EPA's Response to External Peer Review and Public Comments on the "Draft Framework for Assessing Health Risks of Environmental Exposures to Children"

(EPA/600/R-05/093A)

Response to Peer Reviewers' Comments

Key Responses to Charge Question 1

Peer Reviewers: 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.

> **EPA Response:** The first goal of the external draft Framework was deleted as suggested by the peer reviewers, and the second goal is now the document's stated principle goal.

Peer Reviewers: 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 lifestage-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.

> **EPA Response:** The overall flow diagrams for each section have been simplified and reflect the revisions of the document, while maintaining a lifestage-specific focus. Many figures in the hazard section were deleted. The associated figure legends were streamlined, and in most cases the text was moved into the body of the text as suggested. Figures deleted: 2-1, 3-2, 4-3, 4-4, 4-6; Figures edited: 2-2 (now 2-1), 2-3 (now 2-2), 3-1, 3-3 (now Table 3-2), 4-1, 4-2 (now 4-3), 4-5, 4-7 (now 4-4), 4-8 (now 4-5), 4-9 (now 4-7), 4-10 (now 4-8); Figures added: 4-2, 4-6, 5-1; Tables added: 4-1 through 4-8.

Key Responses to Charge Question 2

Peer Reviewers: 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 lifestages. The peer reviewers noted one exception that appeared to imply that only clinically apparent adverse outcomes need to be assessed (see Section 5.1.5).

> **EPA Response:** In Risk Characterization (Chapter 5), the paragraph now reads: "For outputs of this analysis to be most useful in benefits analysis (Chapter 3), the outcomes that are quantified are expressed as changes in adverse outcomes or precursor effects (e.g., change in incidence of illness or symptoms) that are readily understood by the

public. Reliance on single point risk estimates for key conclusions may not be very useful for benefits analysis."

Peer Reviewers: When EPA develops guidance for implementing the Framework…A strategy for streamlining the process to make the lifestage-specific assessment more manageable.

EPA Response: This overarching comment was addressed in several ways. The description of more general risk assessment practices was edited wherever possible to reflect the lifestage-specific focus of the Framework. The graphics were revised to more clearly reflect the lifestage-specific features of the Framework. The context for analyses is more clearly articulated with context to next steps in the process, examples and questions are included to provide more clear lifestage-specific issues for consideration. The weight-of-evidence analysis figure was deleted and the description of this process as it relates to lifestages was significantly enhanced with attendant examples and questions.

Revised draft includes modified text on the problem formulation (Chapter 3) to more fully describe the extent of the assessment. The analysis plan (Section 3.3) and analysis steps (Chapter 4) are problem-driven and thus may not include exhaustive examination of all lifestages or exhaustive analysis (e.g., if only a screening level approach is employed). Because one size does not fit all, EPA has not included a decision tree in the revisions of this document. In the analysis plan (Section 3.3), it now states: "Examination of the most vulnerable age groups and key risk drivers relevant to the problem identified will help conscribe the assessment and shape the decision points and decision tree in the analysis plan." EPA agrees that the decision analysis could be more clearly articulated in a case study.

In addition, EPA has defined what was intended for iteration in the Framework to describe more clearly what are being suggested as dialogue, communication, and coordination across disciplines and among analysts from different disciplines. This is meant to assist the reader in understanding how the loop will be closed in possible iterative steps so that this process will not be so unwieldy.

Peer Reviewers: When EPA develops guidance for implementing the Framework…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.

EPA Response: The prose of the problem formulation section, in particular the scoping section, development of a conceptual model, and analysis plan, has been significantly revised to provide greater clarity. More clarity was added about data limitations and the problem-specific nature of the assessment that provides a context to the decision analysis. In addition, the prose on iteration between analysis steps was edited and reorganized to reflect a more clear context for decision points in the analysis (see narrative sections).

A decision tree was not added to the Framework. This could be a significant part of future guidance and outside the scope of the present Framework. EPA has taken this suggestion under advisement for development of guidance.

Peer Reviewers: When EPA develops guidance for implementing the Framework…An approach is needed for addressing and dealing with data gaps.

> **EPA Response:** Discussion of how data gaps could be addressed is included in the uncertainty analysis of the hazard assessment (Section 4.1.3.1.2.2) as well as in the risk characterization (Chapter 5).
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> The following has been incorporated into the response in Section 4.1.2.10. "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. One- and two-generation reproduction studies are also not conducted for all chemicals and are often limited in having postnatal dosing only via nursing and involve a limited number of outcomes (e.g., reproductive outcomes). Developmental neurotoxicity, developmental immunotoxicity, and other organ system-specific developmental studies also are not commonly performed and have limitations regarding the exposure route and apical outcomes/organ systems assessed. Due to the iterative nature of the evaluation process and the consideration of information from multiple sources, data from other human or experimental animal studies, data on structure-activity relationships (SARs), or TK or TD information, may be used to address uncertainties in a given study."
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> The following has been incorporated into the response in Section 4.1.3.1.2.2. "For example, the combined studies may have assessed outcomes after exposure during all developmental stages except for the peri-pubertal period. If this were the case, then a data gap in coverage of this particular developmental lifestage of exposure would be noted. For any chemical assessment, there will be inevitable gaps in the available lifestage-specific information; it is the relative impact of missing or inadequate information to the overall goals of the assessment that are to be judged. In some cases, information gleaned from the toxicologic profiles of structurally-related chemicals or chemicals with a similar MOA can assist in interpreting the relative importance of a data insufficiency. Sometimes this information can provide a way of bridging a data gap (Julien et al., 2004). When evaluating lifestage-specific uncertainties and data gaps, study design (e.g., measurements, exposure, and outcomes across lifestages) is addressed (U.S. EPA, 1991, Section 3.1.2.1; U.S. EPA, 1996, Section 3.3.1.5; U.S. EPA, 2002d, Section 4.3.1). The characterization of data gaps also includes a determination of whether required toxicologic studies (i.e., by statute or convention) are present (e.g., a rodent and a non-rodent prenatal developmental toxicity study, and a reproduction and fertility effects study)."

Key Responses to Charge Question 3

Peer Reviewers: 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.

> **EPA Response:** In the Introduction to Chapter 4, the document states that, "These iterations are performed to enhance, but not effectively delay, the final assessment." Words such as "critical" or "important" have been deleted or rephrased where possible to allow for greater flexibility. Additional examples have been added to some of the questions, and more examples have been added to the text where appropriate. EPA acknowledges that it would be useful to develop guidance and case studies in the future.

Key Responses to Charge Question 4

Peer Reviewers: 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.

> **EPA Response:** Additional suggestions of team members representing the multidisciplinary effort of experts in children's risk have been added to Section 3.1 as suggested by the peer reviewers.

Peer Reviewers: 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.

> **EPA Response:** This statement has been revised to: "Input from the relevant risk managers may be needed on the scope of the conceptual model and analysis plan, particularly with respect to the questions the assessment is meant to answer." (Note: consensus is no longer a part of the passage.)

Key Responses to Charge Question 5

Peer Reviewers: One disadvantage to the lifestage approach is that it is not clear when the risk assessor should stop; this should be addressed with subsequent guidance.

> **EPA Response:** In the Introduction to Chapter 4, the document states that, "These iterations are performed to enhance, but not effectively delay, the final assessment." EPA acknowledges that future guidance can provide more explicit illustrations as to how the process can be streamlined in a systematic manner.

Peer Reviewers: 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.

> **EPA Response:** Section 4.1.3.1.2 discusses rigor (the degree of proper conduct) that is included in the analyzed studies. "It can be difficult to determine rigor because in some cases, study methods presented in published studies lack sufficient detail. Additionally, rigor is not simply equivalent to conduct under GLP regulations for nonclinical laboratory studies (U.S. FDA, 1978). Many older studies showing early-lifestage sensitivity to carcinogens were rigorously conducted, but before the GLP regulations were first published in 1978; similarly, many rigorous studies in academic institutions do not follow GLP regulations." A question in Table 4-1 states: "Were lifestage-specific studies conducted with appropriate quality laboratory practices and standards (e.g., Good Laboratory Practice) (U.S. FDA, 1978)?" EPA agrees that GLP studies should be given consideration in WOE but that other findings should be considered as well.

Key Responses to Charge Question 6

Peer Reviewers: Discuss how data gaps should be addressed.

> **EPA Response:** Discussion of how data gaps could be addressed is included in the uncertainty analysis of the hazard assessment (Section 4.1.4) as well as in the risk characterization (Chapter 5).

Peer Reviewers: Add an example of how a chemical's mode of action (MOA) differs across lifestages.

> **EPA Response:** The suggested examples were included in the text in Section 4.1.2.7, "For example, diethylstilbestrol (DES) produces reproductive developmental and carcinogenic outcomes after *in utero* exposure which are not observed following adult exposure (Herbst, 1987; Mericskay et al., 2005; Robboy et al., 1982). Also, organophosphorous pesticides inhibit cholinesterase throughout one's lifespan, but certain of these pesticide's inhibitory effects on neuronal differentiation and migration, which are attributed to an alternative, noncholinergic MOA, occur only during *in utero* and early postnatal neurological development (Campbell et al., 1997; Chakraborti et al., 1993; Dam et al., 1998; Young et al., 2005). However, chemicals with more than one MOA, such as methoxychlor, have been described (Chapin et al., 1997; Gaido et al., 2000; Gray et al., 1999). Therefore, it is possible that the activity of the different MOAs may vary across lifestages."

Peer Reviewers: Develop a comprehensive resource index that is periodically updated.

> **EPA Response:** The resource appendix, while a great idea, is not included in the revised Framework. This could be a future activity.

Peer Reviewers: Be certain to also include adults in the risk assessments so their susceptibilities

can be compared to those of immature age groups.

> **EPA Response:** Adults are a lifestage and are considered using this Framework and in scoping of the problem. Additional questions were added, including in Table 4-1, "Were lifestage-specific outcomes assessed in the study (e.g., different outcomes during different developmental stages versus adult stages)?" and in Section 5.1.6, "Were adults considered to be more or less sensitive than other lifestages?"

Peer Reviewers: Add more lifestage-specific considerations.

> **EPA Response:** Examples and questions are included to provide more clear lifestage-specific context to issues for consideration throughout all sections of the document.

Peer Reviewers: Include succinct examples or case studies of specific chemicals.

> **EPA Response:** Case-specific examples have been included in the revised text of problem formulation, analysis, and risk characterization. EPA acknowledges the peer reviewers' stated need for development of guidance and case studies.

Key Responses to Charge Question 7

Peer Reviewers: 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

Peer Reviewers: Incorporate simple illustrations of the utilization of iteration within the lifestage approach.

> **EPA Response:** The discussion of iteration has been consolidated into each narrative section of the analysis phase prior to the description of the narrative for hazard, dose-response, and exposure characterization (Sections 4.1.5, 4.2.9, and 4.3.8).

Peer Reviewers: Avoid over-iteration, which can be excessive and lead to an unnecessary slowing of the assessment.

> **EPA Response:** In the Introduction to Chapter 4, the document states that "These iterations are performed to enhance, but not effectively delay, the final assessment."

Peer Reviewers: Clarify the role of problem formulation in the scoping of the analytical components.

> **EPA Response:** The prose that was dispersed across Chapter 4 regarding scoping has

been consolidated into the problem formulation section (Chapter 3). In the analysis step, scoping is now referred to only in the context of the problem formulation.

Key Responses to Charge Question 9

Peer Reviewers: 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 lifestage 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.

> **EPA Response:** Statements in Risk Characterization include in Section 5.1.4.3, "Critical data gaps, defined by the impact they have on the risk assessment, are identified and described. These critical data gaps may require consideration and application of uncertainty factors (e.g., database UF). In addition, uncertainty of critical data gaps may suggest further studies that may provide new information or insight to reduce uncertainties in a future risk assessment."
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> In Section 5.1.7, "The characterization of risk in many cases reveals lifestage-specific data gaps, but not all of these data gaps may translate into critical research needs. Research needs may be based upon qualitative or quantitative considerations in the database and the prioritization of research needs helps determine whether specific new data could potentially reduce uncertainty in the assessment."
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> Also, in the analysis plan (Section 3.3.), "For example, if the problem formulation suggests that infants have a potentially high risk due to biological susceptibility or probability of increased exposure, then absence of data for that lifestage may affect the relevancy of the risk assessment to address the identified problem or question of the assessment."
>
> EPA acknowledges that development of guidance and case studies would be useful next steps.

Peer Reviewers: Streamline the document to focus on lifestage-specific issues and decision points.

> **EPA Response:** The revised text reflects the reduced amount of basic and generic risk assessment information and is more explicit in lifestage-specific considerations and examples for specific decision points.

Peer Reviewers: Provide strategies that assist the analyst in identifying tools and databases to assess lifestage-specific issues.

EPA Response: Additional references, footnotes, and hyperlinks are provided throughout the document where tools and databases are available.

Peer Reviewers: Use brief examples to bring more of the concepts to life.

EPA Response: More lifestage-specific examples are included throughout the document.

Key Responses to Charge Question 10

Peer Reviewers: 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 needs 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.

EPA Response: These suggestions will be considered as next steps in developing both a short-term and longer-term agenda for follow-up activities to this Framework. The resource appendix, while a great idea, is not included in the revised Framework. This could be a future activity. The Executive Summary and Chapter 6 cite a number of additional areas for the development of potential future guidance. The *Child-Specific Exposure Factors Handbook* (Interim Report) has been updated and the External Review Draft will be released for review and comment very soon.

Response to Public Comments

The American Chemistry Council (ACC)

ACC: The tiered approach of Voluntary Children's Chemical Evaluation Program (VCCEP) should be integrated into the Draft Framework.

> **EPA Response:** The document describes scoping and screening level analysis in the assessment. The Framework does not describe tiered testing and is not intended to be guidance for tiered testing. The principles of tiered evaluation are included in the Framework. Many individuals who participated in VCCEP were authors and reviewers of this Framework, and they did not recommend integration of the VCCEP citations specifically mentioned by ACC as being relevant to this risk assessment Framework.

ACC: Data gaps are not necessarily data needs.

> **EPA Response:** The document specifically addresses the point that not all data gaps are necessarily critical data needs and describes ways that variability, uncertainty, and sensitivity analyses can inform and help prioritize data needs.

ACC: VCCEP-related publications on exposure assessment and VCCEP experiences with exposure assessment should be integrated into the Framework.

> **EPA Response:** VCCEP is a testing program and this Framework is a conceptual overview for evaluation and risk assessment. The VCEEP program is currently a pilot program of eight chemicals that have only proceeded through tier one of testing. The pilot program's success to this point has not been fully evaluated, an issue that has been raised by peer reviewers and by others (e.g., EPA's Office of Children's Health Protection's Federal Advisory Committee). Triggering of additional studies (e.g., tier 2 and 3 testing) also cannot be evaluated at this time because the pilot program has not yet proceeded that far. With these considerations in mind, EPA does not believe the commenter's suggestions are of direct relevance to this Framework.
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> **Peer Reviewers' Response:** 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 commented that they 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.

ACC: Children are not always more vulnerable to chemical exposures than adults.

> **EPA Response:** The revised draft clarified this point in the document. Adults are a lifestage that may be considered when using this Framework and in scoping of the problem. In the Executive Summary, the document now states, "Children may be more

or less vulnerable than adults but without data on exposure and response, and systematic evaluation of these data, it is a challenge to determine which lifestage may be more vulnerable." Additional questions were added, including in Table 4-1, "Were lifestage-specific outcomes assessed in the study (e.g., different outcomes during different developmental stages versus adult stages)?" and in Section 5.1.6, "Were adults considered to be more or less sensitive than other lifestages?"

Peer Reviewers' Response: The peer reviewers did not think that the Framework document said that children are more vulnerable than adults, simply that they might be. 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."

EPA Response to Peer Reviewers' Response: The following statement was added to the Executive Summary, "Children may be more or less vulnerable than adults, but without data on exposure and response and without systematic evaluation of these data, determining which lifestage may be more vulnerable is challenging."

ACC: Clarification of lifestages covered is needed - why is lifestage analysis being carried out past the first two years of life (paraphrase)?

EPA Response: EPA states in the Introduction: "The term "children" as used in this document is shorthand to include the stages of development from conception through adolescence. EPA is concerned about health risks that result from exposure to all lifestages; however, this document focuses on exposures during preconception through adolescence. "Developmental exposure," as used in this document, means developmental lifestage exposures (preconception through adolescence). Health risks may be identified during the same lifestage as when the exposure occurred, or they may not become apparent until much later in life." EPA acknowledges in the Framework that development does not stop after the first two years of life and that expression of adverse outcomes may occur much later in life after early exposure during critical windows of exposure.

Peer Reviewers' Response: The peer reviewers agreed that the Framework document clearly stated which lifestages 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.

ACC: Limitations of EPA's *Supplemental Guidance for Assessing Cancer Susceptibility for Early-Life Exposures* should be more explicit.

EPA Response: Limitation of this guidance to a mutagenic MOA is discussed in the

dose-response section.

Peer Reviewers' Response: 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.

ACC: Weight-of-evidence discussion should address GLP and validation.

EPA Response: Section 4.1.3.1.2 discusses rigor (the degree of proper conduct) that is included in the analyzed studies, and a question in Table 4-1 states, "Were lifestage-specific studies conducted with appropriate quality laboratory practices and standards (e.g., GLP) (U.S. FDA, 1978)?" EPA agrees that GLP studies should be given consideration in WOE but that other peer reviewed findings should be considered as well. This Framework is not intended to provide guidance for evaluation of validated tests or test methods. The WOE analysis would include validated tests as well as considerations of peer reviewed data.

Peer Reviewers' Response: 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 lifestages not covered in the GLP study, those non-GLP studies should be considered and not weighted less than a GLP study. "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."

The Center for Regulatory Effectiveness (CRE)

CRE: Pre-dissemination review and other Information Quality Act requirements and Office of Management and Budget (OMB) peer review bulletin.

EPA Response: Consistent with OMB's Final Information Quality Bulletin for Peer Review (Peer Review Bulletin), *A Framework for Assessing Health Risks of Environmental Exposure to Children* is included in EPA's Peer Review Agenda as influential scientific information. Accordingly, EPA developed a peer review plan for

this effort prior to the release of the external peer review document. Although there were some minor technical difficulties initially, the draft Framework document and the peer review plan were posted on the Agency's Peer Review Agenda Web site. Some of the components of EPA's peer review plan for the draft Framework document included:

- Public availability of the external review draft Framework and peer review plan on the Agency's Peer Review Agenda Web site, including a 2 week opportunity for public comment on the peer review plan
- A 45-day public comment period on the external review draft document announced in the Federal Register
- Public notice in the Federal Register of an independent external peer review meeting, including instructions for public participation at that meeting
- A charge to the independent peer review panelist that included public comments received on the draft Framework
- An independent external peer review, including a public meeting with additional opportunity for public comment

EPA's Information Quality Guidelines reflect our commitment to providing public access to environmental information and ensuring and maximizing the quality of the information we disseminate. The Guidelines are non-binding policy and procedural guidance and are not intended to impose legally binding requirements or obligations on EPA or the public. The certification provisions of OMB's Peer Review Bulletin apply to regulatory actions. This Framework is not a regulatory action. The Framework has been developed in accordance with the information quality principles identified in EPA's Information Quality Guidelines and OMB's Peer Review Bulletin.

Peer Reviewers' Response: Mr. 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. The peer reviewers did not think it was within their purview to discuss the "appropriate" review process since the process 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.

Tetra Tech EM, Inc. (TT)

TT: 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? …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.

> **EPA Response:** EPA will consider this in development of follow-up activities including development of potential guidance.

TT: It would be helpful to include a few examples of how the children's risk assessment framework/process can be applied to different scales of problems.

> **EPA Response:** EPA acknowledges the need for future case studies.

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

> **EPA Response:** Every organ system's temporal development are different. Exposure during a critical lifestage is a temporal period related to physiology, behavior, and development. Therefore, the suggestion to define lifestages based on the timing of specific biochemical parameters alone is not feasible.

TT: 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, lifestage of susceptibility, exposure factors for children, and age binning for exposures) for specific lifestages in the uncertainty discussion….A risk assessor may potentially find it difficult 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….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?

> **EPA Response:** Discussion of how data gaps could be addressed are included in the uncertainty analysis of the hazard assessment (Section 4.1.4) as well as in the risk characterization (Chapter 5).

TT: How uncertainty and variability will in-practice affect the results of the risk characterization could be discussed in more detail.

> **EPA Response:** Statements in Risk Characterization include, "Critical data gaps, defined by the impact they have on the risk assessment, are identified and described. These

critical data gaps may require consideration and application of uncertainty factors (e.g., database UF). In addition, uncertainty or critical data gaps may suggest further studies that may provide new information or insight to reduce uncertainties in a future risk assessment."

"The characterization of risk in many cases reveals lifestage-specific data gaps, but not all of these data gaps may translate into critical research needs. Research needs may be based upon qualitative or quantitative considerations in the database and the prioritization of research needs helps determine whether specific new data could potentially reduce uncertainty in the assessment."

Also, in the analysis plan (Section 3.3.) "For example, if the problem formulation suggests that infants have a potentially high risk due to biological susceptibility or probability of increased exposure, then absence of data for that lifestage may affect the relevancy of the risk assessment to address the identified problem or question of the assessment."

TT: 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 differences for the various lifestages. 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 (Lifestage-Specific Population Characteristics).

EPA Response: The section on Lifestage-Specific Exposure Factors (Section 4.3.2.4), previously titled Life Stage-Specific Population Characteristics, incorporates these comments.

TT: 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 that would be potential users of the children's health risk assessment framework.

EPA Response: EPA will consider the need for future case studies and Web-based training tools in follow-up activities to the Framework.

Peer Reviewers' Response: 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 specific comments for EPA to address.

The Department of Defense (DOD)

DOD: 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?

EPA Response: The comments numbered 1-6 are outside of the scope of this Framework.

DOD: The EPA might apply the Framework to two or more environmental chemical case studies using probabilistic risk assessment techniques where applicable.

EPA Response: Case studies are proposed in our next steps and have been suggested by others.

DOD: Lifestages 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.

EPA Response: The suggestion to define lifestages based on the timing of specific biochemical parameters alone is not a complete approach for considering children's vulnerability. It ignores the physiological parameters and behaviors that influence children's exposures. For example, children drink more, eat more, and breathe more per kg/body weight than adults. Every organ system's temporal development is different. Exposure during a critical lifestage is a temporal period related to physiology, behavior, and development. The approach taken in the document on age binning (Section 3.2.1) is to consider critical windows of development as well as physiological and behavioral factors that influence developmental exposure.

Peer Reviewers' Response: 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 lifestage or an exposure bin.

DOD: 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.

EPA Response: The term "children" as used in this document is shorthand to include the stages of development from conception through adolescence.

Critical windows of exposure for children are defined in Chapter 2: "Preconception is any time before conception; the prenatal stage includes the embryonic and fetal stages from conception to birth; infancy is the period from birth through the first birthday; child encompasses all early postnatal lifestages from birth until adolescence, which occurs approximately between 12 and 21 years of age (with difference between genders). The continuum between the reproductive-age adult and aged adult begins at approximately 21 years of age and reaches aged adulthood at approximately 65 years. Broad exposure interval categories (e.g., child) are shown here for illustration, and divisions between lifestages are not precise (e.g., there is some reproductive age overlap between the adolescent and the adult periods) (U.S. EPA, 2005f, 2002b, Table 3-1)."

An additional note in regard to what other researchers have used as nomenclature and shorthand is that the National Children's Study uses similar terminology in its reference to developmental stages of vulnerability.

Peer Reviewers' Response: 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.

DOD: 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.

EPA Response: All of EPA's regulatory programs are intended to benefit from the development of this Framework.

Peer Reviewers' Response: One peer reviewer understood that the Framework document was applicable across all programs within EPA.

DOD: 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.

EPA Response: The application of ADAFs as used in the "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens" is discussed in this Framework.

DOD: The text of these lines suggests that changes in function are necessarily adverse.

EPA Response: Chemical-induced changes in outcomes and biological events are evaluated in the WOE considerations of the hazard characterization (Section 4.1.3).

Peer Reviewers' Response: One reviewer suggested removing this sentence because it is unknown what the early lifestage 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.

DOD: Comment: Page 57, 4.3.1 Reword this to state, "It is important to involve stakeholders at this point in the assessment to ensure their concerns are addressed." 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.

EPA Response: EPA has augmented the discussion of stakeholder involvement and included specific references to stakeholder involvement described in greater detail in the Framework for Cumulative Risk Assessment (U.S. EPA, 2003a).

DOD: The importance of chemical form used in studies is not mentioned. The importance of chemical bioavailability is not mentioned.

EPA Response: EPA has discussed bioavailability in the section Chemical Properties, Environmental Sources, Fate, and Transport (Section 4.3.2.1).

DOD: Page 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.

EPA Response: EPA uses the term "outcome" in the document to refer to adverse health outcome.