysis paralysis." They also suggested limiting the use of terms such as "critical" and "important," as each consideration is dependent on the type and purpose of the assessment. The peer reviewers' main concern was the need for examples. They recommended that EPA follow the Framework Document with the development of guidance on how to conduct such an assessment, and when and how to move ahead in the absence of data.

Key Responses to Charge Question 4

The Framework Document is clear that the problem formulation stage should involve a multidisciplinary team of experts (e.g., risk assessors, risk managers, stakeholders, toxicologists, exposure assessors, epidemiologists, and child health and behavior specialists). The peer reviewers suggested adding risk communicators, physiologically based pharmacokinetic (PBPK) modelers, and pediatric experts, as well as community groups, manufacturers, attorneys, pediatricians, and parents of young children. They clarified that risk managers should be engaged in the scoping analysis, but should not be involved in the development of the scientific aspects of the analysis plan.

Key Responses to Charge Question 5

The peer reviewers agreed that the Framework Document is a more comprehensive approach to assessing health risks from environmental exposures than are current guidelines. The life stage approach was thought to be essential, more appropriate, and more efficient. They commented that the Framework Document provides a useful starting point for risk assessors to begin to more fully characterize risks to children and to the adults they will become from early-life exposures. The peer reviewers noted the following advantages to the life stage approach:

- Results in a better overall characterization of potential risks of environmental chemicals and increases confidence in the risk assessment.
- Demonstrates what is known and not known with regard to the impacts of early-life exposures.
- Makes use of ancillary data to try to fill data gaps more routine.
- Stimulates more research on the impacts of early-life exposures on the health of the infant, child, and adult they will become.

One disadvantage to the life stage approach is that it is not clear when the risk assessor should stop; this should be addressed with subsequent guidance. In addition, there was a consensus of the peer reviewers that while good laboratory practice (GLP) studies should be given strong consideration in weight-of-evidence (WOE) analysis, findings in other studies should be considered as well.

Key Responses to Charge Question 6

The Framework Document adequately articulates integrating life stage susceptibility, toxicity data, exposure information, and age binning information. The peer reviewers made the following suggestions to clarify the approach:

- Discuss how data gaps should be addressed.
- Add an example of how a chemical's mode of action (MOA) differs across life stages.
- Develop a comprehensive resource index that is periodically updated.
- Be certain to also include adults in the risk assessments, so their susceptibilities can be compared to those of immature age groups.
- Add more life stage-specific considerations.
- Include succinct examples or case studies of specific chemicals.

Key Responses to Charge Question 7

The peer reviewers thought that EPA's intention to move towards a harmonized approach for noncancer and cancer risk assessment is clearly articulated and commendable in the Framework Document.

Key Responses to Charge Question 8

The iterative approach is a strong, positive feature of the Framework Document. The peer reviewers commented that it encourages the various specialties and stakeholders to interact on an ongoing basis to ensure that the various stages are well integrated and adjusted based on information that emerges from the analysis. They recommended the following modifications:

- Incorporate simple illustrations of the utilization of iteration within the life stage approach.
- Avoid over-iteration, which can be excessive and lead to an unnecessary slowing of the assessment.
- Clarify the role of problem formulation in the scoping of the analytical components.

Key Responses to Charge Question 9

The peer reviewers agreed that the risk characterization section of the Framework Document articulates an approach that should be useful in assessing risks to children. However, the document does not provide specific examples of how risk assessments using a life stage approach could be applied over a wide range of scenarios and in situations where substantial data gaps exist. The Agency's plans to prepare a series of case examples, to conduct training sessions for risk assessors, and to develop guidance are essential components to the successful implementation of the Framework Document. The peer reviewers suggested the following:

- Streamline the document to focus on life stage-specific issues and decision points.

- Provide strategies that assist the analyst in identifying tools and databases to assess life stage-specific issues.
- Use brief examples to bring more of the concepts to life.

Key Responses to Charge Question 10

All peer reviewers thought that developing case studies is an excellent idea that will increase the understandability and utility of the Framework Document immensely. They stated that case studies and training modules are essential components to the successful implementation of the document. In addition, all peer reviewers thought that EPA would need to develop guidance for its risk assessors on how to implement the Framework Document. They also suggested compiling a resource database that can be updated as the science evolves, and recommended developing a guidance document or a series of smaller supplemental guidance documents.

1.0 Introduction

This report summarizes an independent peer review, by six experts, of the U.S. Environmental Protection Agency's (EPA's) external review draft document *A Framework for Assessing Health Risks of Environmental Exposures to Children* (EPA 2006). The document was prepared by EPA's National Center for Environmental Assessment (NCEA) in Washington, DC. This report refers to the review document as the "Framework Document." The peer review took place at a meeting on June 6–7, 2006, in Washington, DC. The meeting was open to the public. ERG, under contract to EPA, organized and facilitated the entire peer review. This introductory section provides background information on the review document (Section 1.1), describes the scope of the peer review (Section 1.2), and outlines the organization of this report (Section 1.3).

1.1 Background

The purpose of the document *A Framework for Assessing Health Risks of Environmental Exposures to Children* is to provide an overarching approach for the assessment of health risks to children, taking into account potential exposures during all developmental stages and focusing on the major health outcomes that may occur as a result of such exposures. The Framework Document provides a roadmap for assessing risk of environmental exposures to children, describing the process of children's health risk assessment using a series of questions for each component that lead the reader through the analysis and evaluation. A series of flowcharts are used to illustrate this process. In addition, other resources that provide more detailed information are referenced, and are in a linked database that can be easily accessed by the reader.

1.2 Scope of the Peer Review

ERG managed every aspect of the peer review, including selecting reviewers and coordinating activities before, during, and after the peer review meeting.

1.2.1 Selecting the Peer Reviewers

ERG selected peer reviewers that met the selection criteria specified by EPA in its task order for this project. Those criteria noted that participants shall have expertise, experience, and qualifications from one or more of the following categories:

- Toxicology—as it pertains to risk assessment, including childhood cancer; neurotoxicology; immunotoxicology; cardiovascular, reproductive, and developmental toxicology; asthma/pulmonary toxicology; microbiology; and biostatistics.

- Cell biology—as it pertains to mechanistic considerations of modes of action for cancer and noncancer outcomes.

- Pharmacokinetics/Pharmacodynamics—as it pertains to dose-response extrapolation using pharmacokinetic and physiologically based pharmacokinetic (PBPK) modeling.

- Susceptible populations and risk assessment (especially children, but also aging and/or other susceptible populations)—as it pertains to cancer, reproductive/developmental

epidemiology, environmental epidemiology, pediatrics, and/or behavioral sciences, and exposure modeling.

Based on these selection criteria, ERG conducted a search of subject matter experts to develop a list of highly qualified candidates for this peer review. After carefully reviewing the candidates' expertise and credentials, as well as their conflict-of-interest status, ERG selected six peer reviewers. Appendix A lists their names and affiliations.

1.2.2 Activities Prior to the Peer Review Meeting

Several weeks prior to the meeting, ERG sent the six peer reviewers a copy of the external review draft Framework Document and the peer review charge (provided in Appendix B). ERG also provided the peer reviewers with copies of public comments that EPA received on the Framework Document. The peer reviewers each read the review document and, working individually, prepared responses to the charge questions (provided in Appendix C). ERG held an orientation teleconference with reviewers to clarify the charge and answer any questions about the review purpose and format.

1.2.3 Activities at the Peer Review Meeting

The six peer reviewers and about 25 observers attended the peer review meeting, which was held at the Hyatt Regency in Washington, DC, on June 6–7, 2006. The peer review meeting was open to the public, and the meeting dates and times were announced both on EPA's Web site and in the Federal Register. Appendix D lists the observers who confirmed their attendance at the registration desk. The agenda for the peer review meeting is provided in Appendix E.

The peer review began with introductory comments and opening remarks by the meeting's facilitator (Kate Schalk, ERG) and EPA:

- *Opening Remarks.* Ms. Schalk welcomed the peer reviewers and observers to the meeting, stated the purpose of the peer review, and explained the peer review process. She also referred all observers to materials available at the meeting registration desk, including copies of the agenda and charge questions. Ms. Schalk then introduced Dr. Bob Sonawane, EPA NCEA.

- *Welcome Remarks.* Dr. Sonawane thanked everyone for attending and introduced the interdisciplinary members of the writing team, including three retirees, who worked on the Framework Document, and recognized their efforts. He said that EPA drafted the document in response to a recommendation to help assessors evaluate risks to children. Dr. Sonawane highlighted the history of the document, including an internal Agency-wide colloquium in 2004. He noted that EPA plans to finalize the Framework Document in the next several months, and requested that the peer reviewers be specific in their comments.

- *EPA Background Presentation.* Stan Barone, EPA NCEA, spoke briefly on the Framework Document. Slides for his presentation are included in Appendix F. The purpose of the document is to provide an overarching framework for a more complete

assessment of health risks to children. He emphasized the iterative nature of the framework and noted that "children" were broadly defined as including the stages of development from conception to adulthood. The Framework Document is a conceptual model that EPA plans to supplement with guidance, where needed, and training programs for the program offices and regions. Dr. Barone explained the framework for conducting children's health risk assessments, including problem formulation (which involves 3 steps), life stage-specific analysis (which involves a tiered approach), and life stage-specific risk characterization (which are modeled after current EPA guidelines). He also described the life stage-specific approach to children's health risk assessments, listed the value added of this approach, and pointed out that a lack of data for different life stages is not meant to imply an obligatory use of uncertainty factors (UFs). He stressed the importance of understanding mode of action (MOA) and outcomes from exposure during critical developmental periods. Dr. Barone reviewed the history of the document and commented that EPA plans to have final clearance by September 2006, and develop chemical-specific case studies in 2008.

- *Observer Comments.* The agenda included time for observer comments. Richard Becker (American Chemistry Council) and Scott Slaughter (Center for Regulatory Effectiveness) provided oral comments, which reflected their written comments (included in Appendix G).

  Dr. Becker's main point was that the Framework Document should incorporate the lessons learned and experience gained by EPA's Voluntary Children's Chemical Evaluation Program (VCCEP). He suggested integrating the tiered approach from VCCEP, clearly indicating that a "data gap" is not necessarily a "data need," and utilizing the exposure assessments developed and evaluated for the VCCEP pilot. Dr. Becker also commented that the Framework Document should (1) clarify that children are not always more vulnerable to chemical exposures than adults, (2) clarify the life stages, (3) state the limitations of EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA 2005a), and (4) mention the importance of data gathered in accordance with good laboratory practices (GLPs).

  Dr. Slaughter stated that the Center for Regulatory Effectiveness recommends that the Framework Document be revised to specifically state that EPA's Information Quality Act guidelines and the EPA quality system documents apply to children's risk assessments. He further recommended that the document be revised to state that children's risk assessment include a certification and compliance with these guidelines. The EPA quality system documents are available at http://www.epa.gov/quality/qa_docs.html.

Following these opening presentations, Dr. Lynn Goldman (Johns Hopkins University School of Public Health), a peer reviewer and the designated chair of the meeting, opened the technical discussions among the reviewers to answer the charge questions. The technical discussions were strictly among the peer reviewers, with EPA occasionally answering questions of clarification posed by reviewers. The peer review meeting concluded with a writing session, during which peer reviewers prepared written summaries of their responses to the individual charge questions. All draft responses to charge questions prepared by individual peer reviewers were fully reviewed and vetted by the group. These summaries are included in Sections 2 to 13 of this

report. Additionally, the peer reviewers reviewed the written and oral public comments in a point by point fashion.

1.3 Report Organization

The structure of this report reflects the charge questions. Section 2 summarizes the peer reviewers' general impression of the document. The sections that follow present responses to specific charge questions. Section 14 is a summary of the peer reviewers' responses to the written public comments EPA received on the Framework Document. All references cited in the text are presented in Section 15. The appendices to this report contain the following:

- List of the peer reviewers (Appendix A)
- Charge to the reviewers (Appendix B)
- Pre-meeting comments, organized by charge question (Appendix C)
- List of registered observers (Appendix D)
- Agenda (Appendix E)
- Slides of the presentation by Stan Barone (Appendix F)
- Written public comments (Appendix G)

2.0 General Comments

The peer reviewers agreed that EPA is to be commended for developing the *Framework for Assessing Health Risks of Environmental Exposures to Children*. The document, if implemented and enhanced by development of case studies and guidance, will result in an important and appropriate shift in the Agency's approach to risk assessment by putting the child rather than the adult at the center of the evaluation when data indicate that susceptibility could be greater at the younger ages. This approach is consistent with legislative and administrative mandates requiring that risks to infants and children be explicitly and consistently considered by the Agency. It is also appropriately health protective. People may be more susceptible to effects of environmental toxicants during childhood, in part because certain exposures are greatest during this period. Children drink more water, eat more food, and breathe more air per kilogram of body weight than do adults, due to more rapid metabolism and higher caloric needs. Children also have additional pathways of exposure (hand-to-mouth) and can receive greater exposure than adults through common pathways (e.g., dermal absorption because of crawling). Developing organ systems can be, but are not always, more susceptible to the effects of environmental toxicants. This may be particularly true during fetal development and early infancy when some organs are undergoing rapid growth, development, and differentiation; but detoxifying enzyme systems are not yet fully functional. It is important that the Agency is not proposing that risk assessment necessarily cover all life stages, but rather that the focus be on the stage(s) where exposure and/or susceptibility is suspected of being greatest (page 36). However, to ascertain which life stages will be most exposed or susceptible requires the analyst to give at least some consideration to the various age bins developed in EPA's age grouping guidance for children, which is summarized in Table 4-1 of the Framework Document.

The peer reviewers feel it is important to get this Framework Document published, and then to proceed to develop case studies using the framework and to develop guidance in key areas for risk assessors conducting life-stage analyses.

3.0 Charge Question 1

Is the purpose of this draft framework document clearly articulated? Are the graphic presentations of various concepts and methods (e.g., flowchart approach) and the questions to prompt review considerations clear and useful? Please provide a rationale for your answers. Do you have suggestions for improving clarity?

3.1 Response to Charge Question

The framework provides an overarching vision of the structure, processes, and components important for assessing risks from children's environmental exposures. The peer reviewers were unanimous that the framework provides a scientific basis upon which EPA can achieve the goal of a more complete assessment of health risks to individuals during all stages of development. The purposes of the Framework Document are clearly stated at the beginning of the Executive Summary and the Introduction. The purposes as stated on Page 3 are two fold: (1) to provide a central resource for information that can be used to assess children's risks and (2) to provide an overarching framework for this endeavor. However, the document does not provide "a single resource for information on the assessment of health risks to children as a result of exposures to environmental agents," which is the first stated purpose. Although many useful resources are provided, the peer reviewers concluded that to attempt to do this exhaustively is not a realistic purpose. Rather, the second purpose is more on point to what the document accomplishes (i.e., to provide the framework for conducting child-oriented health risk assessments). As the peer reviewers note in the response to other questions, there is merit to providing a compendium of the resources (e.g., literature references, databases, guidance documents, etc) pertinent to early life stage analysis in one place, where it can be easily accessed and updated. For example, this could be done in an electronic database with links provided within the document. The database will require regular updating as experience is gained through the implementation of the framework. The Framework Document does point to a variety of other resources, including other EPA documents and papers in the published literature, that are useful to conducting an assessment of risk to children from exposure to chemicals in their environment. Online access to the references cited is very useful.

The peer reviewers felt that EPA also needs to better clarify the purpose of the document relative to the distinction between a framework (i.e., concepts, key questions, analytical map) and a guidance document (i.e., specific step-by-step instructions, recommendations). Specifically, clarification is needed on how the document will assist a risk assessor in conducting a child-focused risk assessment, and what it stops short of providing.

Overall, the document reads as if it was written by a committee and is in need of an editor, not only to give it a "single voice" but also to improve the language. Often the figures have too much text in the captions. The captions should fully explain the figures, but the figures should complement, rather than replace, the text within the document.

One overarching comment is that considerations related to life stage analysis should come forward more clearly throughout the document. For instance, many of the graphics and much of the text deal with general risk assessment issues, and the specificities with regard to life stage-specific analyses occasionally seem to be added as an afterthought or to be understated and lost in the generic figures and text. One example is the discussion of weight-of-evidence (WOE). Risk assessors do this routinely, and the WOE discussion should focus more on how life stage-specific considerations can be emphasized in a WOE analysis.

Another overarching comment is the need for a diagram indicating the decision points that will be encountered as one proceeds through the scoping process for exposure assessment and dose-response analysis. As noted in the document, not all risk assessments should require immense resources. Although more detailed guidance will be needed in the future, there needs to be some indication in the framework where the decision points would be for the assessor to move on in the absence of relevant data.

The graphic presentations and the prompting questions are helpful in understanding the basic components of the risk assessment process and the key considerations for a life stage-specific analysis. Some improvements could be made to specific graphs, and additional prompting questions are warranted.

It is somewhat confusing to have prompting questions for the risk assessors both embedded within the text and compiled in Appendix 1 at the end of the document. While Appendix 1 should remain, the editor should make sure that the major points to consider (questions to ask) are also brought forward to the appropriate section.

Some peer reviewers thought that the graphic presentations of concepts and methods are overly complicated. Figures in the beginning sections do not connect readily with one another, for example, Figures 2-1 and 2-2. Three figures intended to describe the entire process, Figures 2-2, 3-1, and 4-2, do so in completely different ways. It would be helpful to have one figure that represented the unifying framework to tie together the contents of Chapters 2, 3, and 4. One way to make the graphics more unified would be to create a simplified version of Figure 4-2 that could be used at the outset (in the place of Figure 2-2) to provide an overview of the entire process. The description of the process at each stage could then utilize this simplified graphic along with a “blowup” of the portion that is under discussion (e.g., as done with Figures 4-3 and 4-4). Such graphics would replace Figures 3-1, 3-2, or 4-1. As written, some reviewers felt that it was not clear how the information flowed, nor whether some steps have to be repeated, such as “scoping” out the numbers of studies. As currently constructed, the differences in each of these areas are lost— a case where the forest hides the trees. There are some important details that are of special interest to one or more of the risk assessment components that may be overlooked because they all look so similar. Some figures (e.g., Figure 3-2) do not contribute much to the text and could be eliminated.

3.2 Specific Comments

On page 5, Figure 2-2 (Children’s health risk assessment framework) could be clearer. “Life Stage-Specific” focus should be presented in Problem Formulation. The sub-box “Characterize Life Stage-Specific Risks” needs clarification. As written, it is not clear whether the objective of

this step is to characterize risk from exposure at specific life stages or risks for that specific life stage. It could be reworded as "characterize the risk to the child and subsequent adult from life stage-specific exposures." This suggested wording reflects the fact that life stages (from conception to old age) are unique stages through which everyone passes. The effects of exposure to chemicals can be manifest at the life stage during which exposure occurs and/or subsequent life stages.

Figure 2-3 is valuable to show how exposures can have long-lasting or delayed outcomes. It would also be good to add several anticipated critical windows of vulnerability, for example, due to ontogeny of male reproductive tract *in utero*, ontogeny of metabolizing systems, critical window of vulnerability for carcinogenic processes, etc. That may be a separate chart, but it would be good to document what is known about critical windows in a flow chart that shows how they are incorporated into the framework. (Also see comment on adding table of critical windows below.)

The shading of Figure 2-3 was confusing and did not come out well in the printed version. As a result, it looks like preconception exposure is not considered. Thus, the artwork should be improved to make sure the figure shading is clear in the printed document.

On page 14, Figure 3-2 does not correspond well to the conceptual model found in the *Framework for Cumulative Risk Assessment* (EPA 2003). If one followed the conceptual model in the cumulative risk framework, the last box should be a health endpoint. The figure is really a mixture of steps in a risk assessment and steps in a conceptual model. The box at the bottom could read "Comparison with health assessment values…."

The questions on page 15, lines 5-14, designed to prompt the risk assessor to identify toxic effects of chemicals under consideration in a risk assessment, are useful. A good question to add to this list is: "Are there any toxicological endpoints noted in animal or human studies that are red flags for possible increased susceptibility of early life stages (e.g., neurotoxicity, immunotoxicity, endocrine disruption, and so forth)?"

On Page 16, the matrix in Figure 3-3 is wonderful, but it will be largely blank for most chemicals. However, this graph is useful to show the risk assessor and involved parties where there are data and where there are not data.

On page 19, Figure 4-1 should state whether the first column of arrows is meant to indicate information from studies in people or animals—the assumption is that it represents data from adult animals. This chart presents a useful model for the way in which animal testing (left column) feeds into risk assessment. However, the figure and text do not present an alternative framework for life stage-specific analysis that is actually more common—that being extrapolation from adult animal to adult human to life stage-specific extrapolation. This option appears as a secondary option in the figure legend. However, the uncertainties in the juvenile animal to child extrapolation and the common use of adult human to child extrapolation makes this option important. It should have equal footing with the option shown in Figure 4-1 and have its own diagram.

In addition, the sentence starting on line 6 states “In instances where there is no mechanistic information, animal dose-response data can be utilized and traditional default methods applied.” This statement seems to preclude a combination of toxicokinetic (TK) and toxicodynamic (TD) data analysis/modeling and UFs. For example, one might be able to account for variability in a TK parameter or parameters, but not for all the TK factors that differ between life stages of animals and humans. In addition, there is even less data on TD differences by life stage for most compounds. Thus, there needs to be room to use modeling where possible, but keep UFs in the tool box where only some of the variability/uncertainty is accounted for. Of course, one can never account for all uncertainty using PBPK and dose-response models.

On page 20, Figure 4-2 is a nice conceptual diagram that shows how the phases interact. However, this figure is too generic, emphasizing the standard Hazard Characterization Framework. For example, too much space is given to the basics of study evaluation, controlling confounders, and characterizing the extent of the database. These are given elements of hazard characterization that should be the building blocks for a life stage-specific version that focuses on such key elements as MOA, variability, data gaps, identifying potential windows of vulnerability, target organ sensitivity, and the potential to imprint toxicity and cause delayed outcomes.

In addition, not every risk assessment would need extensive analysis, nor would data be available to evaluate many of the life stage-specific considerations extensively. Thus, some guidance as to streamlining or simplifying a risk assessment is needed where the assessor either has insufficient data to address some of the life stage-specific considerations or the nature of the risk assessment does not warrant extensive analysis. Clear examples of problem formulation and the feedback between hazard characterization and problem formulation might help the user of this framework understand when to move on when data are limited.

On page 22, Figure 4-3 is generic and unnecessary, as currently constructed. It could possibly be made more useful by pointing out key life stage-specific elements of individual study evaluation—Does the study provide information on early life exposures? If so, does the study provide dose-response information on early life stages? What outcomes relevant to development does the study evaluate? Does the study provide any information on internal dose in juvenile animals?

On page 28, Figure 4-4 is too generic and misses the opportunity to show key WOE decision points in a life stage-specific analysis—Is the MOA likely to be operative *in utero* and at early life stages? If *in utero* effects occur, are they likely to be manifest postnatally as well? Do TK issues of chemical delivery affect potency differences seen across life stage?

On page30, Figure 4-5 is a building block figure that can be taken as a given in hazard characterization. The peer reviewers recommend describing it in text and omitting the figure, unless it can be reframed for a life stage-specific approach.

On page35, Figure 4-6 looks fine except that it calls out “low dose” effects. It would be better to simply state “Identify the NOAELs and LOAELs associated with life stage-specific outcomes.” These no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) may not be at a particularly low dose, depending on one’s frame of reference.

On page 35, Section 4.1.5, the bullets on lines 11–25 describe issues to consider in the life stage-specific hazard characterization narrative. The legend under Figure 4-6 is clearer than what is in the text. The legend has a better description of what the assessor needs to do to characterize hazard than does the first bullet. The last bullet seems out-of-place and does not really fit here. Why mention MOE when discussing selection of outcomes relevant to quantitative dose-response? MOE is only one type of hazard characterization method.

On page 37, Figure 4-7 is a bit too generic and misses some useful life stage-specific dose-response concepts. Additional concepts that could be clearer in the figure include:

- Identify life stages for which quantitative dose-response data are available.
- The confidence in that data and what is its relevance to early life stages in humans.
- What data lend themselves to a full quantitative treatment/benchmark analysis (e.g., the feasibility point in the figure under "Analysis in Range of Observation").
- Whether the data can be modeled *via* threshold or non-threshold approaches.

The key question in Figure 4-7 should probably be: Can early life dose-response assessment be conducted based on early life animal data, based on adult animal data and extrapolation to juvenile animals and then extrapolation to children, or extrapolation from adult animals to adult humans and then to children? What modeling techniques are needed to perform these extrapolations for early life stages? The figure legend does a better job of describing what the assessor is to do for life stage-specific dose-response assessment than the text of this section. The legend should be shortened and the existing legend should be part of the text. In addition, the text should explain the distinction between narrow and broad assessments.

On page 41, the second bullet (line 11-12), the second question talks about pre- and post-pubertal exposures. What about exposures during puberty that are likely to be very important for some chemicals? The peer reviewers suggest rewording the question to "What is known about pre-, peri-, and post-pubertal exposures?" to encompass puberty.

On page 43, line 28 indicates that drug clearance in children may be higher than in adults, but that is not necessarily correct if one expresses clearance on a surface area basis.

Additional concrete examples, as provided to the questions on page 43, would strengthen the document and make it more "user-friendly."

On page 48, Figure 4-8, the peer reviewers suggest changing the title to "Use of BBDR modeling information for a surrogate chemical to inform the dose response for the chemical of interest."

On page 58, Figure 4-9 is generally a useful figure, however, it can be made more life stage-specific in certain areas, see examples below.

- Under Exposure Media Concentrations add "evaluate whether media concentrations for children will differ from adults."
- Add a bullet for life-stage specific dietary factors (unless this is defined as being part of activity data).

- The exposure characterization box is generic and should be made more life stage-specific by adding an evaluation of whether age bins chosen for exposure assessment materially affect dose (they usually do).

The best explanation of the approach is the legend under Figure 4-9. The text should be edited using the figure legend as a model, and the legend could be much smaller.

On page 63, line 17 should be amended to read "Are there biomonitoring data that demonstrate exposure potential and that can be used to estimate a population's exposure?" As it currently reads, it is not clear one can estimate an individual's exposure level from typical biomonitoring data (unless one is actually measuring chemicals in biological media of individuals in the population that is the subject of the risk assessment—an unusual situation).

On page 64, bullets, lines 4-11. There should be a bullet specifically asking "Can the infant be exposed to the chemical through breast milk?" Breast milk is a unique exposure route for children.

On page 66, Table 4-1 (the chart on binning) should be moved earlier in the document, perhaps after Figure 2-3 on page 6. The *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (EPA 2005c) is now finalized, and the chart on binning from this document would provide risk assessors with concrete examples of how to conceptualize age groups for exposure in the risk assessment.

Appendix 1 compiles a number of questions that the assessor can use to guide a life stage approach to risk assessment. These questions are appropriate and useful to the assessor tasked with evaluating potential risks from exposures across life stages. There are a number of more specific questions in Section 4.3.1 of *A Review of the Reference Dose and Reference Concentration Processes* (EPA 2002a) that could be pulled into this Appendix. Some of the questions are similar, but the authors should review the questions in the reference concentration (RfC)/reference dose (RfD) review document to improve Appendix 1. A few specific comments on the questions in Appendix 1 follow:

- On pages 110–111, in the section on Study Design, in the box "All Studies"/"General Questions," the following question should be asked "Was the power of the study adequate to detect an effect?" This is often a limitation that is not adequately discussed when studies are concluded to be "negative."

- On page 111, the first question asked under "Animal Studies" is "Was the study conducted in accordance with good laboratory practice?" While this is an important consideration, it is not the only consideration in the utility of a research paper. Many of the older studies that showed early-life stage sensitivity to carcinogens were conducted before GLP was standardized. Many studies in academic institutions do not follow GLP regulations. It would be a disservice to imply that only GLP studies are to be considered in a risk assessment. A statement to this effect should be added into this table.

- On page 112, under Outcomes, there are some questions related to effects of chemicals on precursor events toward the bottom of the page. A question that should be added is

"Are the toxicities resulting from alteration of precursor events expected to be different depending on life-stage?" This is important because alteration of a precursor event in a mature animal or adult human may not have any significant health consequence, where the same precursor event alteration in a developing organism may have significant health consequences.

- In the section on TK, questions should be added to direct the assessor toward additional TK differences by life stage, other than metabolism. Metabolism is an important determinant of TK differences by life stage, but it is not the only process that affects disposition of the chemical. The differences in gastrointestinal absorption (affected by gastric and gut pH, emptying time, transporter proteins, lung morphology, ventilation rate, skin surface area and permeability, etc), distribution (affected by differences in plasma protein binding, body water/fat content, blood perfusion of various organs, etc), and excretion (affected by renal perfusion/glomerular filtration, hepatic perfusion, etc) can be just as important for some chemicals, age groups, and life stages.

Possible additional figures and tables:

- It might be useful to add a figure near page 75 showing how sensitivity and Monte Carlo analyses can be used to better characterize variability and uncertainty across the population and to compare one life stage (e.g., infants) to another (e.g., adults).

- It also may be useful to add a figure for Section 5 that shows how the analysis just described can culminate to answer the life stage-specific questions raised in Problem Formulation (e.g., standard setting questions such as "What is the appropriate regulatory limit for a chemical in drinking water to protect all life stages and cumulative exposure throughout the lifespan?" The risk characterization would yield a water concentration that is protective of fetal, neonatal, and adult risks by considering the full range of studies and outcomes. Another example would be a site-specific risk question (e.g., How much risk is associated with living at this site?) The assessment would use exposure calculations along with hazard assessment and dose-response assessment to calculate life stage-specific risks. A third example could be the use of qualitative questions (e.g., Are early life stages likely to be at greater risk than adults?) to conduct a comparison of dose-response, exposure, and TK factors across life stages to develop a better informed uncertainty analysis.

- The authors may consider adding Table 4-2 on page 4-17 from the document A *review of the Reference Dose and Reference Concentration Processes* (EPA 2002a) to the Framework Document because it summarizes basic factors to consider when identifying sensitive subpopulations.

- A table summarizing some of the key conclusions from the articles cited on page 23, which arose from the workshop on critical windows of exposure for children, would also be a useful guide. A figure or figures showing the comparability between experimental animal and human life stages for the development of major organ systems would be helpful.

- Page 43 references a number of reviews on age-related differences in absorption, distribution, metabolism, and elimination. Could data from these be highlighted in table format?

4.0 Charge Question 2

This report is intended to highlight specific concerns of children's risk assessment. To what extent is this document consistent or inconsistent with how you have interpreted existing risk assessment guidance and practices? Are there major gaps in what has been presented, for either children's risk assessment or for risk assessment more generally? Considering the various types of Agency chemical assessments that you are familiar with, are there gaps in the process outlined?

4.1 Response to Charge Question

Overall, the Framework Document is consistent with existing risk assessment guidance as laid out in a number of documents including A *review of the Reference Dose and Reference Concentration Processes* (EPA 2002a) and the *Guidelines for Carcinogen Risk Assessment* (including the Supplement) (EPA 2005b). The one clear exception to this is on page 79, lines 12–15. The sentence in the middle of Section 5.1.2 seems to imply that a quantitative risk assessment needs to focus on endpoints expressed as changes in adverse outcomes that "are readily understood and perceptible by the public." The sentence is only referring to endpoints that will be used in a benefits analysis, but appears to imply that only clinically apparent adverse outcomes need to be assessed. This is not consistent with well accepted risk assessment practice, where outcomes such as subtle neurobehavioral changes have been used by risk managers in major public health protection programs (e.g., lead cleanup). Such subtle effects may be sub-clinical in the individual and may not represent overt disease. However, they lead to population-based decrements of public health and physical or mental functioning.

Additionally, the draft framework has several gaps, due in part to the more complex nature of life stage-specific risk assessment. These are described below.

4.1.1 Need to be More Life-Stage Focused

The Framework Document is fairly thorough in its treatment of the basic, underlying data evaluation and risk assessment techniques. However, much of what is encountered in early life risk analysis may be non-standard due to the possibility for unique windows of vulnerability, unique toxic mechanisms, and novel or heightened exposure pathways, all of which typically have very little data for the chemical of interest in early life testing. Therefore, it would be helpful if the document augments the generic descriptions of hazard characterization (e.g., how to evaluate a toxicologic study) and exposure assessment with more life stage-specific material. As one reviewer said, the report included statements regarding "life stages" almost gratuitously throughout. A particular concept would be explained and then followed by an often-terse statement saying that one has to perform this differentially for the different life stages. A suggestion for improvement in this area is to decrease the coverage given to the standard, somewhat generic methods that every risk assessment should follow, and to provide more focus

on the unique issues, questions, and decision points that are specific to a children's analysis. Some examples for hazard characterization follow.

- Are effects from prenatal exposure relevant to postnatal-only exposure or are the effects from *in utero* developmental studies not translatable to the postnatal period (e.g., some may consider *in utero* neurotoxic effects to be relevant for postnatal exposure while many teratogenic effects would likely not be a concern postnatally)?

- What MOAs, target organs, or health outcomes in adult animals raise concerns about the potential for early life vulnerability (possible examples include mutagenic carcinogens, hormonal imprinting, neurotoxicity, immunotoxicity, and the potential to promote the allergic phenotype)?

- If animal testing shows differences in potency between juvenile and adult animals, is it possible that differences in administered dose or TK can explain this, or is it more likely to be a TD (inherent vulnerability) difference? The implications for risk assessment can be very different depending on the mechanism.

Regarding exposure assessment, a key decision point is how to pro-rate exposure (i.e., average the dose over an appropriate time frame). Table 4-1 would suggest averaging exposure doses over the age bins provided; however, there may be TK and TD vulnerabilities that would dictate a different exposure window. For example, the critical window for heightened vulnerability to carcinogenesis may be the first 2 years of life. One may assume that averaging over this age bin (0-2 years) is most appropriate, even though there may be shorter windows when exposures are higher. Since the minimal exposure period to elicit an increased risk is often not known, especially during a window of vulnerability, the choice of exposure period is a critical decision point that integrates toxicology, kinetics, and exposure information.

4.1.2 Need to Discuss Cumulative Risk

It is worth noting that the guidelines for cumulative risk are cited in several places, but the text does not discuss cumulative risk assessment concepts nor does it integrate them into the current framework. This can be brought up in the context of exposure assessment, where early life stages may not have the diversity of exposure pathways as in older children (e.g., nursing infants have a much more limited dietary exposure and are less likely to be exposed to soil and house dust), whereas other age groups may have a greater diversity of exposures (e.g., at school, on a playground, trespassing onto waste sites) and thus a different mixture of toxicant exposures. Is it possible for chemicals to combine differently at early life due to metabolic immaturities, limited protein binding, or novel MOAs. Little is known about chemical interaction in adults and even less is understood in children.

4.1.3 Streamlining the Process

The Framework Document does not really provide a strategy for narrowing a life stage-specific assessment to something that is manageable and feasible. This is especially important in life stage-specific risk analysis because there are many possible life stages to analyze (e.g., Table 4-1), outcomes to consider, and exposure-response arrays to construct. How does one scope the

possibilities for data analysis and risk characterization and then shape the analysis to focus on what are likely to be the most vulnerable age groups and key risk drivers? At what point in the analysis are these decisions made? Which age window(s) is/are likely to have the greatest external exposure, the greatest internal dose, and the greatest inherent vulnerability? The Framework Document should discuss how these factors and decision points can be integrated to define the age groupings that will be analyzed in the assessment. Perhaps a streamlining decision tree can be introduced in this document, with follow-up guidance and brief accounts of case studies providing a more concrete method on how to do this. The streamlining decision tree should address not only age binning but also outcomes that are likely to be of greatest concern to early life based on MOA, juvenile/developmental animal data or early life human data, and target organs for the chemical under analysis.

4.1.4 Approaches for Addressing Data Gaps

The major gaps in the Framework Document are not in the framework itself, but in how the framework should be implemented. In particular, the document is specifically lacking details on how to handle data gaps. This will require the development of succinct case examples of risk assessments conducted within the context of the framework. One of the values of the framework will be to foster awareness of data gaps and data needs for child-oriented risk assessments. As pointed out in the document (page 28), detailing the lack of information about an agent is crucial to an adequate characterization of childhood risks from that agent. The Framework Document may want to say more about the types of data gaps that may be typical for many chemicals. For example, juvenile animal studies are rare. Developmental (*in utero*) studies are more common, but are not done for all chemicals and are limited because they do not involve direct dosing in postnatal life. 1- and 2-Generation reproduction studies are also not conducted for all chemicals and are limited in having postnatal dosing only *via* nursing and involve a limited number of endpoints. Developmental neurotoxicity studies have a good design but are not commonly done and have limitations regarding the exposure route and endpoints/organ systems assessed.

4.1.5 Making Use of Existing Risk Assessments that do not Have a Life Stage Focus

The risk assessor may encounter a well developed risk assessment for the chemical of concern, such as those prepared in EPA's Integrated Risk Information System (IRIS) or in ATSDR's Toxicological Profiles. However, these risk assessments do not typically have early life stages as a major focus. They will be directly useful for assessing adult exposure and risk, and can likely be a springboard for constructing a life stage-focused assessment. The latter will involve further consideration of studies identified in the existing risk assessment to determine their implication for early life stages, additional searching for other studies that may be pertinent to early life, further consideration of MOA to assess potential windows of vulnerability, consideration of TK factors that may impact risk in early life, and evaluation of uncertainties and data gaps specific to early life stages. The existing risk assessment should be identified early in the process and be a major consideration in problem formulation to help shape the type of effort needed to assess children's risks.

4.2 Specific Comments

The peer reviewers agreed that generic study evaluation issues such as WOE should simply reference existing EPA guidance. However, if the EPA wishes to include WOE in the Framework Document, there are specific comments about this approach, which pertain to pages 26–29 and Appendix 1. Examples of issues that are not well explicated are:

- statistical power (numbers of subjects or animals, precision of measures),
- bias (including confounding),
- appropriateness of animal or *in vitro* models,
- relevance of routes of exposures and exposure levels,
- relevance and accuracy of biomarkers of exposure and biological change, and
- quality of assessments of exposure and outcomes.

Along these lines, terms such as "interaction" and "controlling" are used in nonconventional ways. For example, on page 26, one cannot control for study variability (this is probably not what was meant by the authors). On page 29, effect modification and confounding are treated as one and the same entity. Confounding is a form of bias and always needs to be addressed, not only in human but also in animal studies and *in vitro* assays. Effect modification is important in dose-response assessment, but the idea of evaluating effect modification at every life stage for every risk assessment is overkill.

5.0 Charge Question 3

Risk assessment is a multi-step process and done at many different scales depending upon the problem. Do you think the document provides enough flexibility for users to understand how it applies to them? If not, for what audience(s) would you suggest clarification is needed and what kind of clarification?

5.1 Response to Charge Question

The Framework Document is clear that risk assessments are done for many different purposes and at many different scales. It provides a framework, not a prescription, on how risk assessment should be conducted and thus gives adequate flexibility for multiple purposes. The Framework Document recognizes the need for flexibility in approaching the broad range of applications for life stage-based risk assessment. There is brief mention that the framework can be used for chemical-specific or site-specific assessments, which provides additional flexibility.

A number of topics (e.g., TK as a function of maturation) are addressed several times in different sections. While the flexibility of the approach is good, the sheer volume of information limits the document's usefulness for risk assessors. That being said, the information is accurate and pertinent to children's risk assessment and thus, does provide a useful framework.

Although the intention to provide flexibility is clear, at times the document uses normative statements (such as "consideration of MOA is critical" and "characterization of uncertainties at various life stages is important") that may cause risk assessors to perform more elaborate

analyses than might be warranted in a specific situation. The document should stress throughout that whether such considerations are “critical” or “important” is very much dependent on the type and the purpose of the assessment. Likewise, at times the amount of information that must be taken into account may be so overwhelming that risk assessors may suffer from “paralysis of analysis.” There will be so many data gaps for most industrial chemicals that risk assessors and stakeholders may not move forward with an assessment. The quest to conduct uncertainty analysis at every stage is enough to paralyze most assessments, and at a minimum will slow the process considerably. Thus, there is serious need for examples from simple to more complex. Such examples will demonstrate the desired flexibility, and what the risk assessor could do and say where data are limiting. The risk of not providing examples is that people will ignore the guidance completely.

The major concern, which the peer reviewers mention in response to other questions as well, is that there is a need for subsequent guidance on how to conduct such an assessment, and when and how to move ahead in the absence of data. Guidance will be needed to implement the framework; it would give hard and fast directives about how risk assessment will actually be conducted by the multitude of scientists and offices at EPA. Such guidance should provide strategies for streamlining the assessment and focusing on life stages and outcomes most likely to drive risk. This may involve screening level assessments in problem formulation or data analysis. At one point the Framework Document describes screening level versus refined analysis (Exposure Assessment, pages 70–71). Perhaps more of this type of a two-phased approach can be built in with respect to screening the age bins, outcomes, or TK factors that may be of most importance. Additionally, such guidance can address a number of potential questions. When are problems likely to crop up? Are the problems critical in that they are likely to give the wrong answer if typical methods are followed? Is there more to the process than just noting that sensitivity, susceptibility, and impact are different at different life stages?

6.0 Charge Question 4

Is the list of potential involved parties (e.g., risk assessors, risk managers, others) discussed in the problem formulation inclusive enough? If not, please provide suggestions for other involved parties.

6.1 Response to Charge Question

Yes, it is clear that the problem formulation stage should involve a multidisciplinary team of experts that include: risk assessors, risk managers, stakeholders, toxicologists, exposure assessors, epidemiologists, and child health and behavior specialists, depending on the specific goals of assessment. The emphasis on the importance of the problem formulation stage is one of the strengths of the document.

The peer reviewers emphasize that risk managers and program managers within the EPA as well as many stakeholders outside of the EPA—scientists, section chiefs, and administrators at various levels in and outside EPA, as well as state and local health and environmental officials, attorneys, and the regulated community—would want to understand the process. They could thereby determine how they or their work may be impacted, or how they might impact the process. To the list of scientific experts who need to be involved, EPA could add the following:

risk communicators, PBPK modelers, and pediatric experts. When the framework is used for a site-specific risk assessment, it would be good to involve community groups, pediatricians, and parents of young children who may have information and insight that would be useful for the analysis.

The reader is referred to the discussion of stakeholders in the *Framework for Cumulative Risk Assessment* (EPA 2003). In addition, it would be helpful for EPA to insert some of the material from pages 19–21 of the cumulative risk framework into this Framework Document. (Specifically, the box on page 21 might be useful to place in the Framework Document.)

The Framework Document should not imply, as it does on page 16, that the conceptual model and the analysis plan for the risk assessment, including possible outputs for the assessment, will be negotiated among risk managers. Risk managers certainly are involved in scoping out the depth of the analysis (e.g., Is this to be a screening assessment or the development of a national standard?) However, it is important to keep risk management separate from risk assessment when it comes to the development of the scientific procedures for the analysis plan.

7.0 Charge Question 5

The approach described uses a life stage perspective; that is, it focuses on assessing exposures for developmental life stages (embryo, fetus, child, and adolescent) and resulting health outcomes for all life stages (embryo, fetus, child, adolescent, reproductive adult, and aging adult). The EPA is soliciting your input regarding whether this approach is a more comprehensive approach than the focus on organ systems (e.g., neurotoxicity, cancer, reproductive toxicity, and developmental toxicity) used in previous risk assessment guidelines. Please comment on the advantages and disadvantages of this approach within the context of the current scientific understanding of the impact of exposure in different life stages and the available data.

7.1 Response to Charge Question

There was a general agreement that the Framework Document is a more comprehensive approach to assessing health risks from environmental exposures than the existing current guidelines for RfC, RfD, acute reference exposure values, developmental toxicity, reproductive toxicity, and so on. The life stage approach was thought to be both more appropriate and, in the long run, more efficient because exposure is life stage dependent. In fact, as one reviewer comments "…it is impossible, in my estimation, to carry out an adequate risk assessment without considering the maturity of the organ system itself. …" The Framework Document provides a useful starting point for risk assessors to begin to more fully characterize risks from early-life exposures to children and through adulthood. It is increasingly recognized that adult disease may originate from environmental exposures that occurred *in utero* or during early childhood. Likewise, childhood diseases such as asthma and some cancers may also be linked to chemical exposures *in utero* or in infancy and early childhood. The developing organism presents different targets for the action of exogenous compounds that are not present in the adult. In addition to these TD differences, the TK of a compound may differ by age and life stage and have a large qualitative or quantitative impact on toxicity per unit dose. Current risk assessment paradigms only explicitly account for potential differences in health outcome from early life exposures

when there are specific studies of the compound(s) of interest in developing organisms. Otherwise, the basis for most risk assessments is a study done in mature animals or epidemiological studies of adult humans in an occupational setting. It is clear that this information is inadequate to predict what happens in developing organisms, including infants and children. Thus, the current target organ approach (e.g., cancer, reproductive toxicity, neurotoxicity), while very useful, is lacking. This Framework Document broadens the questions the risk assessor asks and provides a pathway to better characterize risks to children. Putting these potential early life risk issues into the midst of the risk assessment process is important and why this framework is so essential.

The *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* published in March 2005 (EPA 2005a) is a significant improvement over previous guidelines, which ignored early-life exposure. The Framework Document provides additional and complementary concepts and questions for the risk assessor to explore in assessing cancer risks from a life stage perspective.

The advantages of this approach are that it will:

- result in a better overall characterization of potential risks of environmental chemicals and increase our confidence in the risk assessment,
- demonstrate what is known and not known with regard to the impacts of early life exposures,
- make use of ancillary data (such as MOA and structure-activity analyses) to try to fill some of the data gaps more routine, and
- stimulate more research on the impacts of early-life exposures on the health of the infant, child, and adult they will become.

The Framework Document seems to have no brakes—when should the assessor stop? When is the assessment adequate given the quality of the available data? Clearly not all assessments require an enormous effort, but it is not clear from the Framework Document how one makes that decision in the problem formulation phase. The challenge is how to streamline the process in a rational and systematic manner. This may be the purview of a subsequent “guidelines” document rather than this Framework Document, but it should be considered. The peer reviewers expressed concern that the approach could cause delays in implementing clean-ups or applying control strategies, if the risk assessor is not provided guidance on how to move forward when the data are limited to answer the questions posed for a life stage assessment of risks. Care must be taken in applying the Framework Document to minimize the potential to be sidetracked from the essential task at hand—incorporating life stage-specific data into the risk assessment process.

The peer reviewers spent a substantial amount of time discussing the need for certification and validation of studies, especially toxicological investigations, using GLP. While there was general consensus that GLP practices are, in some sense, a gold standard, it was pointed out that many high-quality studies were carried out prior to the implementation of GLP regulations. Further, for many life stages and outcomes, GLP practices are not in place. The advancement of regulatory practices in this regard lags far behind the growth of the science, but this lag should not limit the utility of data collected. Many important studies of use to EPA are likely to have come from

testing laboratories following GLP. Academic research laboratories, for example, often supply some of the earliest and most cutting edge data useful for these purposes. Therefore, it is the consensus of the peer reviewers, that while GLP studies should be given strong consideration in WOE analysis, findings of other studies should be considered as well.

8.0 Charge Question 6

The report addresses the integration of hazard data with exposure information from a life stage perspective. This discussion brings together information from the toxicological evaluation, life stage of susceptibility, exposure factors for children, and age binning for exposures. Has the EPA clearly articulated this approach? Are their sufficient data and understanding available to inform such an approach? Do you have additional suggestions that could improve or clarify the approach?

8.1 Response to Charge Question

The Framework Document's authors have obviously worked hard and have done a good job at a "first cut" of integrating life stage susceptibility, toxicity data, exposure information, and age bins. This approach has been clearly articulated in Figures 4-2, 4-7, and 4-9. It would be preferable to incorporate most of the information in these lengthy figure legends into the text.

While the integration of this information has been articulated in the Framework Document, there are ways in which EPA's descriptions can be improved.

8.1.1 Data Gaps

In particular, the manner in which data gaps for early life stages is described is not very specific. Potential considerations and options are unclear. It would be good to begin such a discussion of data gaps by describing the importance of TK and TD data from studies of immature life stages (animals or children). Guidance will be needed with regards to the potential use of UFs in a rational and reasonably health protective manner consistent with pre-existing risk guidance. Other approaches to filling data gaps should be emphasized (e.g., utilize information from well-studied chemicals with similar MOA and/or structures (i.e., structure-activity relationships), extrapolation from adult or other life stages *via* TK scaling or modeling). In the presence of data gaps, assessors can ask if adult toxicity and TK data are available for a particular chemical. If so, estimates of internal dosimetry in children can be obtained by allometric scaling procedures. Also, one can ask if a valid PBPK model exists and can be employed. Relevant child age-specific metabolic and physiologic parameters can be input into the model to generate predictions of doses that when administered to children produce the same target organ doses of toxicant (parent compound or metabolite) as those known to cause injury in the adult.

8.1.2 MOAs in Early Life Stages

On page 25, lines 15–18 state that there are no known examples of how a chemical's MOA differs across life stages. There are actually a number of examples of this phenomenon. Teratogens only produce malformations when exposure occurs *in utero*. Certain receptor or endocrine MOAs (e.g., anti-spermatogenic effects of phthalates *in utero* and

hormonal/imprinting phenomena) may be unique to particular windows of vulnerability. Organophosphates inhibit cholinesterase throughout one's lifespan, but certain of these pesticide's inhibitory effects on neuronal differentiation and migration occur only during late pregnancy and early life.

A question was raised of how best to integrate TK and/or TD windows of vulnerability. One might assume, for example, that averaging exposures over the first 2–3 years of life (the period of heightened cancer susceptibility) would be most appropriate, though there may be shorter periods of relatively high exposures. An observer pointed out that EPA has established age bins for exposure as part of the *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (EPA 2005c).

8.1.3 Potential Development of a Comprehensive Resource Appendix

The pertinent references on critical windows of exposure listed on page 23, and on organ development across species on page 31 will be very useful sources of information for readers. It was generally agreed that such a list of references could be included in an appendix, so they could periodically be updated without having to amend the Framework Document. The reader can be referred in the text to the location of state-of-the-science references in this suggested appendix.

8.1.4 Adult Risk Assessments

There is little emphasis in the document on adult risk assessments. It is important to be able to compare susceptibilities across immature age groups, and to be able to compare them with that of adults. Adults are a critical life stage for analysis for several reasons in any risk assessment since most of the toxicity values that function as points of departure for across life stage comparisons derive from data on adults, and because adults can be the most sensitive life stage in certain cases.

8.1.5 Making the Framework More Relevant to Early Life Stages

As discussed in a previous question, the Framework Document should have less generic evaluation factors and more life stage-specific considerations. While the questions posed throughout the document are useful, they are often general and do not cover age-specific topics such as:

- Risk methodology for extrapolating inhalation dose to early life stages—the RfC methodology was developed for animal-to-human extrapolation but not adult to child. What resources or approaches can one use to address this issue?
- Understanding the critical window of vulnerability such that the time frame over which exposure should be averaged is a significant uncertainty.
- Extrapolating risks to early life for non-genotoxic carcinogens.
- Understanding MOAs in early life and whether novel MOAs and outcomes can be expected from early life exposure.

- Since TK and TD in children can rarely be studied, how is model variability in internal dose and sensitivity to toxicant action best characterized?

There was a consensus among the peer reviewers that a couple of examples or case studies of specific chemicals would be very helpful to risk assessors. It is only when one attempts to use a risk model that he/she learns, sees how well it works, and can recommend modifications. Comprehensive examples of how to conduct a child-specific risk assessment would be included in a subsequent guidance document, but brief accounts of relevant examples to illustrate specific points could be included in the current Framework Document.

8.2 Specific Comments

On page 26, lines 7 and 8 state that variability can be characterized through calculations of central tendency. This is not the case.

9.0 Charge Question 7

Has EPA's intention to move towards a harmonized approach for risk assessment, away from the dichotomous consideration of cancer versus noncancer, been clearly articulated in this document? Please provide a rationale for your response.

9.1 Response to Charge Question

EPA's intention to move towards a harmonized approach for noncancer and cancer risk assessment is clearly articulated and commendable. This approach to risk assessment is mentioned in lines 16–20 on page 36, but there is very little discussion of the issue in the Framework Document. Readers are referred in several other places to the *Guidelines for Carcinogen Risk Assessment* (EPA 2005b) and to *A Review of the Reference Dose and Reference Concentration Processes* (EPA 2002a.). These latter documents include explanations of treating noncancer and cancer endpoints with either thresholds or no threshold (i.e., harmonizing dose-response assessment). The harmonized approach should be mentioned in Section 4.1.3.6 and/or Section 4.1.3.7 of the Framework Document.

10.0 Charge Question 8

Is the iterative approach between the different analytical phases (hazard characterization, dose response analysis and exposure assessment) been clearly articulated in the framework? If not, how can this be improved? How does this iterative approach compare with your practical (or real-life) experience?

10.1 Response to Charge Question

The iterative approach is a strong, positive feature of the framework. This is an appropriate emphasis as it encourages the various specialties (exposure assessment, toxicologic assessment, modelers) and stakeholders to interact on an ongoing basis to ensure that the various stages are well integrated and adjusted based on information that emerges from the analysis. The peer

reviewers recommend several modifications of the way in which the iterative approach is described, as follows:

- Incorporate simple illustrations of the utilization of this approach. It may not be easy for a risk assessor to understand why one would want to iterate back to a different part of the analysis without a few examples that illustrate reasons for doing this. In this way, the framework would do a better job of showing the value added by this approach. For example, the framework could describe how while evaluating exposures, it was found that the 0–1 age bin was more highly exposed due to nursing ingestion than was any other life stage. This prompted the assessor to re-evaluate hazard characterization to make sure that potential vulnerabilities during this age window were well understood. Ultimately, case studies and guidance (yet to be developed) would greatly help the understanding of the iterative approach.

- Avoid over-iteration. The Framework Document should maintain a focus on streamlining the assessment. There is likely a point where iteration can become excessive and lead to unnecessary slowing of the assessment. Therefore, the iterative component should be described in a way that leads to the well-integrated and efficient movement of the analysis towards risk characterization, rather than multiple re-analyses that were not part of the initial problem formulation/scoping phase. Along these lines, the role of certain stakeholders in the iterative process should be limited. For example, risk managers, while critical to problem formulation, are not needed in iterations between analytical components because these are technical areas beyond the expertise of risk managers. When the risk characterization is complete, the risk manager can then review the draft document and comment whether the questions raised in problem formulation have been answered, whether the uncertainties have been clearly described, whether the analytical plan has been followed, and whether the assessment is transparent.

- Clarify the role of problem formulation in the scoping of the analytical components. The organization of the document has problem formulation appearing a number of times—at the outset of the entire process and then as an initial scoping phase for each analytical component. It may be better to have one comprehensive and intact problem formulation at the beginning of the document, and not bring it up in the individual sections. This makes the document longer and less direct. It currently reads as if planning will be done several different times. There could be a description of iteration of the analytical phases with problem formulation, so that the overall scope and shape of the assessment is modified by the data unearthed during the analysis.

11.0 Charge Question 9

With the kind of data typically available for chemicals, do you think an assessor would understand how to use this framework with existing data? If not, what would you suggest EPA needs to clarify? Does the risk characterization section for children risk adequately address data gaps and how they are incorporated into the risk assessment uncertainties? Please provide the rationale for your response.

11.1 Response to Charge Question

The risk characterization section of the Framework Document articulates an approach that should be useful in assessing risks to children. The questions in the tables are relevant and cover important aspects of any assessment. Data gaps aside, it is important to attempt to evaluate exposure at various life stages and to evaluate potential toxicities that might affect different life stages to best account for risks to children and the adults they will become. If anything, this framework will demonstrate that much more information needs to be developed about health effects of chemicals from exposures early in life.

Typically, there is a paucity of TK and TD data for immature animals, as well as for infants and children, for most environmental contaminants of concern. Some exceptions are food use pesticides and a few industrial chemicals that have been studied extensively for risks to children. Regulatory action(s) or voluntary approaches will probably be necessary to acquire toxicity data on many other classes of chemicals. To date, VCCEP has not produced new information in this regards; however, there may be lessons learned from the process to guide regulatory actions or new voluntary approaches in the future.

As has been mentioned in responses to other questions, the Framework Document does not provide specific examples of how risk assessments using a life stage approach could be applied over a wide range of scenarios and in situations where substantial data gaps exist. The Agency's plans to prepare a series of case examples on the implementation of the framework, and to conduct training sessions for risk assessors, are critical and essential components to the successful implementation of the document.

As also has been stated elsewhere in this review, guidance will be required to fully implement the Framework Document. The life stage-specific risk characterization summary is supposed to "provide a justification for the application of life stage specific adjustments for duration-specific health values… if the assessment warrants." However, the Framework Document does not inform the risk assessor how that is done. It will be a challenge to EPA to chart a standardized approach, or guidance to follow in children's risk assessment, when hazard and/or exposure information is incomplete or conflicting.

The Framework Document has much basic information on each analytical area that is not life stage-specific but is described in other documents, and may not be needed in so much detail here. This material, while useful to make sure everyone has the same analytical background, does tend to get in the way of what is new and different about this framework. It may be wise to restructure the document to minimize the "how to evaluate a toxicological study" type information (e.g., pages 21–22) and add more of the life stage-specific issues and analytical decision points. As to

risk characterization, more can be said (e.g., on page 85) about the types of data gaps one can expect in life stage-specific analysis, the impact they may have on the analysis, and how one may want to address them *via* UFs, sensitivity analysis, etc.

This document will be made more useful to risk assessors if:

- It is streamlined to focus on life stage-specific issues and decision points.
- Strategies are provided that assist the analyst to identify tools and databases to assess issues such as which age groups may be most vulnerable to a chemical's toxic effects, how might TK in early life influence the chemical's MOA, and what are the potential for novel MOAs and target organs in early life.
- More examples are used to bring some of the concepts to life.

12.0 Charge Question 10

EPA is planning to develop case studies to demonstrate the applicability of the life stage approach for children's health risk assessment and a training module for risk assessors. Do you have other suggestions that could aid in the implementation of this framework?

12.1 Response to Charge Question

The case studies are an excellent idea. Development of case studies will substantially increase the understandability and utility of this Framework Document. Case studies could give examples of the application of the framework to risk assessments conducted under major statutes such as Superfund, at various levels (e.g., a screening assessment versus a full risk assessment), with various kinds of data sets (e.g., a "rich" dataset such as lead versus one with very little hazard and exposure data for children), and with various scopes (e.g., site specific versus chemical specific). Such additional case examples would strengthen the document as has been done in the discussion on dose metrics and modeling on pages 42–53. The case studies and training modules are critical and essential components to the successful implementation of the document. Such training modules should be a basis for EPA to expand outreach and provide training courses (with instructors) to each program within EPA that has a quantitative risk assessment component, to each regional office, and to state and local risk assessors to assure that the framework is utilized throughout the country. Additionally, a web-based training module would be particularly valuable.

In addition, EPA may want to consider compiling a resource database either as an appendix to this document or separately that gives the assessor handy references or links to key early life TK, TD, and exposure information. The Agency cites resources that the risk assessor can use throughout the Framework Document. As discussed previously, it would be useful if some examples, with appropriate caveats, were also included, perhaps in table format or in appendixes. For example, Table 1-2 of the *Child-Specific Exposure Factors Handbook* (EPA 2002b) provides exposure factor recommendations and confidence ratings, with references to other tables for specific data. Could these factors be compiled into one table for the document or appendix? A table summary of some of the key conclusions from the articles cited on page 23 that arose out of

the workshop on critical windows of exposure for children would also be a useful guide. It would be helpful if EPA could periodically update such a resource database. The science in this area is rapidly evolving and in the view of the peer reviewers it would be helpful to the EPA risk assessors to keep abreast of the science.

As a next step, a guidance document (or a series of smaller supplemental guidance documents) may be needed for this framework to become fully implemented. EPA should consider developing supplemental children's guidance or resources in specific areas such as early life vulnerability windows, early life TK factors, implementation of the children's cancer guidance, and use of the values in the *Child-Specific Exposure Factors Handbook* (EPA 2002b). Such guidance would articulate UFs and other approaches for handling data gaps.

13.0 Additional Comments from the Peer Reviewers

In the Introduction on page 3, lines 1–21. The points made in the first couple of paragraphs are unclear, and this section could use editing. For instance, it is not clear from these introductory paragraphs whether this Framework Document is meant to address risks from exposure to children that are manifest in childhood, or risks from any life stage exposure that are manifest at any time in life. Line 17 states that "if an overall assessment of health risks is needed, the information on risks from children's exposures can be incorporated into the larger assessment"—that would correspond to the latter meaning. The sentence on line 19 then states if "the major concern is about health risks to children as a result of environmental exposure, the information derived from this process could be used directly to assess risk, set standards and mitigate exposures"—that would correspond to the former meaning. Another part of the problem with these two paragraphs is that the definition of "children" is used in the document to include conception through adolescence to adulthood. It would be clearer to indicate that EPA is concerned about health risks that result from exposures to all life stages, including pre-conceptional exposure, and exposures throughout development to adulthood, instead of redefining the term child. Or the text could simply indicate that children can be impacted by pre-conceptional and *in utero* exposure. The sentence in lines 8–9 is poorly worded. The assessment of health risks to children from environmental exposures does not have the same meaning as "children's exposures."

On page 7, lines 3–5, which discuss the life stage approach for evaluation of risks to children, is awkward. It would be more useful to make two sentences out of this one—express the concept of potential outcomes from early-life exposure in one sentence, and then discuss consideration of MOA in another sentence.

On page 7, lines 27–29 needs rewording. EPA probably means "Because children are not a unique population, but rather a series of life stages through which all individuals pass, a child-protective approach is public health oriented."

On page 26, lines 14–16 state that high variability can sometimes render a study uninterpretable. The text should clarify that high variability must be considered in light of the rest of the information on a chemical. If the result is consistent with what else is known about the chemical, then the high variability should not necessarily decrease the study's weight in hazard characterization.

On page 49, lines 28–29 are very awkward. Suggest rewording the sentence to "In animal studies, exposure is almost always discontinuous; use of these studies requires adjustment for dose continuity when extrapolating to humans."

14.0 Peer Reviewer's Discussion on Written Public Comments

The peer reviewers briefly discussed the written public comments EPA received on the Framework Document. They focused on the comments that were scientific in nature, and not already discussed by the charge questions. Not all comments were discussed by the peer reviewers. Below is a summary of their discussions.

14.1 Comments from the American Chemistry Council

14.1.1 The Draft Framework Must Integrate Learnings from the Agency's VCCEP

While the peer reviewers who were familiar with VCCEP thought that it was important to acknowledge that the process exists, they agreed that the program is in its early stages and is not ready to be incorporated into the Framework Document. Some reviewers were not impressed with the program, were "underwhelmed" by the program documents, and expressed concern about data gaps and the lack of transparency in the process.

14.1.2 Data Gaps are not Necessarily Data Needs

One reviewer thought that the Framework Document clearly stated that data gaps are not data needs. Another reviewer said that this is not the point of the Framework Document.

14.1.3 Children are Not Always More Vulnerable to Chemical Exposures than Adults

The peer reviewers did not think that the Framework Document said that children <u>are</u> more vulnerable than adults, simply that they <u>might be</u>. The document justifies its existence by stating that childhood exposures should be evaluated. It is true that there is "mounting scientific evidence to support the vulnerability of the developing fetus and child." One reviewer suggested that the Framework Document use the phrase "children or infants may be more or less vulnerable." Another suggested adding "but there are cases where children may be less sensitive."

14.1.4 Clarification of Life Stages Covered is Needed

The peer reviewers agreed that the Framework Document clearly stated which life stages are included. In response to the comment that Figure 2-3 appears to trivialize adult exposures, the reviewers suggested incorporating a broken line into the figure. The peer reviewers did not think that using the chronic RfD was a problem.

14.1.5 Limitations of EPA's Supplemental Guidance for Assessing Cancer Susceptibility for Early Life Exposures Should be More Explicit

The peer reviewers said it was not appropriate for them to comment on another guidance document. They felt it was clear that the present Framework Document was not a guidance

document, nor was it providing a regulation or law, and that the framework does not apply to mutagens.

14.1.6 WOE Discussion Should Address GLP and Validation

The peer reviewers agreed that all scientific data should be considered, regardless of whether it follows standard GLP requirements. They made the distinction between having "good laboratory practices," which are important for all studies, and following standard GLP requirements. They noted that strong science often comes from research laboratories, and that standard GLP practices do not typically evaluate MOA. In risk assessments, often several studies are evaluated to build a consensus or obtain consistent evidence. Therefore, the peer reviewers recommended that a WOE approach be used to afford more weight to GLP studies, but if other non-GLP studies evaluate life stages not covered in the GLP study, those non-GLP studies should be considered and not weighted less than a GLP study.

14.2 Comments from the Center for Regulatory Effectiveness

The peer reviewers did not think it was within their purview to discuss the "appropriate" review process, since it does not pertain to the science of the Framework Document. One reviewer commented that all quality assurance documents should apply to risk assessments, including those involving children. Another reviewer pointed out that the Framework Document already has an adequate statement about data quality objectives.

14.3 Comments from Tetra Tech EM Inc

The peer reviewers stated that the comments submitted by Tetra Tech were already discussed during the peer review. They agreed that web-based training was a good idea and decided to leave addressing the specific comments to EPA.

14.4 Comments from the Department of Defense

One reviewer summarized that the comments mainly pertained to concern over data gaps leading to the use of additional UFs. However, there are statements in the Framework Document (e.g., on page 56, lines 22–23) that "life stage-specific data gaps to not necessarily imply a greater database UF." One reviewer said that there is debate about whether an internal dose that is 2.5 times higher in a particular life stage is covered by the human variability UF already. Another reviewer said that many of the UFs have been generated from pharmacological studies by the U.S. Food and Drug Administration (FDA), and that collaboration between EPA and FDA would be useful. Other reviewers noted that FDA and EPA have very different regulatory mandates and interagency harmonization may be difficult.

14.4.1 Life stages should be based on the temporal development of functional mode-of-action components such as metabolic enzymes, hormone receptors, neurotransmitters, or cellular membrane and transport proteins rather than anatomy, physiology and behavior.

One peer reviewer commented that there is no reason to revisit the age bins because the experts have already spent a lot of time determining the bins. Another reviewer responded that

development of functional MOA components relates to the window of susceptibility, and not to a definition of a life stage or an exposure bin.

14.4.2 The term "children" as used in the document applies to conception through adolescence to adulthood. This definition is outside standard practice among those who research human development.

The peer reviewers did not feel it was their place to comment on the definition of "child" with respect to abortion and right-to-life issues.

14.4.3 The subject document does not provide discussion on the future (ultimate) application of the information to be assembled, regarding exposure, toxicity, and the assessment of children's health risk from environmental exposures.

One peer reviewer understood that the Framework Document was applicable across all programs within EPA.

14.4.4 Page: 45, Lines: 11 to 13. The text of these lines suggests that changes in function are necessarily adverse. Statistically significant changes are not necessarily biologically significant.

One reviewer suggested removing this sentence because it is unknown what the early life stage implications are of a pre-cursor effect in an adult animal. A pre-cursor effect that has little to no impact on an adult animal may have significant adverse consequences for a developing organism.

14.4.5 Page: 41, Line 12. The mention of "post pubertal exposures" is not understood. Such exposures are by definition not occurring to a child, and therefore should not be given any consideration.

One reviewer pointed out that the reviewer's comment is not true. One is still an adolescent after he/she reaches puberty and until one reaches adulthood.

15.0 References

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EPA. (2002b) Child-specific exposure factors handbook. Interim report. National Center for Environmental Assessment, Washington, DC; EPA/600/P-00/02b. Available online at http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36528.

EPA. (2003) A framework for cumulative risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-02/001F. Available online at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=54944..

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EPA. (2006). A framework for assessing health risks of environmental exposures to children (External Review Draft). National Center for Environmental Assessment, Washington, DC; EPA/600/R-05/093A. Available online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=150263.

Appendix A. List of Peer Reviewers

Peer Review Meeting for EPA Draft Framework for Assessing Health Risks of Environmental Exposures to Children

Hyatt Regency on Capitol Hill

Washington, DC
June 6 – 7, 2006

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Appendix B. Charge to Reviewers

Charge Questions
Peer Review of "A Framework for Assessing Health Risks of Environmental Exposures to Children"

Purpose of the Document

The purpose of the draft document entitled "A Framework for Assessing Health Risks of Environmental Exposures to Children" is to provide an overarching approach for the assessment of health risks to children, taking into account potential exposures during all developmental stages and focusing on the major health outcomes that may occur as a result of such exposures. This draft document provides a roadmap for assessing risk of environmental exposures to children, describing the process of children's health risk assessment using a series of questions for each component that lead the reader through the analysis and evaluation. A series of flowcharts are used to illustrate this process. In addition, other resources that provide more detailed information are referenced, and are in a linked database that can be easily accessed by the reader.

Purpose of Expert Peer Panel Meeting and Review

The purpose of the Expert Peer Review Meeting is to carry out an independent external peer review of the draft document entitled, "A Framework for Assessing Health Risks of Environmental Exposure to Children," addressing the charge questions below. You are also invited to comment on the value added of this approach to the Agency's current practice on children's health risk assessment.

Charge Questions

You are asked to prepare written responses and comments for each of the following charge questions. Please refer to the format guidelines below. Note - you will be sent copies of the public comments that EPA receives on this document *to consider* prior to writing your comments (or view them online at: http://www.regulations.gov/fdmspublic/component/main.) In addition, we will be assigning you 1-2 questions for which you will be asked to prepare a written summary of key recommendations during the writing session on Day Two.

1. Is the purpose of this draft framework document clearly articulated? Are the graphic presentations of various concepts and methods (e.g., flowchart approach) and the questions to prompt review considerations clear and useful? Please provide a rationale for your answers. Do you have suggestions for improving clarity?

2. This report is intended to highlight specific concerns of children's risk assessment. To what extent is this document consistent or inconsistent with how you have interpreted existing risk assessment guidance and practices? Are there major gaps in what has been presented, for either children's risk assessment or for risk assessment more generally? Considering the various types of Agency chemical assessments that you are familiar with, are there gaps in the process outlined?

(over)

3. Risk assessment is a multi-step process and done at many different scales depending upon the problem. Do you think the document provides enough flexibility for users to understand how it applies to them? If not, for what audience(s) would you suggest clarification is needed and what kind of clarification?

4. Is the list of potential involved parties (e.g., risk assessors, risk managers, others) discussed in the problem formulation inclusive enough? If not, please provide suggestions for other involved parties.

5. The approach described uses a life stage perspective; that is, it focuses on assessing exposures for developmental life stages (embryo, fetus, child, and adolescent) and resulting health outcomes for all life stages (embryo, fetus, child, adolescent, reproductive adult, and aging adult). The EPA is soliciting your input regarding whether this approach is a more comprehensive approach than the focus on organ systems (e.g., neurotoxicity, cancer, reproductive toxicity, and developmental toxicity) used in previous risk assessment guidelines. Please comment on the advantages and disadvantages of this approach within the context of the current scientific understanding of the impact of exposure in different life stages and the available data.

6. The report addresses the integration of hazard data with exposure information from a life stage perspective. This discussion brings together information from the toxicological evaluation, life stage of susceptibility, exposure factors for children, and age binning for exposures. Has the EPA clearly articulated this approach? Are their sufficient data and understanding available to inform such an approach? Do you have additional suggestions that could improve or clarify the approach?

7. Has EPA's intention to move towards a harmonized approach for risk assessment, away from the dichotomous consideration of cancer versus noncancer, been clearly articulated in this document? Please provide a rationale for your response.

8. Is the iterative approach between the different analytical phases (hazard characterization, dose response analysis and exposure assessment) been clearly articulated in the framework? If not, how can this be improved? How does this iterative approach compare with your practical (or real-life) experience?

9. With the kind of data typically available for chemicals, do you think an assessor would understand how to use this framework with existing data? If not, what would you suggest EPA needs to clarify? Does the risk characterization section for children risk adequately address data gaps and how they are incorporated into the risk assessment uncertainties? Please provide the rationale for your response.

10. EPA is planning to develop case studies to demonstrate the applicability of the life stage approach for children’s health risk assessment and a training module for risk assessors. Do you have other suggestions that could aid in the implementation of this framework?

Appendix C. Pre-Meeting Comments, Organized by Charge Question

<u>Reviewers' Responses Organized by Charge Questions:</u>
Bruckner (JB)
Ginsberg (GG)
Goldman LG)
Marty (MM)
Ryan (BR)
Whyatt (RW)

1. ***Is the purpose of this draft framework document clearly articulated? Are the graphic presentations of various concepts and methods (e.g., flowchart approach) and the questions to prompt review considerations clear and useful? Please provide a rationale for your answers. Do you have suggestions for improving clarity?***

JB: The purposes, or objectives of this document are clearly stated at the beginning of the Executive Summary and the Introduction. The graphic presentations are helpful in understanding the basic components of the risk assessment process and life stage-specific analysis. Figure 2-3, however, is of questionable value.

GG: The purpose as stated on Page 3 is two fold: to provide a central resource for information that can be used to assess children's risks; and 2) to provide an overarching framework for this endeavor. The 2nd purpose is fairly clear although it may be helpful to state up front what the distinction is between framework (concepts, key questions, analytical map) vs. guidance (specific step-by-step instructions, recommendations). The document should clarify how is will assist someone to do a child-focused risk assessment and what it stops short of providing. The 1st purpose, that of being a central resource for conducting children's risk assessment can be construed in different ways. My first impression was that it meant the document would provide key scientific principles about ontogeny and how it may affect exposure and risk – a resource where you can learn about the subject and locate the key studies and databases that are needed to inform and populate a risk assessment. However, the main thrust of the document is entirely different – it is a resource for learning how to think about assessing children's risks, including identifying which components need to be considered the analysis. This is really the framework goal (purpose 2); not that much of the document is dedicated to being a fact or data-based informational resource and what there is not very complete. Therefore, USEPA may want to consider removing purpose 1 and just sticking with the one purpose. Alternatively, if it is an important goal for this document to be an informational resource, then more of that material would need to be included.
Continued – Question 1:

The flow charts are generally a good idea and useful for understanding how the various pieces of the analysis fit together. Some notes on the charts are as follows:

Fig 2-2, pg 5 – Life Stage Specific focus should be present in Problem Formulation;

Figure 2-3 is valuable to show how exposures and have long-lasting or delayed outcomes. It would also be good to get in several anticipated critical windows of vulnerability due to things like ontogeny of male reproductive tract in utero; ontogeny of metabolizing systems; critical window of vulnerability for carcinogenic processes, etc. That may be a separate chart but it would be good to document what is known about critical windows in a flow chart that shows how they are incorporated into the framework.

Figure 4-1: Should state whether 1st column of arrows is in people or animals – my guess is that it is in adult animals. This chart presents a useful model for the way in which animal testing (left column) feeds into risk assessment. However, the figure and text do not present an alternative framework for life-stage specific analysis that is actually more common – that being adult animal → adult human → life-stage extrapolation. This option appears as a secondary option in the figure legend. However, the uncertainties in the juvenile animal to child extrapolation and the common use of adult human to child extrapolation makes this option important – it should have equal footing with the option shown in Fig 4-1 and have its own diagram.

Figure 4-2: Overall, this figure is too generic, emphasizing the standard Hazard Characterization framework. For example, too much space is given to the basics of study evaluation, controlling confounders, and characterizing the extent of the database. These are given elements of Hazard Characterization that should be the building blocks for a life-stage specific version that focuses on such key elements as MOA, variability, datagaps, identifying potential windows of vulnerability, target organ sensitivity and potential to imprint toxicity and cause delayed outcomes.

Figure 4-3: Generic and not needed as currently constructed. It could possibly be made more useful by pointing out key life-stage specific elements of individual study evaluation: does the study provide information on early life exposures? If so, does the study provide dose-response information on early life stages? What outcomes relevant to development does the study evaluate? Does the study provide any information on internal dose in juvenile animals? Etc. etc.
Figure 4-4: Again, figure is too generic and misses the opportunity to show key WOE decision points in a life-stage specific analysis: is the MOA likely to be operative in utero and at early life stages; if in utero effects, are they likely to be manifest post-natally as well; can issues of chemical delivery affect potency differences seen across life stage; can TK issues be responsible for potency differences seen across life stage; etc.

Figure 4-5: this again is a building block figure that can be taken as a given in Hazard Characterization –recommend describing it in text and omitting the figure unless it can be reframed for life-stage specific approach.

Figure 4-6: looks fine except that it calls out “low dose” effects – it would be better stated: “Identify the NOAELs and LOAELs associated with life-stage specific outcomes” . These NOAELs and LOAELs may not be at particularly low dose, depending upon one’s frame of reference.

Figure 4-7: The figure is a bit too generic and misses some useful life-stage specific dose-response concepts: identify life stages for which quantitative dose-response data are available; what is the confidence in that data and what is its relevance to early life stages in humans; what data lend themselves to a full quantitative treatment – benchmark analysis (that’s the feasibility point in the figure under data analysis); should the data be modeled via threshold or non-threshold approaches. The key question in the figure should possibly be: Can early life dose-response assessment be conducted based upon early life animal data, based upon adult animal data and extrapolation to juvenile animals and then extrapolation to children, or extrapolation from adult animals to adult humans and then extrapolation to children. What modeling techniques are needed to perform these extrapolations for early life stages? Additional point: the figure legend should explain the distinction between narrow and broad assessment.

Figure 4-8: Suggest a change in title to: Use of BBDR modeling information for a surrogate chemical to inform the dose response for the chemical of interest.

Figure 4-9: Generally useful figure – can be made more life-stage specific in certain areas such as Exposure Media Concentrations (add: evaluate whether media concentrations for children will differ from adults); Add bullet for Life-stage specific dietary factors (unless this is defined as being part of activity data); the exposure characterization box is generic and should be made more life-stage specific – e.g., can add: evaluation of whether age bins chosen for exposure assessment materially affect dose (it usually does), etc.

Figure 4-10: looks fine

Possible additional figures: would be good to add a figure near page 75 showing how sensitivity and Monte Carlo analysis can be used to better characterize variability and uncertainty across the population and to compare one life stage (e.g., infants) to another (e.g., adults). May be useful to add a figure for Section 5 that shows how the analysis just described can culminate to answer the life-stage specific questions raised in Problem Formulation: e.g. Standard setting questions (what is appropriate regulatory limit of chemical in drinking water to protect all life stages and cumulative exposure throughout the lifespan?) → Risk characterization yields water concentration that is protective of fetal, neonatal and adult risks by considering the full range of studies and outcomes. Or Site-specific risk questions (how much risk is associated with living at this site?) → Use of exposure calculations along with hazard assessment and dose-response assessment to calculate life-stage specific risks; Qualitative questions (are early life stages likely to be at greater risk than adults?) → comparison of dose-response, exposure, and TK factors across life stages to develop a better informed uncertainty analysis.

LG: The purpose is clearly articulated. However, and perhaps not surprisingly, overall the document reads as if it was written by a committee and is badly in need of an editor, not only to give it a "single voice" but also to improve the language. The graphic presentations of concepts and methods are overly complicated. Figures in the first sections do not connect with one another, for example, Figures 2-1 and 2-2. Three figures intended to describe the entire process, 2-2, 3-1 and 4-2, do so in completely different ways. The document needs one unifying framework to tie together the contents of chapters 2, 3 and 4. One way to make the graphics more unified would be to create a simplified version of Figure 4-2 that could be used at the outset (in the place of Figure 2-2 to provide an overview of the entire process. The description of the process at each stage could then utilize this simplified graphic along with a "blowup" of the portion that is under discussion, e.g. as done with figures 4-3 and 4-4. Such graphics would replace Figures 3-1, 3-2 or 4-1. The message that I want to convey is that as currently configured the three chapters (2, 3 and 4) are not unified and it is not clear how the information flows (nor whether some steps have to be done over and over again such as "scoping" out the numbers of studies. Some figures, e.g. 3-2 and 4-1. don't contribute much to the text and could be eliminated. Often the figures have too much text in the captions. The captions should fully explain the figures but the figures should complement, rather than replace, the text within the document.

MM: For the most part, the purpose of the document is clearly articulated on page 1 lines 3 through 11. It is clear that the document is meant to be a resource to utilize in assessing health risks to children from environmental exposures, and that it is meant to be an "overarching framework" for a more complete assessment of health risks to children. It is also clear that the document is meant to point to a variety of other resources, including other EPA documents and papers in the published literature, useful to framing an assessment of risk to children from exposure to chemicals in their environment. Online access to the references cited is very useful.

The graphic presentations of concepts are useful as are the questions designed to prompt the risk assessor to think about factors that need to be considered in all the phases of the risk assessment effort.

The authors may consider adding Table 4-2, page 4-17, from the document "A review of the Reference Dose and Reference Concentration Processes (2002) to the Framework document because it summarizes basic factors to consider when identifying sensitive subpopulations. Some improvements could be made to specific graphs and additional questions are warranted. In some cases, the explanation under the graphic is better than the explanation in the text itself, so a little editing might improve the clarity of the text. Comments on specific figures and prompting questions follow.

a) Page 5, Figure 2.2 (Children's health risk assessment framework) could be clearer. Specifically, the sub-box "Characterize Life-Stage Specific Risks" needs clarification. As written it is not clear whether this step is to characterize risk from exposure at specific life-stages or risks for that specific life-stage. It could be reworded as "characterize the risk to the child and subsequent adult from life-stage specific exposures". This suggested wording reflects the fact that life-stages (from conception to old age) are unique stages through which we all pass. The effects of exposure to chemicals can manifest at the life-stage during which exposure occurs and/or subsequent life-stages.

b) Page 14, Figure 3-2. The figure does not correspond well to the conceptual model found in the Cumulative Risk guidance document. If one followed the conceptual model in the Cumulative Risk guideline, the last box should be a health endpoint. The figure is really a mixture of steps in a risk assessment and steps in a conceptual model. The box at the bottom could read "Comparison with health assessment values…".

c) The questions on page 15, lines 5-14 designed to prompt the risk assessor to identify toxic effects of chemicals under consideration in a risk assessment are useful. A good question to add to this list is: "Are there any toxicological endpoints noted in animal or human studies that are red flags for possible increased susceptibility of early life stages (e.g., neurotoxicity, immunotoxicity, endocrine disruption, and so forth)?"

d) Page 16, Figure 3-3. This matrix is wonderful but will be largely blank for most chemicals.

e) Figure 4-1, page 19. The sentence starting on line 6 states "In instances where there is no mechanistic information, animal dose-response data can be utilized and traditional default methods applied." This statement seems to preclude a combination of TK and TD data analysis/modeling and uncertainty factors. For example, one might be able to account for variability in a TK parameter or parameters, but not for all the TK factors that differ between life-stages or animals and humans. In addition, there is even less data on TD differences by life-stage for most compounds. Thus, there needs to be room to use modeling where you can, but keep uncertainty factors in the tool box where you have only accounted for some of the variability/uncertainty. Of course, we can't ever account for all of the uncertainty using PBPK and dose-response models.

f) Page 20 Figure 4-2 is a nice conceptual diagram which shows how the phases interact. However, it seems you would need a cast of thousands to implement this model. So, some guidance as to streamlining or simplifying a risk assessment is in order. Clear examples of problem formulation and the feedback between hazard characterization and problem formulation might help the user of this framework understand when to move on when data are limited.

g) Page 35, Section 4.1.5 bullets on lines 11-25, issues to consider in life-stage specific hazard characterization narrative. The legend under figure 4-6 is clearer than what is in the text. It is a better description of what the assessor needs to do to characterize hazard than the first bullet. The last bullet seems out-of-place and does not really fit here. Why mention MOE when discussing

selection of outcomes relevant to quantitative dose-response? MOE is only one type of hazard characterization method.

h) Page 37 figure 4-7. The figure legend does a better job of describing what the assessor is to do for life-stage specific dose-response assessment than the text of this section.

i) Page 41, bullets on exposure and response considerations for examining plausible MOA. In the second bullet (line 11-12), the second question talks about pre- and post-pubertal exposures. What about exposures during puberty which are likely to be very important for some chemicals? I suggest rewording the question to "What is known about pre-, peri-, and post-pubertal exposures?" to encompass puberty.

j) Page 43, line 28. This sentence indicates that drug clearance in children may be higher than adults, but that is not necessarily correct if one expresses clearance on a surface area basis (Hattis ??).

k) Figure 4-9, page 58. The best explanation of the approach is the figure legend (better than the text).

l) Page 63, line 17. The question on line 17 should be amended to read "Are there biomonitoring data that demonstrate exposure potential and that can be used to estimate a population's exposure? It is not clear you can estimate an individual's exposure level from typical biomonitoring data (unless you are actually measuring chemicals in biological media from individuals in the population that is the subject of the risk assessment – an unusual situation).

m) Page 64, bullets, lines 4-11. There should be a bullet specifically asking "Can the infant be exposed to the chemical through breast milk?" Breast milk is a very unique exposure route for children.

n) Appendix 1 compiles a number of questions that the assessor can use to guide a life-stage approach to risk assessment. These questions are appropriate and useful to the assessor tasked with evaluating potential risks from exposures across life-stages. There are a number of more specific questions in Section 4.3.1 of the 2002 document reviewing the RfC and RfD approaches that could be pulled into this Appendix. Some of the questions are similar, but the authors should review the questions in the RfC/D review document to improve Appendix 1. A few specific comments on the questions in Appendix 1 follows:

- In the section on Study Design (page 110-111), It would be useful to explicitly ask if the power of the study was adequate to detect an effect. This is often a limitation that is not adequately discussed when studies are presented as "negative".

- On page 11, the first question asked under "Animal Studies" is "Was the study conducted in accordance with good laboratory practice?" While this is an important consideration, it is not the only consideration in the utility of a research paper. Many of the older studies which showed early-life stage sensitivity to carcinogens were conducted before GLP was standardized. It would be a disservice to imply that only GLP studies are to be considered in a risk assessment. A statement to this effect should be added into this table.

- Under Outcomes, page 112, there are some questions related to effects of chemicals on precursor events towards the bottom of the page. A question that should be added is "Are the toxicities resulting from alteration of precursor events expected to be different depending on life-stage?" This is important because alteration of a precursor event in a mature animal or adult human may not have

any significant health consequence where the same precursor event alteration in a developing organism may have significant health consequences.

- In the section on toxicokinetics, questions should be added to direct the assessor towards additional toxicokinetic differences by life-stage other than metabolism. Metabolism is an important determinant of TK differences by life-stage, but it is not the only TK difference that affects disposition of the chemical. The differences in absorption (affected by gastric and gut pH, emptying time, transporter proteins, lung morphology, ventilation rate, skin surface area and permeability, etc), distribution (affected by differences in plasma protein binding, body water/fat content, perfusion to various organs, etc), and excretion (affected by renal perfusion/glomerular filtration, hepatic perfusion, etc) can be just as important for some chemicals, age groups and life-stages.

BR: There are several questions in this paragraph. And the answers to each differ. I strongly support the flow-chart approach indicating the various concepts and methods. It is a clear presentation that is easy to follow and displays logical flow. But it is also redundant with the material in the text and becomes repetitive after a few of them. This makes for tedious reading. I felt as though I was reading the same words in the same order over and over, without adding a lot of new insight each time.

An alternative strategy would require a substantial re-working of the document. A single over-arching flow chart- perhaps simpler than most of the ones laid out in the text- could be presented early on. This could then be followed by a more detailed exposition for each of the sub-sections, e.g., Hazard Identification, Dose-Response Assessment and so on. I think as currently constructed the differences for each of these areas is lost- a case where the forest hides the trees. There are some important details that are of special inters to one or more of the components that may be overlooked because they all look so similar.

RW: The framework provides an overarching vision of the structure, processes and components important for assessing risks from children's environmental exposures (page 7). However, the document does not provide "a single resource for information on the assessment of health risks to children as a result of exposures to environmental agents", which is the first stated purpose in the executive summary and on page 3. Rather, the second purpose as stated in the executive summary and on page 3 is more accurate, since the document provides the framework, but not the specific information needed for conducting child-oriented health risk assessments. This is an important distinction since risk assessors will not be able to use this framework effectively without additional information on the "how to". The Agency's plans to prepare a series of case studies on the implementation of the framework, and training sessions for risk assessors, are essential components to the successful implementation of the document. The document itself could come closer to fulfilling the first stated purpose if more concrete examples were provided and specific issues to be considered during implementation were discussed. This is done effectively in the discussion of dose metrics and modeling on pages 42-53 and could provide a model for the rest of the document. The Agency cites resources that the risk assessor can use throughout the document, but it would be helpful if the some examples and brief discussions, with appropriate caveats, were also included, perhaps in table format or in appendixes. For example, Table 1-2 of the Child-Specific Exposures Handbook summarizes exposure factor recommendations and confidence ratings, while referring to other tables for the specific data. Could these factors be compiled into one table for the document or appendix? A table summarizing some of the key conclusions from the articles cited on page 23 which arose out of the workshop on critical windows of exposure for children would also be a useful guide. A figure showing the comparability between experimental and human life stages would be helpful. Page 43 cites to a number of reviews on age-related differences in absorption, distribution, metabolism and elimination. Could data from these be highlighted in table format? In particular, data

gaps can be the Achilles heel to the successful implementation of the framework, and specific examples of approaches to handling data gaps would be helpful.

The flowcharts are clear and the questions provide a good format for leading the risk assessor through the issues. However, additional concrete examples, as provided to the questions on page 43, would strengthen the document and make it more "user-friendly". In addition, the chart on binning (No. 4-1, page 66) should be moved earlier in the document, perhaps after the chart No. 2-3 on page 6. The Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants is now finalized, and the chart on binning would provide risk assessors with concrete examples of how to conceptualize age groups in the risk assessment. The shading on chart No. 2-3 is confusing and should be revised.

2. ***This report is intended to highlight specific concerns of children's risk assessment. To what extent is this document consistent or inconsistent with how you have interpreted existing risk assessment guidance and practices? Are there major gaps in what has been presented, for either children's risk assessment or for risk assessment more generally? Considering the various types of Agency chemical assessments that you are familiar with, are there gaps in the process outlined?***

JB: I do not routinely utilize EPA risk assessment methodologies. Therefore it was necessary for me to read the entire document very carefully a couple of times to become familiar with the terminology and components of each phase of the basic risk assessment process. This information was interwoven with a substantial amount of detail about child-specific considerations. The document is very comprehensive and indeed serves as a "single resource for information about children's health risks." Nevertheless, it is so long and detailed that it would probably be of limited value to assessors/practitioners in the field.

GG Response: The framework draft is fairly thorough in its treatment of the basic, underlying risk assessment techniques. The one exception is Risk Characterization (Chapter 5) which provides only 3 pages of narrative and several pages of questions. Sections 5.1.1. thru 5.1.3 can be enhanced in a life-stage specific manner to show what the Risk Characterization should present (e.g., summarize the range of life-stage specific point of departures and summarize why a particular one was chosen to characterize risk; what uncertainties exist by selecting this POD over others? What early life data gaps are critical due to the chemical's toxicology profile? Etc.)

A major concern is that the document goes overboard with the generic approach and does provide enough life-stage specific perspective. This is pointed out above in comments on the figures. Additionally, there are sections of text (e.g., pp) which apply universally to risk assessment and don't keep the document focused on what goes into a life-stage specific analysis. As a result, the document generally feels diffuse with some of the main points potentially getting lost.

A gap in the document is that it doesn't really provide a strategy for narrowing a life-stage specific assessment to something that is manageable and feasible. There are many possible life stages to analyze (e.g., Table 4-1), outcomes to consider, and exposure-response arrays to construct. How does one scope the possibilities for data analysis and risk characterization and then shape the analysis to focus on what are likely to be the most vulnerable age groups and key risk drivers? At what point in the analysis are these decisions made? There are also a number of tools mentioned, PBTK analysis, Monte Carlo, correlational analysis, benchmark dose. Some of these are rather data intensive and require sophistication – you certainly wouldn't want to do these for all life stages and outcomes. This underscores the need for a streamlining decision-tree that can better frame or shape the analysis.

Perhaps this need and certain concepts along these lines could be introduced in this document with follow-up guidance and case studies providing a more concrete method on how to do this.

Another gap is with respect to identifying the key life-stage specific issues a risk assessor is likely to confront. While the questions posed throughout the document are generally useful, they are typically pretty general and don't cover some important topics such as: 1) gap in risk methodology for extrapolating inhalation dose to early life stages – the RfC methodology was developed for animal-to-human extrapolation but not adult to child; what resources or approaches can one use to address this issue? 2) gap in understanding the critical window of vulnerability such that the time frame over which exposure should be averaged is a significant uncertainty; 3) gaps in extrapolating risks to early life for non-genotoxic carcinogens; 4) gaps in understanding MOAs in early life and whether novel MOAs and outcomes can be expected from early life exposure; 5) since toxicokinetics and toxicodynamics in children can rarely be studied, how do we best characterize or model variability in internal dose and sensitivity to toxicant action?

LG: The document is consistent with current risk assessment guidance and practices and I have not identified any gaps in the process.

MM: This report appears to be consistent with existing risk assessment guidance, specifically the guidance for RfC and RfD including recommendations of the Technical Working Group that prepared the 2002 review, and the 2005 cancer risk assessment guidelines (including the Supplement). It does not appear that there are major gaps in the discussion of what to consider when assessing children's health risks from exposure to environmental chemicals. However, there will be many data gaps in attempting to do so, particularly for industrial chemicals which have small toxicological and epidemiological databases, poorly understood MOAs, and so forth.

It is worth noting that the guidelines for cumulative risk are cited in several places, but there is not much discussion of cumulative risk within this document. It is mentioned in several places but the text does not discuss cumulative risk assessment concepts and integrate them into the framework.

BR: The report highlights the "life stages" ideas repeatedly. However, I saw some repetitiveness in this as well. Perhaps repetitiveness is the wrong word. The report was more pedagogical in tone and included statements regard "life stages" almost gratuitously throughout. A particular concept in, say, hazard identification, would be explained. It would then be followed by an often-terse statement saying that one has to perform this differentially for the different life stages.

I found no major, or really any minor gaps, in the proposed risk assessment program. This document lays out standard, state-of-the-art procedures and then points out where care must be taken when considering children. It is complete, almost to a fault.

RW: As stated above, the framework is consistent with legislative and administrative mandates that risks to infants and children be explicitly and consistently considered by the Agency. If implemented, it would result in a shift in the Agency's approach to risk assessment by putting the child rather than the adult at the center of the evaluation whenever data indicate greater susceptibility. It would move away from the current approach of evaluating risks on an organ-by-organ basis for the adults first and then secondarily looking at age-related (and other) susceptibilities (see for example the 2001 Trichloroethylene Health Risk Assessment: Synthesis and Characterization). Instead, it would shift the approach to identification of the life stage(s) at greatest susceptibility first and then moving from there to evaluations of organs systems and disease outcomes. It would likely be not only more health-protective

than the current approach, but could result in evaluations of more endpoints than are now generally considered (e.g. neurobehavioral, endocrine and immune system effects).

As already stated, the major gaps in the document are not in the framework itself, but in how the framework should be implemented. In particular, the document is specifically lacking in details on how to handle data gaps. This will require the development of case examples of risk assessments conducted within the context of the framework. One of the values of the framework will be to foster awareness of data gaps and data needs for child-oriented risk assessments. As pointed out in the document (page 28), detailing the lack of information about an agent is crucial to an adequate characterization of childhood risks from that agent.

3. Risk assessment is a multi-step process and done at many different scales depending upon the problem. Do you think the document provides enough flexibility for users to understand how it applies to them? If not, for what audience(s) would you suggest clarification is needed and what kind of clarification?

JB: Again, I am concerned about the shear volume of information limiting the document's usefulness for risk assessors. A number of topics (e.g. toxicokinetics as a function of maturation) are addressed several times in different sections. This information is accurate and pertinent to children's risk assessment, but it makes the document seem more like a compendium of scientific knowledge about a new subject, rather than guidance on how to conduct such as assessment. Such guidance could be the subject of a subsequent publication.

GG Response: The response to the previous question addresses this issue by stating that there needs to be strategies for streamlining the assessment and providing the most focus on life stages and outcomes most likely to drive risk. This may involve screening level assessments in problem formulation or data analysis. This information would expand the framework in a way that makes it more flexible. At one point the document describes screening level vs. refined analysis (Exposure Assessment, page). Perhaps more of this type of two phased approach can be built in with respect to screening which age bins, outcomes, or TK factors may be of most importance.

Flexibility is also added by the framework if it describes the range of applications for life-stage based risk assessment. There is brief mention that the framework can be used for chemical-specific or site-specific assessments. These options should be described more completely, including how the questions that arise under these options differ, and how the analyses may differ.

LG: I think that the document provides flexibility. However, at times I feel that the document, even while providing flexibility, contains normative statements (such as "consideration of MOA is critical"; " characterization of uncertainties at various life stages is important") that would tend to push risk assessors into more elaborate analyses than might be warranted. I think it is important to stay away from such statements and instead to stress that whether such considerations are "critical" or "important" is very much dependent on the type and the purpose of the assessment.

Likewise the discussion of dose metrics is very complex. I doubt that this entire process would be pursued (or even worthwhile pursing) for most risk assessments.

Another suggestion is that the Risk Characterization section could include a caveat that all the items listed as components will not be available for all risk assessments.

MM: I believe that the framework is meant to provide flexibility, particularly as it describes problem formulation and the scope of the risk assessment. But, I am concerned that the amount of information that must be taken into account is so overwhelming to really adequately assess risks to children with any degree of confidence that risk assessors may suffer from paralysis of analysis. There will be so many data gaps for industrial chemicals in the typical exposure scenario, dose-response assessment by life-stage and so forth, that risk assessors and stakeholders may hold reason hostage and not move forward with an assessment, as uncertain as it may be. The quest to conduct uncertainty analysis at every stage is enough to paralyze most assessments, and at a minimum will slow the process considerably. Thus, there is serious need for examples from simple to more complex, and a very real need for guidance to the risk assessor on when and how to move ahead in the absence of data. Such examples will demonstrate the desired flexibility, and what the risk assessor could do and say where data are limiting. The risk of not providing examples is that people will ignore the guidance completely.

BR: Flexibility is pretty much the hallmark of this document. However, the flexibility introduced becomes problematic when essentially no hard and fast directives are given. Guidelines are brought forward, but there is little detail in assessing them. Most of the guidelines focus on God, country, Mom, and apple pie type issues all of which are quite common-sensical. I think more insight would be useful. When are problems likely to crop up? Are they critical in that they are likely to give the wrong answer if typical methods are followed? Is there more to the process than just noting that sensitivity, susceptibility, and impact are different at different life stages? Is this not well known and accounted for in most risk assessments involving children? Is this document meant to be a compendium of methods or is it deigned to give insight in problem approaches?

RW: The document is clear that risk assessments are done for many different purposes and at many different scales. It provides a framework, not a prescription, on how risk assessment should be conducted and thus gives adequate flexibility for multiple purposes. However, it does not provide adequate detail on how the framework could be implemented for multiple purposes.

4. Is the list of potential involved parties (e.g., risk assessors, risk managers, others) discussed in the problem formulation inclusive enough? If not, please provide suggestions for other involved parties.

JB: I would think that scientists, section chiefs and administrators at various levels in and outside EPA, not to mention state officials, stakeholders, attorneys, etc. would want to understand the process. They could thereby determine how they or their work may be impacted, or how they might impact the process.

GG Response: I would add to the list risk communicators and PBPK modelers; if it is a site specific risk assessment, I would add local health director.

LG: I think that the list is sufficiently inclusive. However, I find the statement on page 16 that the conceptual model and the analysis plan for the risk assessment, including possible outputs for the assessment, will be negotiated among risk managers, to be confusing if not downright dangerous. Risk managers certainly are involved in scoping out the depth of the analysis (is this to be a screening assessment or the development of a national standard?) But (and I hope the document did not mean to convey this) they have neither the scientific knowledge nor the time to develop a conceptual model for an analysis plan.

MM: The list of potential involved parties is not well-described in this document. The reader is referred to the discussion of stakeholders in the Cumulative Risk guidance, but it would be better to just insert some of the material from Sections on pages 19-21 of the cumulative risk guidelines into the framework document (the box on page 21 might be useful to place in the framework).

BR: Stakeholders such as community groups, pediatricians, and parents of young children may offer insight into what is feasible in this type of analysis. I think that such groups should be consulted but the risk assessors and risk managers are ultimately responsible for policy. The more groups contributing to such policy discussions, the more useful information is likely to be gained.

RW: Yes, it is clear that the problem formulation stage should involve a multidisciplinary team of experts that include: risk assessors, risk managers, stakeholders, toxicologists, epidemiologists, and child health and behavior specialists, depending on the specific goals of assessment. The emphasis on the importance of the problem formulation stage is one of the strengths of the document.

5. ***The approach described uses a life stage perspective; that is, it focuses on assessing exposures for developmental life stages (embryo, fetus, child, and adolescent) and resulting health outcomes for all life stages (embryo, fetus, child, adolescent, reproductive adult, and aging adult). The EPA is soliciting your input regarding whether this approach is a more comprehensive approach than the focus on organ systems (e.g., neurotoxicity, cancer, reproductive toxicity, and developmental toxicity) used in previous risk assessment guidelines. Please comment on the advantages and disadvantages of this approach within the context of the current scientific understanding of the impact of exposure in different life stages and the available data.***

JB: I like the life-stage approach, as it forces regulators to consider the potential impact of chemical exposures on all developmental stages, as well as delayed manifestations of early life exposures. Most previous toxicity and carcinogenicity testing protocols have only involved adult animals or humans. The primary disadvantage, of course, is the lack of knowledge about many aspects of neonatal and postnatal toxicokinetics and toxicodynamics. The necessity to fill these gaps should res8lt in exciting new research focus areas.

GG Response: The new framework isn't that much different than what is done traditionally; perhaps the major difference is that in the traditional risk assessment, one would be done with hazard characterization and dose-response assessment when one identified the most sensitive and scientifically sound endpoint. Now one needs to look further for evidence of early life windows of vulnerability due to a variety of potential factors: toxicodynamic (e.g., organs and systems affected in adults may be more vulnerable during development), toxicokinetic, and exposure. Putting these potential early life risk issues into the midst of the risk assessment process is critical and is why this framework is so important. The advantages of the life-stage approach are that it potentially considers all endpoints and life stages, so it should be the most inclusive approach. As stated above, the challenge is how to rationally and systematically streamline it. It also brings up important questions about whether a particular organ or system will be vulnerable at a given life stage. Further, there will be uncertainties about the period of time over which exposure should be averaged to match the critical window of exposure. These issues have to be addressed qualitatively if data are not available. However, the framework should provide resources and an approach for tackling these questions.

LG: I think that this is an appropriate focus and probably the most efficient approach because exposure is lifestage dependent. One place where I think there could be more clarity is that there may be a

difference in the lifestage where a hazard occurs and one where an outcome occurs. For example, a carcinogen exposure in utero can result in a cancer in childhood or even in adulthood. A neurotoxic exposure to an infant or toddler may manifest as an outcome in grade school. A birth defect in the first trimester may be noted in utero via ultrasound or prenatal tests but may not be noted until birth or even later in childhood. This distinction between hazard windows and outcomes needs to be drawn more clearly throughout.

I would like the treatment to be more comprehensive. For example, on page 27, it states that the overall hazard database should include "all studies with developmental exposures, effects or outcomes". Would that clearly include cancers? Would it include triggering asthma onset or asthma attacks? I think that such studies should be included.

MM: The Framework is a more comprehensive approach to assessing health risks from environmental exposures than the existing current guidelines for RfC, RfD, ARE, developmental toxicity, reproductive toxicity, and so on. The Framework provides a very useful starting point for risk assessors to begin to more fully characterize risks to children and to the adults they will become from early-life exposures. It is increasingly recognized that adult disease may have connections to environmental exposures that occurred much earlier. Likewise, childhood diseases such as asthma and some cancers may also be linked to chemical exposures in utero or in infancy and early childhood. The developing organism presents different targets for the action of exogenous compounds that are not present in the adult. In addition to these toxicodynamic differences, the toxicokinetics of a compound may differ by age and life-stage and have a large impact either qualitatively or quantitatively on toxicity per unit dose. Current risk assessment paradigms only explicitly account for potential differences in health outcome from early life exposures when there are specific studies of the compound(s) of interest in developing organisms. Otherwise, the basis for most risk assessments is a study done in mature animals or epidemiological studies of adult humans in an occupational setting. It is clear that this is inadequate to predict what happens in developing organisms including infants and children. Thus, the current target organ approach (cancer, reproductive toxicity, neurotoxicity), while very useful, is lacking. This framework broadens the questions the risk assessor asks and provides a pathway to better characterization of risks to children.

The Supplemental Guidelines for Assessing Cancer Risk to Children published in March 2005 is a great improvement over previous guidelines which ignored early-life exposure, and the Framework provides additional and complementary concepts and questions for the risk assessor to explore in assessing cancer risks from a life-stage perspective.

The advantages of this approach are:

- that it will result in a better overall characterization of potential risks of environmental chemicals and increase our confidence in the risk assessment;
- provide more "truth-in-advertising" by demonstrating what we do and do not know with regard to the impacts of early in life exposures;
- make use of ancillary data more routine such as structure-activity analyses to try to fill some of the datagaps;
- and, hopefully, stimulate more research into the impacts of early-life exposures on the health of the infant, child, and adult they will become.

Disadvantages of this approach include:

- There are many cases where there are so little data, a traditional risk assessment or a qualitative evaluation of risk may be the only assessment possible - the data will be limiting in trying to utilize this framework;
- it may result in "paralysis of analysis" in terms of the assessment of risks because of herculean attempts to look at every possible interpretation of data, uncertainty analysis, and so forth. The framework seems to have no brakes – when should the assessor stop? When is the assessment good enough given the quality of the available data? Clearly not all assessments require an enormous effort, but it is not clear from the framework how one makes that decision in the problem formulation phase.
- The approach could cause delays in implementing clean-ups or applying control strategies if the risk assessor is not provided guidance on how to move forward when the data are limited to answer the questions posed for a life-stage assessment of risks.

BR: I see the currently proposed approach using live stages as an umbrella over the standard methods. Organ-system approaches should still be implemented, but with the understanding that such approaches are likely to be different when, say, the organ system is just being developed in utero than it would be in an adolescent. It is a more comprehensive approach. It is impossible, in my estimation, to carry out a sophisticated risk assessment without considering the maturity of the organ system itself. It is established, for example, that exposure to specific compounds during specific developmental stages can have devastating effects- incomplete formation of organ systems, permanent damage, etc., while exposure at another stage is essentially harmless. This should be evaluated in every risk assessment.

RW: As discussed above, the approach described is more comprehensive than the current risk assessment paradigm because it takes as its starting point the life stage(s) at potentially greatest risk, and from there evaluates organ systems and disease outcomes. It is likely that this approach could expand the organs and systems beyond those that have traditionally been considered in Agency risk assessment. For example, our own research and that of others indicates that neurobehavioral effects that emerge during childhood following exposures during gestation to environmental neurotoxicants are critically important endpoints to evaluate. However, neurobehavioral effects have not traditionally been considered in many U.S. EPA risk assessments. The organ systems (e.g. nervous, reproductive, kidney, lung, liver) and outcomes (e.g. cancer, developmental) that are currently included in Agency risk assessments should obviously continue to be evaluated.

6. ***The report addresses the integration of hazard data with exposure information from a life stage perspective. This discussion brings together information from the toxicological evaluation, life stage of susceptibility, exposure factors for children, and age binning for exposures. Has the EPA clearly articulated this approach? Are their sufficient data and understanding available to inform such an approach? Do you have additional suggestions that could improve or clarify the approach?***

JB: The document's authors have obviously worked hard and done an admirable job at a "first cut" of how to integrate life stage susceptibility, toxicity data, exposure data and age binning. This new undertaking will require many additional considerations including prioritizing data needs, selection of criteria for acceptability of studies and study end points, circumstances for utilization of animal data, default criteria, etc. It would be very helpful to include a couple of examples to illustrate how the risk assessment process would work. One example might be a chemical with a relatively complete database for immature subjects; the other might be a compound to which immature rodents are susceptible, but human data are lacking.

GG Response: This is a very broad question that covers virtually all aspects of the framework. The goal of conducting life-stage specific risk assessment raises numerous challenges, some of which have been well represented in this document. However, there are certain areas where greater clarity or more information would be beneficial as follows:

Problem formulation has an exposure assessment component that begins with a preliminary examination of certain data (page 13). However, left off of this list is an evaluation of the site-specific data that are available – what media have been tested, what has been detected

The organization of the document has problem formulation appearing a number of times, at the beginning of each of the major topic areas. However, it may be better to have one comprehensive and intact problem formulation at the beginning of the document and not bring it up as a scoping phase for the individual sections, which makes the document longer and less direct. There could be a description of iteration with problem formulation during each of the major steps so that the overall scope and shape of the assessment is modified by the data unearthed during the analysis.

Given that a common datagap will likely be early life toxicity data suitable for dose-response analysis, the assessor may be confronted with extrapolating from adult animal or human data to early life. The key question is whether the standard 10x UF is sufficient to cover across-age susceptibility differences while also covering other intra-human variability factors. While this document is a framework and not guidance, it would be good for the document to show that adult PODs may need to be extrapolated, via appropriate analyses and perhaps UFs, to toxicity values protective of early life.

The framework is vague on the issue of age binning for exposure and risk analysis. If one uses the binning chart in Table 4-1 for exposure analysis (as suggested), how does one integrate this with the need to create different sized age bins to account for TK or TD windows of vulnerability? Should the age binning chart be brought closer to the front of the document and used as a guide throughout?

The framework should highlight the fact that adult is a lifestage that needs to be included in the evaluation and serves as a key point of comparison to children. Right now the report does not spend much time on adults or the opportunity for intra-species comparison of exposures and toxicity.

Hazard characterization has a number of life-stage specific issues that would be good to identify and to offer some advice or resources for how to think about them. These include:

- Issue of relevance of pre-natal effects for post-natal developmental windows; when should one assume that effects seen in utero will also occur post-natally?
- Are we to assume a single MOA for all life stages? The framework does raise this as an issue but doesn't provide any useful information about the issue. Are there certain chemical characteristics that would make one worry about unique MOAs in early life? (Multiple TK and TD mechanisms; agents that affect hormonal systems, signal transduction, gene expression/imprinting). Are there age-specific or growth-specific characteristics that would suggest unique vulnerabilities and MOAs?
- What kinds of endpoints do we expect children to be more sensitive to? Neurodevelopmental endpoints (Hg, Pb)? Cancer (as per supplemental guidance for cancer risk assessment)? Immunotoxicity and allergy due to unique aspects of early life immune system development? Ideally the document would provide some insight and a strategy for developing hypotheses about what endpoints may be of greatest concern to early life stages. Then one can evaluate the early life database to see if there are critical datagaps.

- The framework may want to discuss the state of the art of toxicity testing protocols and where there are gaps in terms of assessing post-natal exposures and near term and latent effects.
- On page 27 the document talks about evaluation of the hazard database; for a life-stage specific analysis, it would seem that this task should start by organizing the database according to life stage exposed and endpoints measured.
- Note that Page 42, top, the discussion is confusing as to whether there is concordance or not between early life and adult only cancer outcomes.

In terms of exposure assessment, a key issue that is not adequately covered is how to pro-rate exposure – dose averaging over what time frame? Table 4-1 would suggest to dose average exposures over the age bins provided; however, there may be TK and TD vulnerabilities that would dictate a different exposure window. For example, the critical window for heightened vulnerability to carcinogenesis may be the first 2 years of life. One would assume that averaging over this age bin (0-2) is most appropriate, even though there may be shorter windows where exposures are higher.

This document provides an excellent starting point for the identification of critical resources for a life-stage specific analysis. However, it may be advantageous to the reader to organize these resources by topic in an appendix. Example topics could be TK factors in early life, known TD vulnerabilities in early life; exposure factor databases, etc.

LG: This approach has been clearly articulated. Also it is clear that the data may or may not be available to support this approach in many if not most cases. In such cases, after the scoping phase of the exercise, much of the rest of the assessment will be focused on a very small area within the overall framework of the document. Although I think that such "stopping points" (or at times "branching points") in the process are described, that they are not more clearly articulated. A decision diagram might be helpful in this regard. The issue of metabolites and co-products is important. Although mentioned in the "scoping" phase of the document, it is not clearly carried through to other phases, e.g., outcomes, biological effects, exposure assessment.

On page 25 it is stated that while it is possible that a MOA may differ by lifestage, there are no known examples of this. There are teratogens which can provide examples of this.

On page 26 it is stated that variability can be characterized through calculations of central tendency. This is not the case.

On page 31 the list of papers on organ development is interesting and these are good examples. However, this is a snapshot at a point in time and these papers should not be taken as the last word on this subject; this is a rapidly evolving area (as evidenced by all of these publications being very recent.)

MM: It is clear that the framework takes the approach of combining information about exposures for specific life-stages and age bins, evidence of windows of susceptibility, and the available toxicological and epidemiological data in assessing risk. Figures 4-7 and 4-9 diagram the approach. (The best explanation of the approach is in the figure legends.)

For some chemicals there may be sufficient data to be fairly confident this can be accomplished. For most industrial chemicals, data will be limiting. Nonetheless, the framework provides a path for the assessor to utilize information he or she may not have thought of including in the current traditional risk assessment paradigm. For instance, analyzing the possibility of differential impacts on the developing human in the absence of clear studies on the chemical of concern is part of this approach. Using

information from chemicals with similar MOAs, or which are structurally similar, or which demonstrate toxicity that should be a red flag for developing organisms (like immunotoxicity and neurotoxicity for example) has not been done routinely in the past – this framework gives the risk assessor the opportunity to utilize such ancillary information to better characterize potential risks to children from early-in-life exposures.

As noted earlier, it is difficult to review and will be difficult to use this framework without examples. According to charge question 10, the EPA intends to develop case studies. Numerous case examples should be developed using chemicals with and without strong toxicological databases. As with any paradigm, it is only when one attempts to apply the model that one can clearly see how well it works, how it needs to be modified.

BR: This is an excellent and necessary approach. EPA has articulated the need well. No suggestions are apparent.

RW: Yes, the Agency has clearly articulated the approach. However, a discussion of limitations in the approach due to data gaps should be added to the document. Development of case studies of the application of this approach to a broad range of risk assessments including those with insufficient data is critical to the successful implementation of the document. This can be incorporated either with the document (for example in appendices) or as a supplement to the document.

7. Has EPA's intention to move towards a harmonized approach for risk assessment, away from the dichotomous consideration of cancer versus noncancer, been clearly articulated in this document? Please provide a rationale for your response.

JB: EPA's intention to move towards a harmonized approach for noncancer and cancer risk assessment is clearly articulated and commendable. I am concerned, however, about EPA's past history of reluctance to acknowledge when the weight-of-evidence favors a threshold mode for action for an animal carcinogen (e.g., chloroform, trichloroethylene). Cancer risks will almost always be the "driver" when there is a default to a linear dose-response model.

GG Response: Perhaps I missed this aspect of the document – it didn't come across strongly. I would have expected to have seen it on pages 44-46 but there is minimal mention of it there. It would also be expected to have a discussion in the exposure assessment section because the way the dose is calculated (pro-rated) has traditionally differed between cancer and non-cancer assessments. However, I did not see mention of this issue there either.

LG: Yes, it has.

MM: EPA's movement towards harmonizing approaches to assessing risk from carcinogens and for noncancer health endpoints is articulated in the document, although there is not much discussion of the issue. On page 36, lines 16-20, the harmonization of approaches to cancer and non-cancer risk assessment is mentioned. In several other places in the document, the reader is referred to the latest cancer risk assessment guidelines (2005) and the 2000 review of the RfD and RfC methodologies. These documents have further explanation of treating cancer and noncancer toxicological endpoints as if they could be either threshold or non-threshold endpoints (i.e., harmonizing dose-response assessment).

BR: Since I was a post-doc, I had wondered why there was such a dichotomy in establishing risk values between cancer and non-cancer endpoints. Harmonization is key. EPA has taken a major step forwarding in implementing such as strategy here.

RW: Yes this intention has been clearly articulated in the document and is one of the strengths of the document.

8. Is the iterative approach between the different analytical phases (hazard characterization, dose response analysis and exposure assessment) been clearly articulated in the framework? If not, how can this be improved? How does this iterative approach compare with your practical (or real-life) experience?

JB: The iterative approach between the different analytical phases has been clearly explained. Again, illustrations of utilization of this approach would be very helpful.

GG Response: The iterative approach is difficult to relate from arrows on charts and descriptive text. It needs to be exemplified so that the reasons for going back to a phase while in another phase is clear. One ideal in risk assessment is for the process to be efficient and streamlined. A back-and-forth iterative approach is not streamlined, yet can be quite valuable. The framework can do a better job of demonstrating the value added of iteration by providing an example for each type of iteration recommended (e.g., while evaluating exposures, it was found that the 0-1 age bin was much more exposed due to nursing ingestion than was any other life stage; this prompted the assessor to re-evaluate the hazard characterization to make sure that potential vulnerabilities during this age window were well understood).

LG: Yes, but see my comment to question number 1.

MM: The iterative approach between the hazard characterization, dose-response assessment and exposure assessment is emphasized throughout the document. It is difficult to review the concept without examples, but it is clear that the framework is designed to have an iterative approach. In practice, currently the hazard identification, dose-response assessment and exposure assessment are different parts of a site-specific or chemical-specific risk assessment, and most of the time, little iteration occurs. So compared to current practice, it is a more flexible and comprehensive approach. The iterative approach is designed to more thoroughly account for effects from early-life stage exposures by focusing the assessor on questions pertinent to early-life exposures, instead of staking the risk assessment on a dose-response analysis using available toxicological studies in adult animals, and an exposure assessment based on adult exposure factors.

BR: This iterative approach is a new concept- at least for me- and one that is needed. The fact that a material is hazardous and has an established dose-response relationship over some dosing regime is of little consequence if exposure doesn't exist. Further, if exposures are known, then the does-response relationship should be evaluated in this realm, not in the "lamppost" region of high exposures. The presentation is fairly well articulated here.

RW: One of the strengths of the document is that the importance of the iterative approach between the different analytical phases in the risk assessment is clearly emphasized both in the text and graphically in the flow charts. The document also clearly articulates that a risk assessment involving a life stage approach will require collaboration between multiple disciplines. The emphasis in the documents on the importance of the problem formulation phase should help shape the risk assessment, so that problem

areas and data gaps are identified early in the process and an appropriate team with the expertise needed can be assembled.

9. ***With the kind of data typically available for chemicals, do you think an assessor would understand how to use this framework with existing data? If not, what would you suggest EPA needs to clarify? Does the risk characterization section for children risk adequately address data gaps and how they are incorporated into the risk assessment uncertainties? Please provide the rationale for your response.***

JB: There is a paucity of TK and TD data for immature animals, as well as for infants and children, for most chemicals of concern as environmental contaminants. Such data are being generated in animal studies for a variety of pesticides, but regulatory action(s) will probably be necessary to acquire toxicity data on many other classes of chemicals. Another option is to include sizable childhood uncertainty factors as defaults where there are important data gaps. It will be a challenge to EPA to chart a standardized approach, or guidance to follow in children's risk assessment, when hazard and/or exposure information is/are incomplete or conflicting.

GG Response: The document has much basic information on each analytical area that is not life-stage specific but is described in other documents and may not be needed in so much detail here. This material, while useful to make sure everyone has the same analytical background, does tend to get in the way of what is new and different about this framework. It may be wise to restructure the document, especially in hazard characterization, to minimize the "how to evaluate a tox study" type information (e.g., pgs 21-22 and put in more of the life-stage specific issues and analytical decision points. More can be said in risk characterization (pg 85) on the types of data gaps one can expect in life stage specific analysis, the impact they may have on the analysis, and how one may want to address them via uncertainty factors, sensitivity analysis, etc.

This document will be made more useful to risk assessors if:

1) It is streamlined to focus on life-stage specific issues and decision points
2) Strategies are provided that assist the analyst to identify tools and databases to assess issues such as which age groups may be most vulnerable to a chemical's toxic effects, how might toxicokinetics in early life influence the chemical's MOA, and what are the potential for novel MOAs and target organs in early life.
3) more examples are used to bring some of the concepts to life

LG: See my response to question 6. I think that a (simplified) decision diagram would be very helpful. Risk assessors often will find, with scoping, that age-bin specific hazard and/or exposure information is lacking and that it would be necessary to use bridging data or information. At other times they will conclude that some life stages are less critical to the assessment of an individual chemical and to stop that portion of the assessment. It would be helpful for the overview of the process to clearly identify these decision points in the analysis and how these connect to the discussion of uncertainties. For example, the discussion of exposure assessment clearly lays out that there can be a "screening" assessment and a "refined" assessment. But it is not clear in which context, given the scoping of the assessment in Chapter 3, these two approaches would be utilized. Nor is it clear what the commensurate level of hazard analysis would be.

When it comes to review of study designs, there are a number of issues that need to be more clearly drawn out, mostly in areas of statistical, experimental and epidemiological design. Since EPA relies on

weight of evidence approaches it needs to clearly articulate the bases upon which studies are determined to have stronger or weaker contributions to the WOE. Examples of such issues that are not well explicated are: statistical power (numbers of subjects or animals, precision of measures), bias (including confounding), appropriateness of animal or in vitro models, relevance of routes of exposures and exposure levels, relevance and accuracy of biomarkers of exposure and biological change, and quality of assessments of exposure and outcomes. Along these lines, terms such as "interaction" and "controlling" are used in nonconventional ways. For example, (page 26) one cannot control for study variability (and I don't think that was meant by the authors.) On page 29, effect modification and confounding is treated as one and the same entity. Confounding is a form of bias and always needs to be addressed, not only in human but also in animal studies and in vitro assays. Effect modification is important in dose response assessment. It is important but I think that the idea of evaluating effect modification at every lifestage for every risk assessment is overkill.

MM: The kind of data typically available for chemicals is somewhat dependent upon the use of the chemical. For pesticides, there are generally much more toxicological data available than for industrial chemicals. It would likely be easier to use this framework for pesticides than for many other types of environmental contaminants due to the larger available database. The risk assessor tasked with evaluating risks of exposure to non-pesticide environmental contaminants may simply have so little data available on the substances in question that this framework may be academic. It would really help to have some examples in the framework of chemicals with a large database and chemicals with a much smaller database to demonstrate the framework's utility in assessing risks to children.

The risk characterization section of the framework articulates an approach that should be useful to assess risks to children. The questions in the tables are relevant and cover important aspects of any assessment. Data gaps aside, it is important to attempt to evaluate exposure at various life stages and to evaluate potential toxicities that might affect different life stages in order to best account for risks to children and the adults they will become. If anything, this framework will demonstrate that much more information needs to be developed about health effects of chemicals from exposures early in life.

I do not see enough information in the Framework regarding how to incorporate the inevitable and sometimes large data gaps into the risk assessment. The life-stage specific risk characterization summary is supposed to "provide a justification for the application of life stage specific adjustments for duration-specific health values… if the assessment warrants". However, the framework does not inform the risk assessor how that is done. Again, examples would be very beneficial and make this framework much more useful.

Page 79, lines 12 -15. The sentence in the middle of section 5.1.2 seems to imply that a quantitative risk assessment needs to look at endpoints expressed as changes in adverse outcomes that "are readily understood and perceptible by the public". The sentence is only referring to endpoints that will be used in a benefits analysis, but appears to imply that only monetizable outcomes need be assessed. Thus, 1) the document needs to clarify that the risk assessment should be accounting for any potential health outcomes, not just monetizable health outcomes, and 2) a section briefly describing benefits analysis should be added and this sentence should be moved to that section.

BR: The presentation of a series of case studies or examples would help immensely here. Even artificially contrived examples could go a long way towards characterizing this approach.

RW: No, as discussed above, the major weakness in the document is that it does not provide specific examples of how risk assessments using a life stage approach could be applied over a wide range of

scenarios and in situations where substantial data gaps exist. The Agency's plans to prepare a series of case examples on the implementation of the framework, and to conduct training sessions for risk assessors, are critical and essential components to the successful implementation of the document.

10. EPA is planning to develop case studies to demonstrate the applicability of the life stage approach for children's health risk assessment and a training module for risk assessors. Do you have other suggestions that could aid in the implementation of this framework?

JB: See my previous comments.

GG: Response: The case studies are an excellent idea. In addition, EPA may want to consider compiling a resource database either as an appendix to this document or separately that gives the assessor handy references or links to key early life TK, TD and exposure information. Finally, a guidance document may be needed for this framework to become fully implemented. EPA may want to develop supplemental children's guidance or resources in specific areas such as early life vulnerability windows, early life TK factors, implementation of the children's cancer guidance, and implementation of the Exposure Factors Handbook.

LG: See my response to question 6. I think that a (simplified) decision diagram would be very helpful. Risk assessors often will find, with scoping, that age-bin specific hazard and/or exposure information is lacking and that it would be necessary to use bridging data or information. At other times they will conclude that some life stages are less critical to the assessment of an individual chemical and to stop that portion of the assessment. It would be helpful for the overview of the process to clearly identify these decision points in the analysis and how these connect to the discussion of uncertainties. For example, the discussion of exposure assessment clearly lays out that there can be a "screening" assessment and a "refined" assessment. But it is not clear in which context, given the scoping of the assessment in Chapter 3, these two approaches would be utilized. Nor is it clear what the commensurate level of hazard analysis would be.

When it comes to review of study designs, there are a number of issues that need to be more clearly drawn out, mostly in areas of statistical, experimental and epidemiological design. Since EPA relies on weight of evidence approaches it needs to clearly articulate the bases upon which studies are determined to have stronger or weaker contributions to the WOE. Examples of such issues that are not well explicated are: statistical power (numbers of subjects or animals, precision of measures), bias (including confounding), appropriateness of animal or in vitro models, relevance of routes of exposures and exposure levels, relevance and accuracy of biomarkers of exposure and biological change, and quality of assessments of exposure and outcomes. Along these lines, terms such as "interaction" and "controlling" are used in nonconventional ways. For example, (page 26) one cannot control for study variability (and I don't think that was meant by the authors.) On page 29, effect modification and confounding is treated as one and the same entity. Confounding is a form of bias and always needs to be addressed, not only in human but also in animal studies and in vitro assays. Effect modification is important in dose response assessment. It is important but I think that the idea of evaluating effect modification at every lifestage for every risk assessment is overkill.

MM: Development of case studies will increase the understandability and implementability of this framework immensely. Training modules are useful, but EPA should expand outreach and at a minimum provide training courses (with instructors) to each program within EPA which has a quantitative risk assessment component and to each regional office. Just handing out training modules

to use at the discretion of the program will not be enough. In addition, outreach to state risk assessors is really necessary to ensure that the framework is utilized throughout the country.

BR: See my responses above.

RW: As discussed above, the case studies and training modules are critical and essential components to the successful implementation of the document. A web-based training module would be particularly valuable. The inclusion of additional case examples would strengthen the document as has been done in the discussion on dose metrics and modeling on pages 42-53. It is likely that the Agency will need to articulate uncertainty factors and other approaches for handling data gaps. To the extent that these can be articulated within the document, they would prove helpful as examples. The Agency cites to resources that the risk assessor can use throughout the document. As discussed above, it would be useful if some examples, with appropriate caveats, were also included, perhaps in table format or in appendixes. For example, Table 1-2 of the Child-Specific Exposures Handbook provides exposure factor recommendations and confidence ratings, with references to other tables for specific data. Could these factors be compiled into one table for the document or appendix? A table summary of some of the key conclusions from the articles cited on page 23 that arose out of the workshop on critical windows of exposure for children would also be a useful guide.

OTHER COMMENTS FROM REVIEWERS:

MM: The text of the framework is jargon laden, and somewhat difficult to read and understand. Editing could improve the clarity of this document, which in turn would enhance its utility. Sections 4.2.3, 4.2.4 and most of section 4.3 were the clearest and well-written.

1) In the introduction lines 1-21. The points of the first couple of paragraphs are somewhat muddy, and this section could use editing. For instance it is not clear from these introductory paragraphs whether this framework is meant to address risks from exposure to children which manifest in childhood, or risks from any lifestage exposure which manifest at any time in life. Line 17 states that if an overall assessment is needed, then risks from children's exposures are incorporated into the larger assessment – that would correspond to the latter meaning. The sentence on line 19 then states if "the major concern is about health risks to children as a result of environmental exposure, the information derived from this process could be used directly to assess risk, set standards and mitigate exposures." - that would correspond to the former meaning. Another part of the problem with these two paragraphs is the definition of "children" as used in the document to include conception through adolescence to adulthood. It would be clearer to indicate that the EPA is concerned about health risks that result from exposures to all life-stages including preconceptional exposure, and exposures throughout development up to adulthood, instead of redefining the term child. Or the text could simply indicate that children can be impacted by preconceptional and in utero exposure. The sentence on line 8-9 is poorly worded. The assessment of health risks to children from environmental exposures does not have the same meaning as "children's exposures".

2) Page 7, sentence on line 3-5. This sentence, which is discussing the life-stage approach for evaluation of risks to children, is awkward. It would be more useful to make two sentences out of this one; suggest expressing the concept of potential outcomes from early-life exposure in one sentence, and then discuss consideration of mode(s) of action in another sentence.

3) page 7 sentence on lines 27-29. This sentence needs rewording. I think what you mean is "Because children are not a unique population but rather a series of life-stages through which all individuals pass, a child-protective approach is public health oriented."

4) Page 22, lines 17-20. I would explicitly include statistical power as an important aspect of study design.

5) Page 25, lines 15-18. The editors should probably strike the words on line 16 "Although there are no known examples of this,…" I'm sure I can think of one or two. It is entirely plausible that different toxic effects at different life-stages result from different MOAs.

6) page 26, line 14-16. The text states that high variability can sometimes render a study uninterpretable, etc. The text should clarify that high variability must be considered in light of the rest of the information on a chemical. If the result is consistent with what else is known about the chemical, then the high variability should not necessarily decrease the study's weight in hazard characterization.

7) page 29, lines 24-30. This section seems out of place. While it is important to evaluate effect modifiers or confounders, it is not possible to "focus on <u>all</u> potential life stage-specific effect modifiers and confounders and how they could affect the study outcomes or interpretation of study results". I suggest striking the word "all" – one will never know about "all" effect modifiers and confounders.

8) page 31 section on TK and TD. This could be expanded quite a bit to provide examples of TK differences that may be important to evaluating risks from exposure to chemicals in a life-stage specific approach.

9) Page 49 line 28 and 29. This sentence is very awkward. I suggest rewording the sentence to: "In animal studies, exposure is almost always discontinuous; use of these studies requires adjustment for dose continuity when extrapolating to humans."

RW: The U.S. Environmental Protection Agency is to be commended for developing the "Framework for Assessing Health Risks of Environmental Exposures to Children". The document, if implemented, will result in an important and appropriate shift in the Agency's approach to risk assessment by putting the child rather than the adult at the center of the evaluation if data indicate that susceptibility could be greater at the younger ages. This approach is consistent with legislative and administrative mandates requiring that risk to infants and children be explicitly and consistently considered by the Agency. It is also appropriately health protective. Humans are likely to be more susceptible to effects of environmental exposures during childhood in part because exposures are generally greatest during this period. The young drink more water, eat more food and breathe more air per kilogram of body weight than do adults due to more rapid metabolism and higher caloric needs. The young also have additional pathways of exposure (hand-to-mouth) and can receive greater exposure than adults through common pathways (i.e., dermal absorption because of crawling). And the developing organ systems can be, but are clearly not always, more susceptible to the effects of environmental toxicants. This may be particularly true during fetal development and early infancy, when organs are undergoing rapid growth, development and differentiation but detoxifying systems are not yet fully functional. It is important that the Agency is not proposing that risk assessment necessarily cover all life stages, but rather that the focus be on the stage(s) where susceptibility is greatest (page 36).

Appendix D. List of Registered Observers

United States
Environmental Protection Agency
Office of Research and Development

Peer Review Meeting for EPA Draft Framework for Assessing Health Risks of Environmental Exposures to Children

Hyatt Regency on Capitol Hill

Washington, DC
June 6-7, 2006

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Appendix E. Agenda

Peer Review Meeting for EPA's "Draft Framework for Assessing Health Risks of Environmental Exposures to Children"

Washington, DC
June 6 - 7, 2006

Final Agenda

TUESDAY, JUNE 6, 2006

8:30 am	**Registration**
9:00 am	**Opening Remarks and Announcements** ..... *Kate Schalk, ERG*
9:05 am	**Welcome Remarks** ..... *Bob Sonawane, U.S. EPA* *National Center for Environmental Assessment (NCEA)* *U.S. Environmental Protection Agency (EPA)*
9:10 am	**Background** ..... *Stan Barone* *National Center for Environmental Assessment (NCEA)* *U.S. Environmental Protection Agency (EPA)*
9:30 am	**Observer Comments**..... *Facilitated by Kate Schalk*
10:00 am	**Review of Charge and General Impressions** ..... *Lynn Goldman, Chair* *Johns Hopkins University School of Public Health*
10:15 am	BREAK
10:30 am	**Discussion of the Charge Questions** **Question 1** **Question 2** **Question 3** **Question 4**
12:00 pm	LUNCH
1:00 pm	**Discussion of the Charge Questions** **Question 5** **Question 6** **Question 7**
2:45 pm	BREAK

(over)

Agenda – continued

TUESDAY, JUNE 6, 2006

3:00 pm	**Discussion of the Charge Questions**
	Question 8 **Question 9** **Question 10**
4:30 pm	**General Comments and Discussion**
5:00 pm	Wrap Up/Writing Assignments
5:30 pm	ADJOURN

WEDNESDAY, JUNE 7, 2006

8:30 am	**Review of Writing Assignments**	
8:45 am	**Writing Session**	*Reviewers and ERG*
10:00 am	BREAK	
10:30 am	**Writing Session Continues**	*Reviewers and ERG*
12:00 pm	**Writing Session Closes**	*Reviewers and ERG*

Appendix F. Slides of the Presentation by Stan Barone, EPA

A FRAMEWORK FOR ASSESSING HEALTH RISKS OF ENVIRONMENTAL EXPOSURES TO CHILDREN

Overview for Independent Peer Panel Workshop

Stan Barone, Ph.D., NCEA/ORD
June 6, 2006

barone.stan@epa.gov

Disclaimer: The views of the authors of this document do not represent Agency policy or endorsement.

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- Tracey Thomas *AAAS/NCEA* (retired)*
- Chad Thompson, NCEA *(AAAS/NCEA*)*
- Carole A. Kimmel, *Past Chair, NCEA* (retired)*

** Previous Position*

RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions
2

Purpose

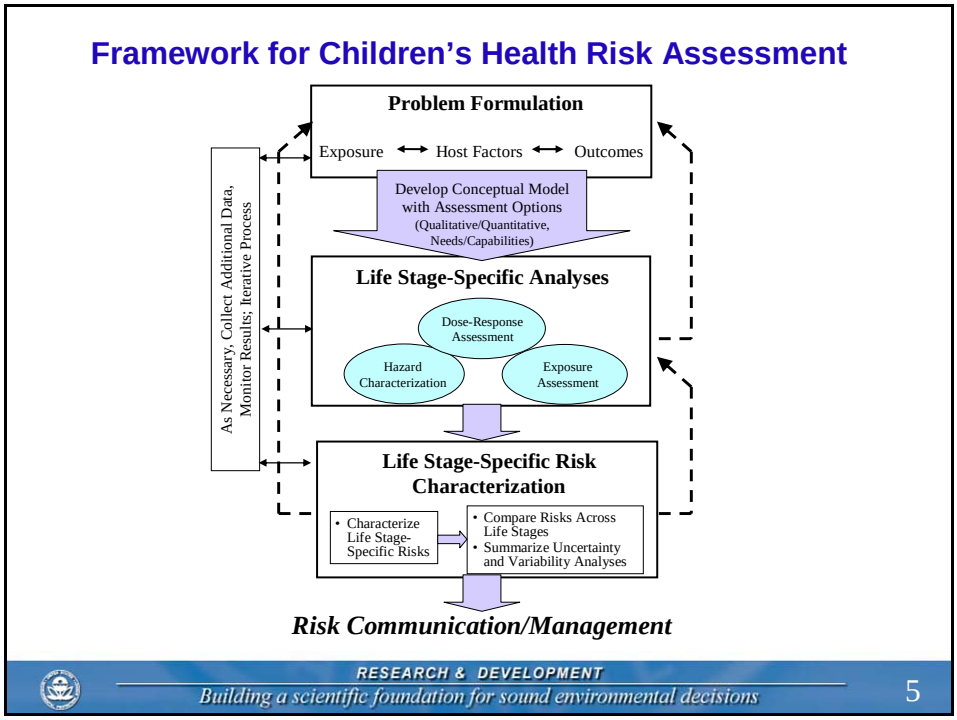
Key Objective: To provide an overarching framework for a more complete assessment of health risks to children* that:

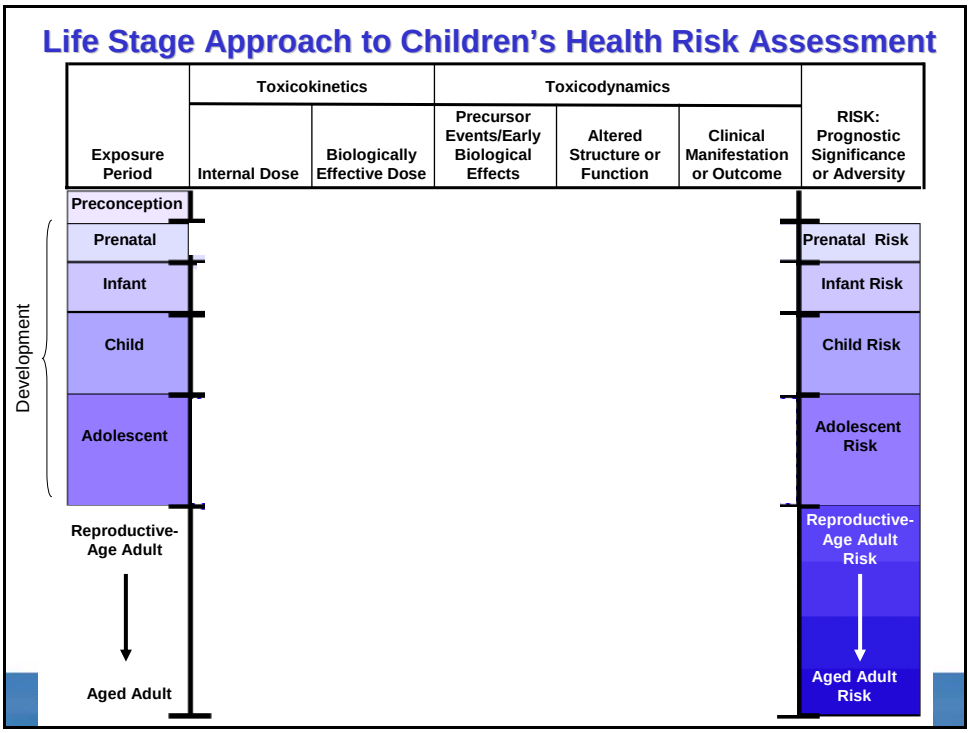
- examines potential exposures during all critical stages of development while emphasizing the iterative nature of the analysis phases with a multi-disciplinary team

* "children" is broadly defined in this document as including the stages of development from conception to adulthood.

Context

- Develop Framework
  - Conceptual model
- Identify needs for implementation of Framework
  - Identify gaps in guidance.
  - Identify training needs


Framework for Children's Health Risk Assessment
Problem Formulation
Exposure
Host Factors
Outcomes
Develop Conceptual Model with Assessment Options
(Qualitative/Quantitative, Needs/Capabilities)
Life Stage-Specific Analyses
Dose-Response Assessment
Hazard Characterization
Exposure Assessment
Life Stage-Specific Risk Characterization
• Characterize Life Stage-Specific Risks
• Compare Risks Across Life Stages
• Summarize Uncertainty and Variability Analyses
As Necessary, Collect Additional Data, Monitor Results; Iterative Process
Risk Communication/Management
RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions
5


Life Stage Approach to Children's Health Risk Assessment
Toxicokinetics
Toxicodynamics
Exposure Period
Internal Dose
Biologically Effective Dose
Precursor Events/Early Biological Effects
Altered Structure or Function
Clinical Manifestation or Outcome
RISK: Prognostic Significance or Adversity
Development
Preconception
Prenatal
Infant
Child
Adolescent
Reproductive-Age Adult
Aged Adult
Prenatal Risk
Infant Risk
Child Risk
Adolescent Risk
Reproductive-Age Adult Risk
Aged Adult Risk

Life Stage Approach

- Value Added:
  - More complete evaluation of the potential for vulnerability of various populations at different life stages
  - Encourages evaluation of potential for toxicity at all developmental life stages
  - Addresses integration of toxicity and exposure information across life stages
  - Focuses on understanding underlying biological events and critical developmental periods (MOA)
- Disclaimers:
  - Lack of data for different life stages is not meant to imply an obligatory use of uncertainty factors
  - Not a guideline; framework employs problem-driven questions leading an assessor through the process

Problem Formulation

- Three major steps
  - Define purpose of assessment
    - Is the scope of assessment site-specific, regional or national?
  - Define scope of analysis (tiered approach)
    - Do all life stages have to be examined or are exposure concerns limited/restricted to certain critical periods?
  - Define conceptual model and plan of action
    - How do exposures, individual characteristics, and outcomes fit into conceptual model?
    - Can the conceptual model include considerations for benefits analysis?

Life Stage Approach to Hazard Characterization

Emphasizes:

- ✓ Life stage comparative approach:
  - Considering exposure by life stage; evaluation of potential for toxicity after exposure during preconception and developmental stages
  - Considering outcomes by life stage (including adult life stages)
- ✓ An understanding of mode of action and critical developmental periods and their relationship

Analysis Approach to Exposure Assessment

- Approach depends on the purpose of the assessment
- Tiered approach
  - First tier – screening level to identify bounding exposures
  - Refined assessment – to provide increased level of detail.
  - Supplemental data collection- can reduce Uncertainty in exposure assessment

Life Stage-Specific Risk Characterization

- Modeled after the Science Policy Handbook on Risk Characterization (2000) and Guidelines for Reproductive Toxicity Risk Assessment (1996)
- Summarizes the major conclusions for each component of risk characterization
- Focuses on the life stage-specific aspects
- Derives risk conclusions and comparison
- Narrative defines certainty in conclusions, data gaps, sources of variability and uncertainties

Peer Review & Outreach

- Conducted Agency colloquium (Oct 2004)
- Briefed OCHP children's FACA (March 2005)
- Presented overview of framework at Human Health Board of Scientific Counselors (HHR program review March 2005)
- Presented overview of framework at SOT (March 2005)
- Presented overview of framework at regional risk assessors meeting (June 2005)
- Presented overview of framework at the Science Forum (June 2005)
- Presented overview of CHRA at WHO meeting (Nov 2005)
- Present overview of CHRA at SRA meeting (Dec 2005)
- Document underwent OMB/interagency review fall 2005
- Incorporated suggestions into draft document report

Next steps

- Get Framework externally peer reviewed by independent expert panel
- Incorporate peer review public comments into revised document
- Final clearance of document anticipated FY06.
- Planned/anticipated
  - Develop chemical-specific case studies FY08
  - Develop adjunct guidance where needed
  - Develop training for Program Offices/Regions and other risk assessors
  - Apply life stage approach in future risk assessments.

Thank You

Appendix G. Written Public Comments

Dr. George W. Alapas
Acting Director, National Center for Environmental Assessment
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Washington, DC 20460

April 28, 2006

RE: "A Framework for Assessing Health Risks of Environmental Exposures to Children" EPA/600/R-05/093A March 2006 External Review Draft; Docket ID No. EPA-HQ-ORD-2006-0134

Dear Dr. Alapas:

The American Chemistry Council appreciates the opportunity to comment on the Agency's external review draft report entitled *A Framework for Assessing Health Risks of Environmental Exposures to Children, EPA/600/R-05/093A March 2006* (referred to below as the "Draft Children's Health Risk Assessment Framework" document or "Draft Framework"). The American Chemistry Council (ACC or the Council) represents more than 90 percent of the productive capacity for basic industrial chemicals within the United States and its members are the leading companies engaged in the business of chemistry. Council members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer.[1] Protecting the health and well being of children is a fundamental value the chemical industry shares with society. Children live safer, healthier lives thanks in part to the development of chemical products and technologies that improve public health and safety. Children also benefit from the industry's commitment to health and environmental research. Chemistry companies invest more in research and development than any other business sector. The chemical industry's enduring commitment to health and environmental research and ACC's Responsible Care® initiative, a condition of membership, represents a commitment by our members and partners to make continuous progress toward a shared vision of no accidents, injuries or harm to the environment.

The Agency's Draft Children's Health Risk Assessment Framework document represents an important step in EPA's efforts to improve quantitative risk assessment. Regrettably, while the Council joins others in supporting EPA's efforts to more clearly and accurately evaluate potential risks to children, we believe that the Draft Framework needs considerable improvement before EPA even moves forward with peer review.

1 The Council is committed to improved environmental, health and safety performance through Responsible Care®; common sense advocacy designed to address major public policy issues; and health and environmental research and product testing. The business of chemistry is a $454 billion enterprise, a key element of the nation's economy and is the nation's largest exporter, accounting for ten cents out of every dollar in U.S. exports.

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The Council supports the efforts of the Agency to incorporate advances in scientific methods and practices in EPA's risk assessments. Our members are committed to conducting research and developing safety and health risk data on our products using the best scientific methods available. EPA, too, must ensure that the science used is the best available science. The Council endorses the Agency's efforts to apply scientific data first, before invoking default, conservative assumptions in risk assessment. The starting point for any risk assessment should be "a critical analysis of the available information" rather than default assumptions. We believe EPA must utilize all available scientific evidence to provide accurate risk assessments that can support risk management decisions that are health protective and do not unnecessarily expend limited resources.

A. The Draft Framework Must Integrate Learnings from the Agency's Voluntary Children's Chemical Evaluation Pilot Program

First and foremost, the Draft Framework fails to include and integrate knowledge and lessons learned from experiences of the Agency with its Voluntary Children's Chemical Evaluation Pilot Program (VCCEP). In point of fact, the Draft Framework never once even mentions the VCCEP. This is a considerable oversight, since this major initiative was launched by EPA in 2000 to focus explicitly on developing and evaluating quantitative risk assessments for children's potential exposures. The specific chemical substances the Agency selected for VCCEP were those the Agency believed were of high concern for potential exposures to children. It is simply inconceivable that the VCCEP framework and the experience gained by the Agency in the VCCEP assessments and peer consultations would not play a central part in the Agency's development of the Draft Framework.

The VCCEP was expressly designed by the Agency to provide data to enable the Agency and the public to better understand the potential health risks to children associated with certain chemical exposures.[2] To date, the VCCEP program has produced 8 complete assessment documents, each of which includes four sections: Hazard Assessment; Exposure Assessment; Risk Assessment; and Data Needs Assessment. Further, each VCCEP submittal was evaluated by a peer consultation panel for scientific review to determine the quality, thoroughness, and transparency of the quantitative exposure and risk assessment. Moreover, EPA itself has issued formal findings[3] ("Data Needs Decisions"), representing the Agency as a whole, on a number of the VCCEP chemicals. EPA's findings, based in part on the conclusions of the peer consultations, encompass and represent all relevant EPA programs. For all VCCEP substances considered to date, with the exception of three polybrominated diphenyl ethers, the Agency has concluded that no further toxicological data or exposure information are required to characterize the chemicals risks to children. This signifies that the risk assessment process under VCCEP has shown, in accordance with the objectives of the Agency, that "there are adequate

2 http://www.epa.gov/fedrgstr/EPA-TOX/2000/December/Day-26/t32767.htm
3 http://www.epa.gov/chemrtk/vccep/status.htm

toxicity and exposure information available to adequately characterize the risk to children."[4]

1. The Tiered Approach of VCCEP Should Be Integrated into the Draft Framework
Furthermore, the tiered approach embodied by the VCCEP, for hazard assessment, exposure assessment and risk characterization, should be interwoven into the Agency's Draft Framework. Clearly, the VCCEP program has provided essential information for Agency decision making with respect to developing and integrating hazard information with exposure information to evaluate potential risk to children.

Therefore, if the Draft Framework is indeed slated to "provide a single resource for information on the assessment of health risk to children as a result of exposures of environmental agents", prior to moving forward with the Draft Framework, even before initiating external peer review, the Agency should revise the Draft Framework to reflect the important scientific advances gained from the VCCEP.

2. Data Gaps Are Not Necessarily Data Needs
With respect to toxicity and hazard assessment, the Draft Framework should clearly indicate that a "data gap" is not necessarily a "data need."[5] Again, the VCCEP model has shown that the absence of one or more toxicity tests does not mean that there is a data need for collection of such information. Instead, VCCEP has shown that when exposure information is integrated with hazard information, it is both feasible and scientifically supportable to conclude that risk to children has been adequately characterized, even if the database is lacking in some manner.

Furthermore, the tone of the Draft Framework seems to imply that the hazard characterization dataset for all chemicals must comport to that required under FIFRA for active ingredients. This is clearly not the case, and needs to be corrected. For example, on page 33 of the Draft Framework, EPA states "The characterization of data gaps also includes a determination of whether required studies are present (those that are required by statute or convention, e.g., a rodent and a non-rodent prenatal developmental toxicity study and a reproduction and fertility effects study)", implying that the base set of toxicity information requires both a rodent and non-rodent prenatal developmental toxicity study. However this is not universal across different regulatory programs. While both studies are included in the base set of toxicity tests for pesticide actives, they are not required for the OECD SIDS, the HPV base set or for inert ingredients. Industrial chemicals, like inert ingredients, differ substantially from pesticide active ingredients. Industrial chemicals and inert ingredients are not intended to poison pest organisms, and

4 See for example http://www.epa.gov/chemrtk/vccep/pubs/finalacetone.pdf
5 In the context of the VCCEP *data gaps* are any areas in which information is lacking, and *data needs* are those data gaps for which additional information is required before the potential risk to children can be adequately characterized
(http://www.tera.org/peer/VCCEP/MEK/VCCEP%20MEK%20report%20final.pdf)

therefore, industrial chemicals and inerts are generally less toxic because they were not designed to specifically exert biological activity, in contrast to active ingredients in pesticides. The base set of data required for pesticide actives by FIFRA regulations was designed to define the characteristics of a substance that was already known or suspected of being biologically active, and thus suspected of being potentially hazardous to human health. For pesticide inerts the Agency has developed and recommended a tiered data screening methodology for chemicals of apparent low or low/moderate toxicity.[6] In fact, the Agency states that such a tiered approach should be considered for other substances of similar toxicity, which implies this would cover a large number of industrial chemicals as well. The Agency's tiered approach for such substances would apply to exposures to children as well as adults. Therefore, the Draft Framework should be revised to bring it into alignment with both the VCCEP tiered evaluation process as well as the Agency's tiered process for pesticide inerts. The Draft Framework should be consistent with EPA's policy that "It would be a poor use of societal resources to routinely require the submission and governmental review of an estimated 12 million dollars worth of data (the estimated current cost of the 40 CFR Part 158 (food-use) dataset) for every inert ingredient…."[7]

3. VCCEP Related Publications on Exposure Assessment and VCCEP Experiences with Exposure Assessment Should Be Integrated into the Framework

One of the first activities EPA initiated for the VCCEP pilot was to hold a workshop to provide a forum for sharing ideas about resources and approaches for collecting and presenting exposure information for the VCCEP assessments. The outcome of the workshop, published by EPA[8], provided a rich perspective on both specific methods as well as alternative approaches that could be used to evaluate children's exposures – yet it has not been incorporated into the Draft Framework. Furthermore, the Draft Framework makes no mention of two publications specifically focused on methods to evaluate children's exposures for risk assessment (A tiered approach for assessing children's exposure, Armstrong et al., *Environ Health Perspect.* 2000 Jun;108(6):469-74; and A framework and case study for exposure assessment in the Voluntary Children's Chemical Evaluation Program, Reiss et al., *Risk Analysis,* 23:1069-1084.

It is unclear why the Draft Framework has not utilized (or even cited) the extensive exposure assessments developed and evaluated for the VCCEP pilot. These provide very useful examples of approaches for evaluating potential exposures to children. Furthermore, these assessments have been subjected to both peer consultation review and review by the Agency, and found to be sufficient for characterizing children's risk.

6 Methodology for Determining the Data Needed and the Types of Assessments Necessary to Make FFDCA Section 408 Safety Determinations for Lower Toxicity Pesticide Chemicals http://www.epa.gov/fedrgstr/EPA-PEST/2002/June/Day-1 3/p14996.htm; www.pestlaw.com/x/guide/2002/EPA-20020607A.pdf
7 ibid
8 http://www.epa.gov/chemrtk/vccep/pubs/expsmrpt.pdf

Therefore, the Draft Framework should be revised to include experience gained through exposure assessments approaches discussed and utilized within the VCCEP pilot program.

B. Children Are Not Always More Vulnerable to Chemical Exposures than Adults

Another area that needs improvement in the Draft Framework is the manner in which the Agency deals with the potential for children to experience differential sensitivity to chemical exposures. The Agency's underlying premise seems to be that irrespective of the agent, children should always be considered more vulnerable to chemicals than adults. However, the scientific literature is clear that children will not always experience greater susceptibility or sensitivity to chemical substances in their environment, when compared to adults. The issue of children and chemical susceptibility should be considered on a chemical-specific or case-by-case basis. Evaluation of the available data indicates that susceptibility clearly depends on the substance and the exposure situation for any subpopulation, and that children are in some cases more susceptible, but in other cases less susceptible, than other age groups and subpopulations. Data have consistently shown that once a child reaches 6 months of age, metabolic activity is similar to the adult level and type of activity. Any categorical assertion that children are consistently more susceptible to environmental agents simply because they are smaller or are undergoing periods of rapid development is not substantiated by the overall weight of scientific evidence.[9] Therefore, EPA's assertion (both in the Preface of the Draft Framework and throughout the text of the document as a whole) that there is "mounting scientific evidence to support the vulnerability of the developing fetus and child" should be revised to reflect the full breadth of the scientific literature on this topic.

The Draft Framework will require additional clarification and revision with respect to the life stages covered. Inconsistencies appear throughout the document with respect to the inclusion or exclusion of parental preconception exposures. Certainly preconception events can potentially influence conception and gestation, however, the Agency should consider whether or not preconception exposures and events are better addressed in specific guidance on reproductive toxicity and risk assessment.

9 International Life Sciences Institute (ILSI). 1992. Similarities and differences between children and adults: implications for risk assessment (eds. P.S. Guzelian et al.), International Life Sciences Institute, Washington, D.C.; National Research Council. 1993. Pesticides in the Diets of Infants and Children. National Academy Press, Washington, D.C.; Dourson, M. Et al. 2002. Differential sensitivity of children and adults to chemical toxicity. Regul. Tox. Pharmacol. 3 5:429-447; Kamrin, M.A. 2002. Toxicology and Children's Health. In: Are Children More Vulnerable to Environmental Chemicals? Scientific and Regulatory Issues in Perspective (ed. DR Juberg), American Council on Science and Health, New York;

C. Clarification of Life Stages Covered Is Needed

Although not stated directly, the tone of the Draft Framework implies that the Agency has in the past neglected to fully consider children's potential exposures and risks. This is certainly not true. Key to assessing the risks for children is whether the available toxicological data set includes the life stages of particular relevance to children i.e., *in utero* or post natal development and growth. Any potential unique sensitivity of children is accounted for by the toxicity studies which examine these life stages. In fact, for both the HPV Challenge and the OECD SIDS, the base set of toxicity data required includes information from studies of developmental toxicity and reproductive toxicity.[10] It has been argued that physiological, allometric and behavioral differences between children and adults result in potentially higher exposures of children. Any difference in patterns of exposure of children and adults requires separate consideration and is dealt with within the exposure assessment.

It is certainly recognized that there is the potential for differences in exposure of children, compared to adults. However, these differences have been, are, and should continue to be evaluated within the exposure assessment component of a safety assessment when exposures to children are of concern. The Agency has a long track record in determining potential risk to the entire population, including children and other subpopulations. In fact, the Agency's hallmark toxicity criteria, Reference Doses, specifically include child exposures. The Agency defines the oral RfD as "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used." In cases where the critical study/critical endpoint (the lowest NOAEL) is a toxicological effect on the developing organism, the Agency has always used this critical endpoint in the dose-response assessment for derivation of RfDs. The Draft Framework should be revised to more clearly illustrate and document the Agency's long standing risk assessment practices which clearly have, and continue to, apply to children as well as other subpopulations.

In an attempt to simplify and illustrate child developmental life stages, Figure 2-3 can be easily misconstrued. Specifically, this scale of this figure portrays the development period as comprising approximately 1/3 of the lifetime. To more accurately communicate, it would be better if the life stages depicted were accurately scaled, using a linear metric, to represent the relative time periods taken up by each life stage. In other words, the scale of the y-axis should be years and the time of each life stage (in years) should be depicted proportionately.

10 The basic screening endpoints required for the HPV Challenge and OECD SIDS are: acute toxicity, chronic toxicity, developmental and reproductive toxicity, mutagenicity, ecotoxicity, environmental fate, & physical-chemical properties.See http://www.epa.gov/chemrtk/hpvq&a.pdf and http://www.epa.gov/sids/sidsman.htm

In Section 4.2.1.3. *(Regulatory Needs and Considerations) the* Draft Framework discusses use of chronic, life-time health risk criteria (e.g., chronic reference doses (RfDs) or reference concentrations (RfCs)) to evaluate potential systemic toxicity of children's exposures. The Draft Framework implies that chronic RfDs can be readily used for exposures of 7 years during childhood. This is not correct, and the Agency should reevaluate and revise the Draft Framework accordingly. In risk assessment it is critical to match the fraction of lifetime exposed in the study that forms the basis of the toxicity criteria to the fraction of lifetime of anticipated human exposure of concern.

Thus, chronic RfDs which represent intakes that are safe for an entire lifetime of exposure, are based on toxicology data pertaining to chronic, lifetime exposure and should be used to evaluate risks from exposures spanning a significant portion or the entire lifetime of an individual. The Draft Framework implies that chronic RfDs can be used when exposure covers just 10% of a lifetime. This suggestion is questionable. The more appropriate and scientifically sound approach would be to match the duration of exposure of interest to the duration (as a fraction of the lifetime) of the toxicity study used as the basis for the health criterion. Thus, it would be more scientifically relevant to use toxicity criteria derived from rodent developmental toxicity studies or postnatal endpoints from rodent reproduction studies or systemic endpoints from subchronic rodent studies, rather than a chronic RfD, to evaluate a 7 year exposure period for a child.[11]

D. Limitations of EPA's Supplemental Guidance for Assessing Cancer Susceptibility for Early Life Exposures Should Be More Explicit

With respect to the discussion of EPA's new Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens (US EPA 2005; page 55), the Draft Framework should be more explicit in describing the limitations underlying EPA's Supplemental Guidance. For example, the Draft Framework should explicitly acknowledge that the Agency states the "Supplemental Guidance is intended for guidance only. It does not establish any substantive "rules" under the Administrative Procedure Act or any other law and has no binding effect on EPA or any regulated entity, but instead represents a non-binding statement of policy."[12] Furthermore, the Draft Framework should note that the Agency has fully evaluated modes of action beyond mutagenicity and determined "In the case of nonmutagenic carcinogens, when the mode of action is unknown, the data were judged by EPA to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied."[13] Further, as has been pointed out, the datasets used by EPA to develop the Supplemental Guidance have significant shortcomings.[14] In fact, EPA's own data analyses indicate that for the repeat dose studies, 58% of the data sets showed equal

11 http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/comment/01 052006comment.pdf
12 http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=43 9798
13 ibid
14 http://birenheide.com/sra/2005AM/program/singlesession.php3?sessid=W23&order=1#1

or less sensitivity of the early life exposure period compared to exposure later in life. Similarly, of the 515 datasets analyzed by the Agency (acute dose studies), 45% showed

equal or less sensitivity of the early life exposure period compared to exposure later in life. Therefore, EPA's hypothesis that exposure to mutagenic carcinogens early in life leads to increased probability of tumor development (compared to exposure commencing later in life), lacks substantial support.

E. Weight Of Evidence Discussion Should Address GLP and Validation

The discussion on Weight of Evidence in the Draft Framework fails to mention the importance of studies conducted and data gathered in accordance with Good Laboratory Practices (GLPs). GLPs provide the Agency and stakeholders assurance that studies performed for regulatory purposes meet high standards of quality and integrity. In general, it is expected that studies used for regulatory purposes should adhere to GLP, such that studies are conducted and reported to regulatory bodies in a manner that enables an appropriate level of independent auditing of the study records. GLP requirements include, among others, developing a written protocol, standard operating procedures, maintaining records of instrument calibrations, having written procedures for accurate and full data collection and specimen retention procedures. Satisfying GLP also requires test article stability and purity and confirmation of the concentration and amount of material administered. In addition, GLP mandates documentation of study conduct and results, and ensures that a full record of the study, from start to finish, is preserved for subsequent review, if and when necessary. Under GLP, an independent quality assurance unit must monitor the study. Moreover, the laboratories conducting studies for use by regulatory agencies are subjected to periodic compliance reviews by government inspectors. Countless examples show the importance of adhering to rigorous record keeping and sound laboratory practices. In a weight of evidence evaluation, GLP studies should be afforded greater weight than non-GLP studies.

Similarly, studies conducted using validated assays should be given greater weight than new and novel scientific methods. New and novel types of studies are significantly different from laboratory studies using standardized and validated techniques. Research laboratory studies reporting novel test methods, non-standardized and validated methods and non-standard test species generally lack quality criteria for regulatory purposes. For example, they may lack appropriate documentation in terms of reliability of the performance of the test method and the relevance and significance of the endpoints evaluated for such results to be viewed as possessing the requisite degree of scientific certainty for unambiguous interpretation. Thus, such novel research studies should not be afforded the same weight as results from standardized and validated test methods. New or revised test methods should only be considered validated for regulatory purposes, when it has been demonstrated that these methods meet the criteria specified by ICCVAM[15]. Validation of a test method is a prerequisite for it to be considered for regulatory use. Importantly, the extent of test variability, and the reproducibility of the test method within and across laboratories must have been demonstrated, and sufficient

15 http://iccvam.niehs.nih.gov/docs/guidelines/criteria.htm

data should be provided to permit assessment of a test method's performance, reproducibility and limitations.

In conclusion, while the Draft Framework represents an important step by the Agency to improve quantitative risk assessment for children, there are a number of critical limitations in the document at this time which should be addressed by the Agency even before initiating peer review. We appreciate the opportunity to review the risk assessment methodology proposed by the Agency. Should you have any questions or desire additional clarification on any of the issues raised by ACC, please do not hesitate to contact me at 703/741-5210 or by e-mail at Rick_Becker@americanchemistry.com.

Sincerely

Richard A. Becker Ph.D. DABT
Toxicologist, Sr. Director
Health, Product and Science Policy Team
American Chemistry Council

COMMENTS BY THE CENTER FOR REGULATORY EFFECTIVENESS
ON
A FRAMEWORK FOR ASSESSING HEALTH RISKS
OF ENVIRONMENTAL EXPOSURE TO CHILDREN
(Docket ID No. EPA-HQ-ORD-2006-0134)

The Center for Regulatory Effectiveness ("CRE") appreciates this opportunity to comment on the above-captioned document ("Children's Health Assessment"). As discussed below, CRE wishes to commend EPA for acknowledging in its *Federal Register* notice that the Children's Health Assessment must comply with the pre-dissemination review requirements of the Information Quality Act ("IQA"). CRE recommends that the Children's Health Assessment be revised to explicitly reference the various IQA requirements.

CRE also believes that EPA's external peer review of the Children's Health Assessment must comply with the requirements of OMB's Final Information Quality Bulletin for Peer Review ("Peer Review Bulletin").

PRE-DISSEMINATION RE VIE W AND OTHER IQA REQUIREMENTS

In the Agency's *Federal Register* notice soliciting comment on the Children's health Assessment, EPA states:

> "EPA is releasing this external review draft document solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. This draft document has not been formally disseminated by EPA. It does not represent and should not be construed to represent any Agency policy or determination."

71 FR 13125 (March 14, 2006).

We commend EPA for including this statement that the Agency must comply with the IQA pre-dissemination review requirements. We assume that EPA will create a separate section of the record/docket for the Children's Health Assessment that

- identifies the IQA pre-dissemination review requirements;
- explains how the Agency has complied with those requirements in disseminating the Children's Health Assessment; and
- includes a certification from an appropriate EPA official that those requirements have been met.

If EPA does not intend to perform the actions identified in the three bullet items above, then we ask the Agency to explain why not.

We also note that the current draft of the Children's Health Assessment does not include any reference to the IQA requirements as binding upon EPA's assessment of children's health risks. We recommend that the Children's Health Assessment be revised to include

- a statement that the IQA requirements are binding on EPA's assessments of Children's health risks; and

- an explanation of how the IQA requirements should be met when EPA assesses children's health risks.

If EPA does not intend to perform the actions identified in the two bullet items above, then we ask the Agency to explain why not.

OMB PEER RE VIE W BULLETIN

We were surprised to find that the Children's Health Assessment is not included on EPA's Peer Review Agenda website. [1] We assume that this omission is an oversight that will now be corrected. We further assume that EPA will conduct peer review of the Children's Health Assessment in accordance with the requirements of the OMB Peer Review Bulletin.

The Children's Health Assessment is at least "influential scientific information" as defined by the OMB Peer Review Bulletin: "scientific information the agency reasonably can determine will have or does have a clear and substantial impact on important policies or private sector decisions." [2]

We believe that the Children's Health Assessment is a "Highly Influential Scientific Assessment" because it "is novel, controversial, or precedent-setting, or has significant interagency interest."[3] For example, the Children's Health Assessment explains that "[p]arallel activities have been or are being developed at other agencies such as the U.S. Food and Drug Administration (FDA)," and that "there can be significant overlap with assessments conducted to determine risk to children from environmental exposures." [4]

1 Http://cfpub.epa.gov/si/si_pr_agenda.cfm

2 *Id*.

3 *Id*.

4 Children's Health Assessment, page x. 2

To the best of our knowledge, the Children's Health Assessment has only been informally, internally reviewed within EPA. We do not believe that this internal EPA review qualifies as the prior peer review with associated charge that would exempt the Children's Health Assessment from compliance with the OMB Peer Review Bulletin during the current, formal external peer review of the Assessment. [5]

If EPA believes that the Children's Health Assessment is exempt from the requirements of OMB's Peer Review Bulletin, then we ask the agency to explain why.

Once again, we thank EPA for this opportunity to comment, and we look forward to the Agency's response to comments.

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[5] See OMB Peer Review Bulletin, Section XI, at http://www.whitehouse.gov/omb/inforeg/peer2004/peer_bulletin.pdf

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April 28, 2006

Office of Environmental Information Docket (Mail Code: 2822T)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

via facsimile

Re: EPA Docket No. **EPA-HQ-ORD-2006-0134**
Submission of Comments on **"Framework for Assessing Health Risks of Environmental Exposures to Children"**

On behalf of Tetra Tech EM, Inc., we are submitting the attached comments and responses to EPA's charge questions on the External Review Draft of the *Framework for Assessing Health Risks of Environmental Exposures to Children*, dated March 2006.

The Framework is a commendable start at outlining an approach for assessing health risks for specific life stages from conception to adulthood, both in summarizing previous EPA documents and highlighting the many sources of variability and uncertainty. The Framework is consistent with and further articulates EPA's interest for a harmonized approach for evaluating cancer and non-cancer risks, and will be a useful tool for encouraging comprehensive evaluations of human health risks for all life stages.

Should you have any questions regarding this submittal, please feel free to contact Maxene Dwyer at:

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Sincerely,

Tetra Tech EM, Inc.

Maxene R. Dwyer, PhD,
DABT Senior Toxicologist

Allison Jenkins,
MPH Toxicologist

Attachment: Response to EPA Charge Questions and Additional Comments

EPA Docket No. EPA-HQ-ORD-2006-0134

Submission of Comments on:

"Framework for Assessing Health Risks of Environmental Exposures to Children"

Submitted to:

Office of Environmental Information Docket (Mail Code: 2822T)

U.S. Environmental Protection Agency

1200 Pennsylvania Avenue, NW

Washington, DC 20460

Prepared by:

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April 28, 2006

Responses to the External Peer Review Panel Meeting Charge Questions on "Framework for Assessing Health Risks of Environmental Exposures to Children"

Question 1. Is the purpose of this draft framework document clearly articulated? Are the graphic presentations of various concepts and methods (e.g., flowchart approach) and the questions to prompt review considerations clear and useful? If not, do you have suggestions for improving clarity?

Response: The general framework approach is modeled on other published EPA guidelines (e.g., the EPA 's 1998 Guidelines for Ecological Risk Assessment) and follows the same basic steps: problem formulation, analysis, and risk characterization. The graphic presentations of the various concepts are consistent with other published graphic presentations, and were appropriately modified, where adapted, to incorporate the concept of evaluation of specific life stages.

The purpose of the document is clearly stated in the executive summary and introduction, which states on page 7 that "this framework document is not a guideline or science policy paper, but rather describes an overall vision of the structure, process, and the components considered important for assessing risks as a result of children 's exposure." Since this document does not present specific guidance on conducting children's risk assessment, will there be a future children 's risk assessment "guidance" or "guideline" that will utilize the structure and approach presented in this framework document?

Question 2. This report is intended to highlight specific concerns of children's risk assessment. However, there are some general aspects of risk assessment that need to be described. To what extent is this document inconsistent with how you have interpreted existing risk assessment guidance? Are there major gaps in what has been presented, for either children's risk assessment or for risk assessment more generally? Considering the various types of Agency chemical assessments that you are familiar with or anticipate performing, are there gaps in the process outlined?

Response: The intended purpose (scope) of document may be more useful if the framework discussed possible solutions to some of the highlighted specific concerns of children 's risk assessment. That is, not only posing the relevant questions, but providing a process within the risk assessment framework as to how these specific concerns may be addressed considering known data gaps and the potential limitations of these data gaps on the implementation of the framework described.

For example, in Section 6 (page 87) of the report, the relevance of specific developmental outcomes for application to risk assessments for various exposure durations (i.e., acute, short-term, longer-term, and chronic) is mentioned (highlighted) as being considered in many of the risk assessments currently conducted across EPA, yet this issue was not addressed in the framework considering specific life stage exposures.

Question 3. Risk assessment is a multi-step process and done at many different scales depending upon the problem. Do you think the document provides enough flexibility for users to understand how it applies to them? If not, for what audience(s) would you suggest clarification is needed and what kind of clarification?

Response: The document does not clearly articulate how the steps can be applied at various levels depending upon the scale of the problem. For example, for a risk assessor/consultant (potential user), the varying levels of the complexity of integrating the children 's framework protocol into preparing a risk assessment for a Superfund site vs. a school or daycare is not very apparent. It would be helpful to include a few examples of how the children 's risk assessment framework/process can be applied to diferent scales of problems.

Question 4. Is the list of potential involved parties (e.g., risk assessors, risk managers, others) discussed in the problem formulation inclusive enough?

The problem formulation section of the document adequately addresses the involvement of the various parties such as the risk assessment team, risk management team, and various stakeholders. The examples provided demonstrate the need for a risk team that is comprised of a multidisciplinary panel of experts and suggest that a single individual would not be capable of completing the approach. In addition, the need for early input in the planning and scoping phase from the risk management team and relevant stakeholders was cleared articulated.

Question 5. The approach described uses a life stage perspective; that is, it focuses on assessing exposures for developmental life stages (embryo, fetus, child, and adolescent) and resulting health outcomes for all life stages (embryo, fetus, child, adolescent, reproductive adult, and aging adult. The EPA is soliciting your input regarding whether this approach is a more comprehensive approach than the focus on organ systems (e.g., neurotoxicity, cancer, reproductive toxicity, and developmental toxicity) used in previous risk assessment guidelines. Please comment on the advantages and disadvantages of this approach within the context of our current understanding of the influence of exposure in different life stages and the available data.

Response: The EPA 's current focus on promoting the evaluation of risk for specific life stages is commendable, and will ensure that risk to children (a potentially sensitive population) are not evaluated secondarily (less important) to adults in a risk assessment and overall will promote a more thorough evaluation of risk at all life stages. The focus in this direction is definitely supported by available studies that suggest that early -life stages (e.g., in utero and after birth) may be a period of greater susceptibility for some chemical exposures due to the rapid growth and development that occurs during those phases, as well as the immature development of the metabolic system in early life stages.

The assessment of risk for developmental life stages should be integrated with the existing approach that considers organ systems. An approach that combines both concepts (i.e., evaluation of life-stages and organ systems) would provide a more comprehensive evaluation of human health risks for all life stages.

Question 6. The report addresses the integration of hazard data with exposure information from a life stage perspective. This discussion brings together information from the toxicological evaluation, life stage of susceptibility, exposure factors for children, and age binning for exposures. Have we clearly articulated the approach? Are their sufficient data and understanding available to inform such an approach? Do you have additional suggestions that improve or clarify the approach?

Response: The report clearly articulates the approach. Further clarification of the approach does not seem warranted; however, a discussion of some of the limitations of the framework approach due to data gaps (e.g., some of gaps issues presented in Section 6 of report) may be noteworthy. Specifically, expanding and clarifying how to interpret the lack of data for toxicity and exposure (e.g., information from the toxicological evaluation, life stage of susceptibility, exposure factors for children, and age binning for exposures) for specific life-stages in the uncertainty discussion.

Question 7. Has EPA's interest in moving toward a harmonized approach for risk assessment, moving away from the dichotomous consideration of cancer versus noncancer been clearly articulated within this document?

Response: The approach of the framework outlined is consistent with and further articulates EPA 's interest for a harmonized approach for evaluating cancer and non-cancer risk. Similar themes discussed in the EPA 's 2005 Guidelines for Carcinogen Risk Assessment and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens were noted. However, as stated previously, it may be beneficial to articulate more in this framework that there may several instances where this general framework (approach) may not be feasible. These instances include the lack of quality data on toxic efects of early -life stages as well as the lack of suitable data and information to adequately characterize children 's exposures for early life stages.

Question 8. Is the iterative approach between the different analytical phases (hazard characterization, dose response analysis and exposure assessment) clearly articulated in the framework? If not, how can this be improved? How does this iterative approach compare with your practical (or real- life) experience?

Response: The iterative process is clearly demonstrated in the graphic presentations (flow chart) and is indicated in the text where an iterative step (input) would be warranted. Figure 2-2 (Children 's Health Risk Assessment Framework) is particularly helpful in illustrating the framework. Based on experience, an iterative approach is common in doing non life-stage based risk assessments. Additional needs and information frequently arise following problem formulation and as more people become involved in the assessment.

Question 9. With the kind of data typically available currently for chemicals, do you think an assessor would understand how to use this framework with existing data? If not, what would you suggest we clarify?

Response: A risk assessor may potentially find it dificult to apply the framework process using available data for most chemicals due to the number of data gap issues that are likely to arise at the various steps of the framework process.

Question 10. Does the risk characterization section for children risk adequately address data gaps and how they are incorporated into the risk assessment uncertainties?

Response: The risk characterization section summarizes (points out) potential data gaps, but does not adequately discuss how these data gaps could impact the usability of the approach or clearly how they should

be incorporated into the uncertainties of a risk assessment. The process was not clear as to how a risk assessor should interpret lack of data in the risk assessment – an additional uncertainty or just a data gap?

How uncertainty and variability will in -practice afect the results of the risk characterization could be discussed in more detail. Discussion of uncertainty/variability in risk assessments is sometimes overlooked and should be emphasized in risk communication. Discussion of the data gaps is particularly critical when doing life-stage specific characterizations as adequate data will often be lacking and there are minimal government guidance documents that can provide additional information. Exposure assessment information for children obviously is lacking, as well as guidance on how to evaluate chemicals with limited toxicity data and benchmark levels. We appreciate the Tables in Section 5 (e.g., Tables 5-1 through 5-3) that will be useful in summarizing risk characterizations.

Editorial comment: Missing period at end of line 9, page 85.

Question 11. EPA is planning to develop case studies to demonstrate the applicability of the life stage approach for children's health risk assessment and a training module for risk assessors. Do you have other suggestions that could aid in the implementation of this framework?

Response: The development of case studies with "real-life" examples would facilitate understanding of how the approach can be implemented given a specific scenario. A web-based training module would possibly facilitate reaching a large audience or group who would be potential users of the children 's health risk assessment framework.

Specific Comment

Section 3.2.1 Exposure Considerations

Section 3.2.1 outlines the exposure considerations for the conceptual model and provides considerations specific to children including exposure media, behaviors, activities, and locations that are a function of age/developmental stage, individual and community characteristics, and physical environment (e.g., climate). Section 4.3.4.1 (Chemical Properties, Fate, and Transport) is provided as a source for more information on the physical environment; however, Section 4.3.4.1 discusses climate in the context of environmental fate of chemicals/agents. Climate could also be better discussed/outlined as a factor in exposure diferences for the various life stages. Potential regional variations in climate (e.g., temperature, humidity, rainfall, sun exposure) and activities (e.g., types of sport/other activities, length of sport seasons, physical education requirements) should be clarified in Sections 4.3.4.3 (Life Stage-Specific Population Characteristics).

Comment Info: ==========

== General Comment: April 26, 2006

Subject:
The Emerging Contaminant Directorate (located in the Office of the Secretary of Defense) provides the Environmental Protection Agency these comments on “A Framework for Assessing Health Risks of Environmental Exposures to Children” (EPA/600/R-05/093A, March 2006 External Review Draft).

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The Department of Defense (DOD) recognizes that the environmental health vulnerabilities during early human development vary from those experienced through mature life stages. While we endorse the practice of incorporating margins of safety in the face of scientific uncertainty to ensure adequate health protection, we believe that the Framework, as written, will lead to compounded and broadly applied margins of safety. Because the technical considerations that underlie the derivation of margins of safety are based on EPA science policy that has not been reviewed for several years, we recommend a review of this science policy in the context of the more recent advances in biomedical science. Specific technical review questions should include:

1) Are the current uncertainty factors independent or interdependent?
2) Is it appropriate to multiply uncertainty factors or is portioning a standard safety margin the approach to take?
3) Is the breadth of the safety factor, when all uncertainty is applied, reasonable when compared to the breadth of human dose response to therapeutics?
4) For the sake of interagency harmonization of health risk assessments, is it most appropriate to develop child protective environmental health policy in the context of the ongoing discussions about pediatric doses of therapeutics?
5) Can the reliability of health risk assessment be improved by considering mode -of-action in the context of mode-of-reaction, i.e., compensatory and homeostatic responses?
6) What interagency science policy must be developed to adequately address the emerging issues related to early life exposures as the basis for adult disease?

Overall, we recommend that the science policy review be an interagency review. The rational is that environmental health is just one component of public health and prioritizing a broader suite of competing risks is an interagency responsibility.

EPA-derived margins of safety, while protective of environmental health, do not adequately consider all other competing federal risks. Therefore, we recommend that an interagency science policy review take place prior to advancing the Framework.

Specific Comments

Comment: page 8, line 7 & 8 and figure 3-3 on page 16- In its introduction the Framework states that, "...the lack of data for certain life stages is not meant to imply greater uncertainty in the assessment to risk to children." However, the Framework broadens the scope of environmental health risk assessment and increased uncertainty with corresponding reduction in reliability emerges as an issue. Will the Framework yield assessments of sufficient level of reliability as to provide risk managers with a tool for prioritizing competing risks? A demonstration is needed.
Recommendation: Demonstrate whether competing risks are (or are not) distinguishable. The EPA might apply the Framework to two or more environmental chemical case studies using probabilistic risk assessment techniques where applicable.
Rational: If the EPA cannot demonstrate that the Framework informs Federal risk prioritization then the Framework should not be used for risk assessment. In this regard, the best application of the Framework might be as a tool to inform programmatic biomedical research decisions.

Comment: Page 1, Line 17 to 20. Life stages should be based on the temporal development of functional mode-of-action components such as metabolic enzymes, hormone receptors, neurotransmitters, or cellular membrane and transport proteins rather than anatomy, physiology and behavior.
Recommendation: Redefine the life stages based on the temporal development of the molecular components of mode-of-action.
Rational: Risk assessment has evolved such that a molecular event (such as iodine uptake inhibition) is identifiable as the critical event on which a bench mark dose is derived. Therefore, the best approach to defining life stages is to base them on temporal development of the molecules and cellular structures that are involved in the chemical-specific mode of action.

Comment: Page 3, Line 6: The term “children” as used in the document applies to conception through adolescence to adulthood. This definition is outside standard practice among those who research human development.
Recommendation: Use common terms such as conceptus, fetus and infant for refer to stages of human development as is common practice in the research community.
Rational: The definition as written could raise very sensitive abortion/right-to –life issues that are probably not intended to be addressed or implied by this document and therefore should remain beyond the scope of the document.

Comment: The subject document does not provide discussion on the future (ultimate) application of the information to be assembled, regarding exposure, toxicity, and the assessment of children’s health risk from environmental exposures.
Recommendation: Indicate what programs (Superfund, Pesticides, etc.) are intended to benefit from the development of this framework.

Page: 56, Lines: 1 to 14
Comment: Up to this point the document placed an emphasis on assessing children for their unique exposures and toxicological responses. Here the Framework gives license to using existing adult-based toxicity information, by applying (age-dependent) adjustment factors.
Recommendation: Acknowledge how applying age-dependent factors does not constitute an enhancement for our present-day child assessments.

Page: 45, Lines: 11 to 13
Comment: The text of these lines suggests that changes in function are necessarily adverse. Statistically significant changes are not necessarily biologically significant.
Recommendation: Revise the identified text so as not to give the impression that chemical-induced changes in biological measures are not assumed to be adverse. A recommended reference, which could be cited here is: Tannenbaum, L.V., 2001. What's So Bad About Weight Loss, Blood Chemistry Effects, Kidney Toxicity, etc. in a Modeled Ecological Receptor Human and Ecological Risk Assessment, Volume 7(6): 1765-1767.

Comment: Page 57, 4.3.1 at the second paragraph where the draft states, "Depending on the risk assessment objectives, it may be important to involve stakeholders at this point in the assessment to ensure that their concerns are addressed."
Recommendation: Reword this to state, "It is important to involve stakeholders at this point in the assessment to ensure their concerns are addressed."
Rational: The goal is to enhance the conceptual model by describing all potential exposures that may possibly take place, the stakeholders are an important information source and must be included early on in the process to ensure that the health risk assessment is as accurate as possible and correctly reflects site-specific conditions.

The following are less substantive comments and/or edits
Page: 22, Line: 16
Comment: The importance of chemical form used in studies is not mentioned.
Recommendation: Include that it is important to consider the chemical form that is used in the studies being evaluated. The experimental chemical form should be relative to the appropriate exposure pathways in the environment.

Page: 23, Line: 1
Comment: The importance of chemical bioavailability is not mentioned.
Recommendation: Include that it is important to consider that the bioavailability of the substance that was used in the toxicity studies be comparable to those found in the field.

Line, 15, page 3, misspelling, "singly"

There is an apparent inconsistency: line 6/7 page 4 with line 4 page 5

Comment: p. 11 line 12 uses "outcomes" to mean outcomes of the assessment, which aren't necessarily health outcomes. Page 12 also uses outcomes in such contexts as "optimum timing of outcome evaluation" line 9, and "public health outcome" line 10.
Recommendation: Ensure the uses of "outcome" make sense and/or use adjectives more often, such as "health outcomes" or "developmental outcomes". As an example

Page: 1, Line: 4
Comment: In line 4, a wording change is recommended.
Recommendation: Please modify the text as: " . . . as a result of exposures to environmental agents . . ."

Comment: The document's title does not clearly express the intent in the most understandable fashion.
Recommendation: In concert with the text at the beginning of the Executive Summary (page 1, lines 3 and 4), consider revising the title as: A Framework for Assessing Health Risks to Children from Environmental Exposures.

Page: 2, Line: 7
Comment: A word is missing on line 7.
Recommendation: Please modify the text as: “ . . . the evaluation of all outcomes.”

Page: 3, Lines: 6 and 7
Comment: The text of lines 6 and 7 provides, in words, the upper end of the age

range of concern, namely “to adulthood”. However, this upper bound is not expressed as a numerical age until page 66.
Recommendation: Have the text of this Section’s opening paragraph indicate that “childhood” concerns cease at age 21.

Page: 3, Lines 13 and 14
Comment: The text of lines 13 and 14 should be reworded for clarity.
Recommendation: Consider changing the question to: “What are the health risks to children from environmental exposures”.

Page: 38, Lines 20 and 21
Comment: There is an error in the text of these lines. RfDs and RfCs are not risk estimates. They are respectively, a dose, and a concentration.

Page: 41, Lines, 9 and 12
Comment: A closing parenthesis is missing after the word “childhood” on line 9. Also, the mention of “post pubertal exposures” on line 12 is not understood. Such exposures are by definition not occurring to a child, and therefore should not be given any consideration.
Recommendation: Make the identified correction on line 9. Remove the reference here to post pubertal exposures, and do so for any other such references throughout the document.

Page: 48, Line: 24
Comment: The end of the sentence on line 24 is not understood. It appears that “non-toxicological” is the wrong adjective to use.

Page: 49, Line: 12
Comment: On line 12, the sentence should end with the words “ . . . measures of risk or hazard.”

Page: 49, Line: 28
Comment: It is not clear to the reader what is meant (on line 28) by animal exposure studies “almost always being discontinuous”.

Page: 60, Lines: 26 and 27
Comment: The last bullet point requires a modifier.
Recommendation: Modify the bullet point to read: “What are the potential post-birth activities that may lead . . .”

Page 108, Line 14
Comment: The reference list skips from U.S. EPA 2003c to U.S. EPA 2003e.
Recommendation: Edit the references in glossary to include a reference for U.S.EPA 2003d and edit all corresponding citations in the main text.

Page: 6, Figure 2-3
Comment: This figure does not illustrate the intended point. Rather than showing the continuous nature of development and the potential for effects of exposure much later in development, it appears to make clear distinctions in

the stages of development. Later in the document it is stated how much person-to-person variability there is in the stages.
Recommendation: Use a figure that illustrates continuity better. Perhaps a segmented circle or chain in which one piece or group of pieces can be taken out.

Page: 7, Line 27
Comment: The text of line 27 says that children are not a unique population, but in Superfund health risk work, children are most certainly recognized as one (of several) “sensitive subpopulations”.

Page: 5, Line: 2
Comment: The word “performed” is misspelled on line 2.

Page: 20, Figure 3-1
Comment: The use of the terms Hazard Characterization and Risk Characterization may cause confusion.
Recommendation: Use the more traditional term, Hazard Identification.

Page: 15, Line: 11
Comment: The phrase “specific periods of concern” is unclear; does it refer to timing of exposure or timing of observed effects?

Page: 24, Line: 20
Comment: On line 20, “mom” should be “mother”.

Page: 31, Line: 25
Comment: The terms “Toxicokinetics” and “Toxicodynamics” have already been abbreviated in the text. Several other acronyms/abbreviations are not consistently applied. As an example, “MOA” for Mode of Action, is spelled out when it doesn’t need to be (see for example, page 36, line 9).

Page 89-97, Glossary:
It may be helpful to not only mention its existence at the beginning, but also italicize (or in some other way note) the words that can be found in the glossary when they are in the text. There are many misspellings.

frl 8044-6
id 2006-0134

please send me a copy of "a framework for assessing health risks of environmental exposure to children". please extend time for public comment. please make sure i can join the teleconference where you hire a special firm to work on this report since i would like to see what this private firm does. also, is this "private firm" to be hired one with political connections or truly independent.

i note that epa continually has approved the use of thousands of toxic chemicals on completely negligent information submitted. i think epa is the cause of environmental health risks for our children, along with fda and usda. approval of a toxic chemical because it did not create a seen problem in rats is no way to tell if something is safe or not. that was good for l500 a.d. it is not satisfactory today at all.

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