# Peer Review of the Draft Document Entitled
## *Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants*

**Prepared for:**
Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

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**Chair's Executive Summary**

**Executive Summary**:

INTRODUCTION

The U. S. EPA is to be commended for developing a framework for assessing childhood exposures.  This guidance document represents a significant, timely effort by the agency to highlight the importance of considering physiological changes and behavioral changes that occur during development and which define what, how, how much and when environmental exposures can occur during childhood.  This document has great potential to serve as a consistent starting point for program-specific risk assessments however as written will require additional context and clarification. The proposed guidelines should facilitate much-needed cross-program consistency in risk assessments, particularly for the youngest age levels where susceptibility is likely to be greatest.

Most of the reviewers of the document asked the agency to provide additional clarification of the purpose of this document by giving a greater emphasis to its context and rationale. Several reviewers suggested that a conceptual framework was needed in the introduction to provide context for the purpose and scope of this new guidance within the agency and to relate this new guidance with relevant existing guidance and technical reports.  Clarification of the intended audience was also requested.

Regarding the workshop reports, many reviewers felt it was essential that the document include considerations of prenatal exposure.  Excellent rationale for inclusion of this developmental period was cited by reviewers and was based on the workshop recommendations, current research and published literature.

Reviewers identified other recommendations from the workshops that needed to be included in this guidance document. These included consideration of prematurity and gender. Some reviewers recommended more discussion of the potential for multiple or combined exposures. Several reviewers also encouraged the agency to not forget special population considerations such as ethnic and cultural variability (for example consideration for Native American populations). The reviewers noted that the document was also relatively silent on demographic, socioeconomic, geographic and seasonal effects on exposure and risk.

Although the guidance document provided options and flexibility to the user many reviewers felt that more information was needed.  The document had a lack of details, especially as it related to approaches for dealing with data insufficiency, criteria for prioritization of critical data needs and sufficiency of data to propose alternatives to the default age group factors.

Reviewers noted an overall lack of references and suggested increased use of citations and links to useful and relevant websites both within and outside the agency.  Reviewers also requested new tables and figures (including figure legends) that would more clearly highlight key points.

In summary, the reviewers were highly encouraging to EPA in their refinement of this important guidance. Their reviews were very constructive and provided specific suggestions in their advice for clarifying and providing context for this new document.

RESPONSE TO CHARGE QUESTIONS

*1. Please comment on whether the guidance appropriately reflects the recommendations of these expert deliberations and whether the process of selecting the age groupings is adequately described?*

Reviewers applauded the Agency for including multiple bins during the first years of life and for acting on most of the Workshop recommendations. However, most of the reviewers requested additional clarification of the rationale for selection of the age grouping and rationale for not including others.

One reviewer noted that the issue of grouping age groups for exposure was confused with binning of data used in exposure assessment and emphasized that these concepts needed to be well defined and carefully introduced. They further noted that the guidance document repeatedly stated that standardizing the age groupings would improve risk assessments, but the reasoning behind that assertion was poorly articulated.

Reviewers noted that it was essential for the document to provide the risk analyst with guidance on how to prioritize specific age groups for detailed analysis. These reviewers suggested that if such advice could be brought into the current framework, then the value of the guidance to children's risk assessment would be significantly enhanced.

For example, one reviewer noted that as discussed at the Workshop, the early postnatal period is characterized by rapid growth and development in many systems (nervous, renal, respiratory, GI), changes in skin permeability and the ratio of skin surface area/body weight, and increases in metabolic capabilities. For these reasons, the neonatal period has been estimated to be more different than any another age group (childhood through adult) in terms of physiologic development (1). The differences are likely to affect both exposure and susceptibility, and, therefore, multiple age bins during this early period are warranted. Studies have indicated that certain exposures can also be appreciably higher during the preschooler years (ages 1-3) than later in life, and, thus, separate age bins during these years are also appropriate.

Reviewers stated that current statements justifying age grouping were too general and uninformative and that as currently written the document did not provide adequate justification or reference to other documents which provide justification. The document should, at a minimum, "show some of the key data that distinguishes one age group from another."

Reviewers suggested that the document clarify at the beginning of the guidance that the groupings are based upon exposure pathways only, with toxicodynamic factors not taken

into consideration. Thus, if a particular age group is of special concern due to vulnerability, this window may need to be evaluated even if the current age group framework does not specify that age group.

Reviewers did identify several areas of significant differences from workshop recommendations. One of these was the failure of the document to include consideration of the prenatal exposure period. The significance of this omission was reflected in specific comments by numerous reviewers and was a key focus of two of our telephone conversations. Note that several reviewers provided excellent detailed discussions with examples why consideration of exposures during the gestational period are essential.

Several reviewers also noted that the guidance differed from the workshop recommendations on issues of "prematurity" and their relationship to age categories. Reviewer felt this recommendation needed to be addressed in the document. Reviewers noted that the decision to start the age bins at birth without consideration of the timing of birth was contrary to Workshop recommendations. Panelists at the Workshop recommended that premature babies represent a special subpopulation, and suggested that an age bin for premature infants could go up to the expected date of delivery.

Reviewers also noted that the discussion on breastfeeding should be expanded to include workshop recommendations to consider exposures to lipophilic compounds and also nonlipophilic substances.

Reviewers identified other places where the guidance document varied from the workshop reports. The behavior workgroup initially lumped children between birth and <3 months rather than dividing it into two groups as in the guidance document. In addition, the behavior workgroup *had combined children from 2 to <6 years* rather than subdividing it into 2 to <3 and 3 to <6 years. In addition the behavior work group combined children between 16 to < 18 years and 18 to < 21 years. Reviewers noted that it was unclear from the guidance document why these are separated, since the two teen-aged groups were not recommended by either workshop group. Reviewers varied in their suggestions for the age groups > 6 years. Reviewers with physiological training requested that additional age bins be evaluated for this time period due to the multitude of dramatic physiological and behavioral changes that occur in this period.

Reviewers noted that gender specific differences were not addressed in the guidance document although they were discussed during the workshop and in the Child-specific Exposure Factors Handbook.

Reviewers went on to note that it would be helpful to have the current document develop criteria for evaluating age group heterogeneity based upon the information provided in prior documents and elsewhere. Reviewers felt that it was not feasible for the current guidance to provide a statistical evaluation of variability within the proposed age groups, then this could be mentioned as a data gap, and the document should be clear that the groupings are based upon a process that involves mostly qualitative judgment.

A reviewer noted that at the workshop, both the physiologic and behavior sub-groups raised concerns with attempts to create age bins based on either behavioral or physiologic changes which are continuous variables with sometimes very different age distributions. In addition, the workshop participants emphasized that the agency should not consider the age bins as discrete entities, but that each bin was based on underlying distributions, and that the distributions were driven by a range of behavioral and anatomical developmental factors, and were effected by gender. The guidance document needs to discus these points.

Reviewers encouraged the Agency not to neglect the philosophy expressed during the EPA Risk Assessment Forum of July 2000 where the ideal situation for considering development was discussed as a continuum of exposure values. Since age groupings must be considered, then this reviewer emphasizes that the principles for binning should express representative and relevant metrics for all the individuals grouped within each bin, and the binning process should not mask any truly unique profile within the bin ("don't hide the significant peak"). To further clarify this approach another reviewer suggested that in a "discussion of the possible need to combine groups and determination of representativeness of such recombinations", a tiered approach for flexibility in age "binning" could be warranted.

**2.** *Section 2 of the guidance concludes by presenting three recommended points for discussion by the assessor when combining or eliminating age groups in a particular exposure assessment. These points include: (1) the basis for the determination; (2) description of uncertainties and biases; and (3) discussion of the types of data and information, if available, which would allow combined groups to be separated in future analyses. Please comment on:*
1. *Whether the guidance adequately reflects the need for flexibility in using these age groupings?*
2. *What more specific guidance regarding application of the 3 points identified above might be provided to risk assessors; for example, discussions of statistical considerations, or temporal and interindividual variability?*
3. *Are there additional points beyond the 3 identified that should be highlighted in making the decision to use an age grouping for a particular exposure scenario and data set?*

A. The majority of reviewers felt that the guidance adequately reflected the need for flexibility in using the age groupings and that this was an important aspect of the report. However most, asked for additional guidelines and criteria when no data or very little data was available.

Reviewers suggested that adding some examples with references would be useful for demonstrating how to be flexible without completely ignoring the recommended age groups.

This opinion was not unanimous and some reviewers felt that the discussion of the need for flexibility in using the age groupings was minimal and needed to be expanded.

One reviewer noted that there was more space spent discussing the three points for justifying combining or eliminated age groups in an exposure/risk assessment than in actually discussing the need for flexibility.

The document should stress the lack of information for many parameter values.

B. Several reviewers felt that the advice for combining age groups was inconsistent and vague. One reviewer suggested that the guidance should provide a tiered approach for organizing/evaluating age group-specific data and then prioritizing age groups for subsequent more detailed analysis. In particular, a 3 phase approach to using these age groups was suggested with a data gathering and organizing step, a prioritization stage for identifying age groups and a third phase only for detailed analysis. Many reviewers on the conference call echoed support for such an approach.

Reviewers made specific recommendations for how to improve this section however a majority identified the lack of data as the critical impediment in making the decisions regarding combining or eliminating age groups and felt that the guidance document needed to provide additional guidance.

Reviewers noted that it was essential that those using the age categories have a good understanding of the distributions, uncertainties, and potential conflicting data that are imbedded in the age categories. They felt that the current document does not provide such information as it is currently written however it could be improved by either providing supporting documentation and/or references in the guidance document. At present the documentation is inadequate.

C. Without additional guidance reviewers felt that assessors may "omit age groups or exposure factors associated with specific age groups for lack of data rather evaluating the uncertainties associated with data issues. Reviewers felt there was a need to be an evaluation of the impact of this course of action on exposure assessments.

Reviewers also felt that the guidance document should expand upon the introduction to explain the rationale used by the different program offices to select specific age groups for their assessments. Without that information this reviewer can make no recommendation at this time regarding any additional points to be considered in making age-grouping decisions

Reviewers also recommended expanding the discussion of inter-individual variability.

Reviewers felt that the guidance captured the recommendations from the Workshop regarding the importance of exposure assessors working together with toxicologists and other health scientists.

*3   Section 3 of the guidance contains recommendations for a set of critical exposure factors pertaining to further analysis and research. Subject to EPA approval and finalization of this guidance, the Agency anticipates re-compiling its Child-Specific Exposure Factors Handbook – Interim Final Report ( EPA-6006P-00-002B, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145 ).  As a preliminary exercise along these lines, the guidance includes recommendations for further analysis/research on child specific exposure factors.  Please comment on:*
A.  *The accuracy of the statements about our current knowledge regarding each of these exposure factors.*
B.  *The priorities and recommendations for further data collection activities (Table E-3 in Guidance document).*
C.  *Whether any critical exposure factors have been overlooked in these recommendations?*
D.  *Whether there are any additional or developing sources of information that could be used to improve or fill exposure factors data gaps related to the recommended set of age groupings.*

A.  In general, most reviewers felt that the guidance document did an excellent job of summarizing both the availability and lack of availability of exposure factors data as compiled by the Risk Assessment Forum Technical Issue Paper (Age Group Recommendations for Assessing Childhood Exposure and the Adequacy of Existing Exposure Factors Data for Children). Reviewers identified numerous individual investigator as well as multi-investigator center grantees that were generating relevant new data for children's exposures.

From a "guidance" perspective, it appeared to several reviewers that some of the information from the reports was not addressed in this document.  Reviewers noted that the guidance document should address the importance of using NHANES III data to update age-specific exposure factors.  The 2001 issue paper cautioned against using outdated information such as the use of the two-decade old NHANES II data to derive total body surface area values for current age groups. For example, one reviewer noted that there has been an upward shift in the prevalence of obesity among children and adolescents such that age-specific total surface area values based on NHANES II data would not be representative of the current populations.

B.  In general, reviewers agreed with the document recommendations for further data analysis and collection.  They supported this priority as such data analysis could be done immediately and that they would be substantially cheaper to implement than new data collection studies.  Further, the reviewers suggested that these approaches should provide a great deal of useful information in the short term.  However, reviewers also noted that funding should be allocated to fill in the gaps in the data as well. For example, soil ingestion rates for children in the age groups suggested are very poorly known at present. This was true whether the child is a normal child or suffers from pica.  The reviewers suggested that the information required for such studies would be substantially more

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detailed and stratified than earlier studies and this could suggest a costly data collection procedure.

Reviewers also noted that some studies suggest that American Indian and Alaska Native children may have a higher proportion of fat-free mass than the national reference standards and that such information needs to be included in the guidance document.

Reviewers felt that Table E-3 provided a compelling list of future research needs. However they also noted that there were two ongoing initiatives that may help to fill some of these data gaps. Specifically, the Chemical Working Group of the National Children's Study is currently preparing a white paper on techniques for assessing childhood exposures to support the National Longitudinal Cohort Study. Reviewers also identified 12 NIEHS/EPA-funded Children's Environmental Health Centers which are currently collectively preparing a series of manuscripts summarizing the lessons learned through their longitudinal cohort studies, including *in utero* and childhood exposures.

Reviewers noted that almost all of the recommendations were discussed and utilized in the document and nine broad categories of exposure factors were listed in the guidance document as needing further analysis and research. They also note however that one recommendation was not included from the Child-specific Exposure Factors Handbook and that is regarding consumer products. Inadequate justification is given in the guidance why this recommendation was dropped.

Reviewers noted that the document was uneven in detail in the justification for data needs. Reviewers highlighted that the document recommendation for data needs focused on activity patterns for children 'less than 4 years and children aged 11 years and older, however the document did not provide details on whether there was adequate data on children 5-10 years old?

C. Reviewers noted that one of the recommendations from the workshop was for research into lipophilic and nonlipophilic substances in breast milk however this was not discussed in the guidance document. Reviewers also emphasized the need for information on consumption of fish and ethnic foods for children.

Reviewers felt that the section on soil ingestion needed to specifically include house dust ingestion and that the guidance should address the effects of dermal reloading on exposure.

Each of the reviewers identified many additional specific studies for the document and these need to be pulled into the document. In addition, reviewers also encouraged further analysis of specific existing datasets, e.g., CSFII, NHANES, etc. Many of the studies identified by the reviewers included EPA STAR program grants and the Children's Environmental Health Centers.

**4.** *Section 4 of the guidance is intended to alert assessors to uncertainties and biases that can be introduced through the use of models, time weighted doses and the like. Please comment on the utility of this discussion and what additional points, if any, should be highlighted.*

Reviewers suggested a more complete discussion on the temporal variation in exposures among the different age groups. They suggested that this is a very difficult but important problem to tackle, especially when exposures are episodic and highly variable

The reviewers agreed with EPA in their encouragement to exposure assessors to develop a full understanding of the model constructs, including uncertainties and biases and to risk assessors who needed to be encouraged to develop an understanding of the biologic phenomena.

Most of the reviewers made suggestions for calibrating and validating the models. They requested better citations and documentation. Reviewers suggested that the document needs to capture the recommendations from the Workshops that models be validated using direct measures, including measures of both exposure and biomarkers. Reviewers also felt that additional details were needed in this section. For example, the document frequently "raises the question but the solution to the problem is not clearly laid out." Critical details on the models mentioned in this section are needed including how each of the models differs, what algorithms are used, and what probabilistic sampling functions are used. Clarity of uncertainty and inter individual variability is needed in the text. Some of these issues (relevance of long-term chronic dose vs. short-term acute dose to toxic mechanism and window of susceptibility) are pertinent to prioritization of age groups for detailed analysis and for informing the option of condensing age groups.

CORRECTIONS

Reviewers have provided detailed notes on corrections that are needed throughout this report. For example, reviewers have provided corrections for discussion of LifeLine which are needed to correct modeling discussion, metrics, and databases.

DEFINITIONS

Reviewers recommend that the agency improve consistency in use and definition of abbreviations. Abbreviations should be defined when they are first used in document.

The beginning of the document needs to clearly define "behavior related" and "physiology related".

REFERENCES

Reviewers have provided an extensive list of additional references that should be added to the document. They also recommended that references reported in the text need to be properly presented and cited in the reference section.

FIGURES AND TABLES

Overall the reviewers recommended that the report needed to develop graphics and figures that would clarify the important points rather than confuse the reader. Improved quality of graphics was also suggested. Numerous reviewers made specific suggestions for the types of figures they would like to see in the document. These included figures emphasizing the physiological changes as well as those providing more detail on exposure considerations.

Reviewers suggested that figures and/or graphs could be used to show relationships of exposure and effect susceptibility across life stages. The majority of reviewers felt that the titles and figure legends for the figures should be greatly expanded and improved. Several reviewers felt that for clarity the figures and tables should "stand alone" and be understandable without the text.

**Review by**
**Timothy J. Buckley, Ph.D.**

Review of EPA/630/P-03/003A, "Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants"

General Impressions

The stated purpose of the document is to "provide guidance to EPA scientists on the appropriate age groups to consider when assessing childhood exposure and potential dose to environmental contaminants." This is potentially a unique and important document identifying age resolved assessment of behavioral and physiologic factors that alter the pattern, magnitude, and/or route of exposure to chemical environmental hazards. The report identifies four age groups prior to one year of age (birth to <1 month, 1 to <3 months, 3 to < 6 months, and 6 to < 12 months) and another 7 age groups (1 to <2 years, 2 to < 3 years, 3 to < 6 years, 6 to < 11 years, 11 to < 16 years, 16 to < 18 years, and 18 to < 21 years) from 1 to > 21 years. This is an important goal, however, it is not achieved through the current document due to a number of serious limitations in the current document.

1.        The report lacks a coherent rationale and conceptual framework. The stated rationale (pg iii) of "A consistent set of childhood age groups, supported by an underlying scientific rationale, will improve Agency exposure and risk assessments for children and will assist the Agency in implementing such regulatory initiatives as Presidential Executive Order 13045" is unconvincing. How will children's risk assessment be improved by a consistent set of childhood age groups? The "Guidance on selecting the appropriate age groups . . ." is presented in the absence of a conceptual framework. Such a framework will be particularly valuable as a means to unambiguously define the scope and focus of this report while at the same time establishing its role within a risk assessment context. This framework should clearly define the inter-relationships between key discrete elements of the report (e.g., environmental media, exposure, exposure factors, contact rates, time-activity patterns and behaviors and physiology) in the context of exposure and risk assessment. The current document is ambiguous in its treatment of key concepts including exposure factors, contact rates, and behavior and physiologic determinants of exposure. It should be made clear that the scope of this document is to identify behavioral and physiologic factors that influence time-activity patterns and contact rates which then modify exposure. The report is ambiguous as to the scope of anatomical/physiologic factors. Do the authors mean to include factors that influence both exposure and susceptibility? These are very different concepts which need to be treated separately. Susceptibility to the effects of exposure should be considered in the context of dose-response. Ideally, age dependent changes in both exposure and effect susceptibility will be considered however the concepts and factors should be treated separately. The authors might illustrate this point through a graph where both exposure and effect susceptibility are plotted as a function of age. Lead would be a good example where there is sufficient information to characterize both profiles. An idealized schematic could be used to show how the proposed age categories captures the bulk of the variability in physiology and/or behavior factors that drive the exposure. In general, the report can be strengthened through the use of examples or case studies. The report lacks consideration of the underlying concept forming the rationale

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for this report, i.e., capturing variability in behavior and/or physiology that underlies exposure. Distributions should be used to illustrate the variability in these parameters over age. It should be pointed out that within these distributions are highly exposed subpopulations (e.g., kids with pica). It may be that the mean or median increase in population exposure is driven by subpopulation behaviors (e.g., pica or breast feeding). The report can be strengthened by more effectively taking into account who and how this assessment will be used.

2.      I question the underlying premise to this report that a consistent set of childhood age groups will improve Agency exposure and risk assessment. The "Introduction" suggests that a case-by-case assessment of age specific exposures is problematic. In fact, such assessments ideally would be conducted on a chemical by chemical basis since the behavioral and physiologic determinants are chemical and media specific. There is no defensible scientific rationale for applying the same age groups for an assessment of children's exposure to ozone and chlorpyrifos. Differences in age groups by program (as indicated in Figure 1) in fact are scientifically appropriate when different chemicals in different environmental media are being considered. Such cross-program differences may be problematic only when different age classifications are applied to the same chemicals within the same media. As suggested in the Executive Summary:

> "there may be instances where combining some of these age groups (e.g., combining the first three groups into one representing birth to <6 months) when estimating exposure or potential dose, especially if little variation might be expected. In addition, there may be instances where it is not necessary to address every age group listed above . . ."

Such a recommendation is likely to lead exactly to the outcome identified in Figure 1. Whereas exposure should be considered on a pollutant and media specific basis, behavior and physiology are pollutant independent and should be consistently considered across programs. Is this what the authors intended? If so, a more precise and scientifically justifiable title for this effort would be "Guidance on Selecting Appropriate Age Groups for Assessing Behavioral and Physiologic Determinants of Exposure."

3.      The report's recommendations are largely subjective and unsubstantiated. For example, Tables 1 and 2 that are at the heart of this report, there is not a single reference or quantitative assessment. What are the rates of breast verses bottle feeding and how does this distribution change with age? Why not show the rate of growth and weight gain as a function of age? Is there a break at 1 year as suggested in the Table? On what data did the authors rely for this assessment? Why do Tables 1 and 2 list "examples"? Isn't this analysis the primary outcome of the report? The assessment represented by these tables should be comprehensive, quantitative, and based on published literature. The report's scientific credibility is directly proportional to the extent to which the primary literature underpins its recommendations.

**Response to Charge Questions**

1.      The use of the information presented at the 2000 peer involvement workshop coupled with a subsequent analysis of exposure factors data formed the basis for the subject guidance. Please comment on whether the guidance appropriately reflects the recommendations of these expert deliberations and whether the process of selecting the age groupings is adequately described?

It is difficult to assess how well the current report reflects the recommendations of the expert panel deliberations because I did not participate in the panel.  However, based on a cursory review of the "Summary Report of the Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy when Assessing Exposure to Children" it appears that it, like the current report, provided a qualitative expert opinion on the assessment on the age-dependent influence of behavior and anatomy on environmental exposure.  Based on the title, it appears that the Technical Workshop had a more appropriate focus on behavioral and anatomical determinants of exposure rather than the current documents focus on exposure.

2.      Section 2 of the guidance presents recommended points for discussion by the assessor when combining or eliminating age groups in a particular exposure assessment, including: (i) the basis for the determination; (ii) description of uncertainties and biases; and (iii) discussion of the types of data and information, if available, which would allow combined groups to be separated in future analyses. Please comment on: A. Whether the guidance adequately reflects the need for flexibility in using these age groupings? B. What more specific guidance regarding application of the 3 points identified above might be provided to risk assessors; for example, discussions of statistical considerations, or temporal and interindividual variability?  C.  Are there additional points beyond the 3 identified that should be highlighted in making the decision to use an age grouping for a particular exposure scenario and data set?

As argued above, I disagree with the premise that a standard set of age groups should be defined for assessing childhood exposures to environmental contaminants.  Such assessments should be conducted on a contaminant and media specific basis.  There is a scientific rationale for the common identification and adoption of distributions of behavioral and physiologic factors as determinants of exposure.  It should be the rule that age groups are defined specific to pollutant and media rather the exception.

3.      Section 3 of the guidance contains recommendations for a set of critical exposure factors pertaining to further analysis and research. Subject to EPA approval and finalization of this guidance, the Agency anticipates re-compiling its Child-Specific Exposure Factors Handbook.  As a preliminary exercise along these lines, the guidance includes recommendations for further analysis/research on child specific exposure factors.  Please comment on:

A.  The accuracy of the statements about our current knowledge regarding each of these exposure factors. B. The priorities and recommendations for further data collection

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activities (Table E-3 in Guidance document). C.  Whether any critical exposure factors have been overlooked in these recommendations? D.  Whether there are any additional or developing sources of information that could be used to improve or fill exposure factors data gaps related to the recommended set of age groupings?

Section 3 does not describe our current knowledge regarding exposure factors but rather reiterates previously specified definitions of pathway specific potential dose and identifies exposure factor research gaps.  The Technical Issue Paper "Age Group Recommendations for Assessing Childhood . . ." prepared by Versar, Inc. appears to be much more comprehensive in this regard.

Table E-3 provides a reasonable cursory summary of the exposure factors research gaps. The authors might consider an additional category related to breast milk because of its importance for infant intake of environmental chemicals.  Soil ingestion should be expanded to include "house dust".

4.      Section 4 of the guidance is intended to alert assessors to uncertainties and biases that can be introduced through the use of models, time weighted doses and the like. Please comment on the utility of this discussion and what additional points, if any, should be highlighted.

Section 4 is important in describing state-of-the-art models and modeling approaches that integrate distribution estimates of environmental concentrations, time-activity patterns, and exposure factors to arrive at an estimate of aggregate or cumulative exposure.  These modeling approaches are useful in defining the parameters and distributions that are necessary for estimating exposure.  Furthermore, through such models research gaps quickly come into focus.  As written, this section has little to do with identifying "uncertainties and biases that can be introduced through the use of models."  This section can be more effectively developed to serve the purpose of: 1) introducing state-of-the-art modeling approaches; 2) using these models to show how and where human behavior and physiology fits into cumulative exposure assessment and their importance (e.g., sensitivity analysis); 3) demonstrating the effect that different age groupings has on estimates of exposure.

**Specific Observations**

1.      Table E-2 can be strengthened by including a category something like "exposure relevance" to describe the implications of behavior and physiology.  For example, for the birth to < 1 month category, this category might describe that infants are vulnerable to high levels of chemicals in human such as PCBs and PBDEs.

2.      Pg 4.  The need to include prenatal development in this assessment can be high-lighted by including it within the conceptual model.  Because of its importance, the authors need to provide a more compelling justification for its exclusion from this report other than "was outside the scope of the workshop discussions".  It should be

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acknowledged as a critically important interval of human exposure due to the vulnerability of the developing fetus.

3.       Presentation of "Examples of Characteristics . . . " in Table E2 within the "Executive Summary is weak.  This portion of the report should contain a summary of the most important elements of the report.  This table should be removed from the Executive Summary or enhanced to identify "Primary age-dependent exposure determinants".

**Review by**
**Christine F. Chaisson, Ph.D.**

Re: Executive Summary and Introduction:

General Concepts

**Issue**: The justification for why this project exists and why guidance is needed.
- The overall topic and justification are not adequately treated, and the issue will not be easy to understand without such a discussion
- The issue of grouping age groups for exposure is confused with binning of data used in exposure assessment. These concepts need to be well defined and carefully introduced.

This is a general theme in the guidance document and in discussions of the Risk Forum. It is repeatedly stated that standardizing the age groupings will improve risk assessments, but the reasoning behind that assertion is poorly articulated. Components of risk assessment (exposure and hazard) should be referenced in this logic. For example:

I.    Key components of risk (exposure x hazard = risk) are age dependent.
      A. It is vital to measure, describe and quantify exposure in terms of magnitude, duration, frequency, periodicity, route and source as part of the risk assessment. These parameters and their metrics change with age because of changes in exposure opportunities and the dynamics/kinetics of interaction of the person with their environment. The person changes (physiological parameters, anatomy, etc.) and their activities change (where they are, what they are doing, how they are doing it, what and how much they eat, etc.).

      B. Hazard changes with age because of changes in the uptake kinetics physiology of the person, anatomical relationships, immunocompetency, and toxicity potential (qualitative and quantitative) as a function of magnitude, duration, and periodicity of dosage.

II.   The ideal risk assessment would be expressed as a continuum through all ages. This option may be frustrated by the limitations of the underlying data. Further, data on exposure should be matched to the data on hazard in terms of temporal relationships and other important aspects. Binning thte data can compensate somewhat for the weakness of the data on any one age group. Proper binning can improve the description of variability as well as the norm. Improper binning can, however, dilute the description of unique and important moments of vulnerability and/or exposure scenarios.

**Issue**: No mention is made of the prenatal period and the dilemma about dealing with age definition for early months after premature births.

Many authorities recognize infancy as a life stage on a continuum beginning with conception or even pre-conception exposure to the parents. If EPA defines exposure to children as an event that begins upon the birth event, that declaration should be made as a point of policy—but not necessarily as a point of science. Exposure and risk models CAN deal with this issue

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if so directed, but to date the models servicing most EPA programs do not do so as a matter of unspoken policy or "tradition".

The birth event commences "infancy", but the infant's true age grouping is a function of the tenure of pregnancy. A 1-3 month-old infant, born at full pregnancy term is not equivalent to a 1-3 month-old infant born after the second trimester of pregnancy. The guidance paper is silent on this issue, and promotes the age groupings for <1 year without reference to this dilemma.

**Issue:** Page vii, paragraph 1, sentence 1. Discussion of the possible need to combine groups and determination of representativeness of such recombinations.

This paragraph tends to give license to abandon the groupings of the guidance document in those cases where some justification can be made. The criteria for such divergence is vague and seems to permit wholesale adoption of other approaches. This liberal attitude is juxtaposed to the firm attitude about the need for conformity in age grouping across the EPA risk assessments. Rather than strike a formatted rule and then "give it up" so easily, a tiered approach might serve the purpose. A tiered approach might also bring concordance for this grouping scheme with previous doctrines that suggest exposure be attuned to categories such as ILSI's groupings of preconception, embryo/fetal, NB/pre-weaning, juvenile, adolescence, adulthood and old age.

An example of this would be:

| Newborn / pre-weaning   (B-12 months) | | | |
|---|---|---|---|
| Newborn (B-3 months) | | Infant—pre-weaning  3-12 months | |
| Birth to <1 month | 1 to <3 months | 3 to <6 months | 6 to <12 months |

The guidance document can make it clear that the finer level of definition is preferable, but if necessary, higher tiers can be utilized. Or, if a data set does not contain some element of the spectrum, the grouping should be highlighted. For example, imagine a data set that includes only infants up to 6 months of age. Using this data to represent children of B – 12 months would be discouraged.

Issue: Characterizing "patterns of children's behavior" and generalizations about groups of children is a topic on which everyone is an expert. Discussions and opinions often pivot around anecdotal evidence. And everyone has many anecdotes from which opinion is fashioned. Personal experience and local observation fills the void of data and guidance. Facts don't necessarily support opinion and a few correlations are easily extrapolated far beyond their merits. Yet, discussions on page viii of the guidance document endows Agency scientists the discretion to consider merits of exemptions from the suggested structure (page vii) based on their best scientific judgment. In the end, the risk assessment will be fashioned on the best judgment of Agency scientists, but the guidance document should do two things:

- Admonish the scientist to guard against judgment based on personal anecdotal observation and require a more substantive basis for decision-making;
- Provide more structured guidance on some critical issues that remain vague or on which the present document is silent.

One example of that silence is on how much demographic, temporal and spatial factors can influence the criteria for the groupings and the "behavioral" or "physiological" characteristics that define these groupings. We know that factors such as socioeconomics, ethnicity, cultural settings, geography, and seasonality affect exposure and risk. How do these factors affect the behavioral or physiological characteristics? Which of these two would be most affected by any of these factors? How do we know this? Should these factors be elements to be included in studies and/or recorded?

There is evidence that ethnicity may significantly influence age related physiological factors such as height/weight relationships, teething schedules, walking (mobility) age, immune competence etc. These characteristics in turn can greatly influence activity patterns, diet and metabolism.

We know that cultural practices influence breast feeding choice, feeding traditions, mobility permissiveness (thus time on the floor, range of environment) and other key factors in defining the opportunities for exposure (behavior related characteristics).

The guidance document is silent on these issues even when the regulatory mandate specifically includes reference to unique subpopulations. Silence on this issue can contribute to poor scientific discretion during the regulatory implementation.

Specific editorial comments about the text:

Page v and forward…

It would be helpful to orient the reader to the meaning of "behavior related" and "Physiology related" characteristics in terms familiar to risk assessment. The "behavior related" characteristics speak to the exposure parameters and the "Physiology related" characteristics speak to the hazard parameters in the risk assessment equation.

Page vi Table E-2

The description of behavior related characteristics for 2 to <3 year olds (as well as following groups) cite specific scenarios such as "occupancy of outdoor spaces increases". Well, the occupancy of new indoor spaces increases as well when the child goes to indoor places besides his own home (pre-school, day-care, etc.). It may be better to describe the issue as an increase in different environmental scenarios and exposure opportunities, including new indoor spaces and outdoor environments. By years 6 to <11, there are additional new environmental scenarios for additional exposure opportunities and an expanding menu of foods and changes in the forms in which the

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foods are consumed. New eating patterns emerge which may be influenced by their environment as well as by their changing physiology.

Page ix to Page 1, Table E-3

Food Intake: The recommendations have already been implemented and are publicly available in the LifeLine™ model. The 1998 Continuing Survey Children has supplemented the 1994-96 CSFII database in the model and the EPA/USDA definitions of food forms has been implemented. Thus, one can determine the intake of any crop that becomes a food or ingredient of a food, and the intake of any food in the CSFII and its contribution to exposure. The technical descriptions of the data utilization is part of the Technical Documentation.

Water Intake: The recommendation is also implemented already and is publicly available in LifeLine ™ and may be available in other models as well. This is not a research need.

Inhalation Rate and Activity Patterns: There is no mention of the need for factoring in the effect of health problems on these parameters. For example, the growing incidence of asthma, diabetes and childhood obesity is a reality that should be reflected in the exposure and risk assessments by the Agency. These health issues impact inhalation rates associated with a given activity and the activity patterns may be affected at the macroenvironment and microenvironment levels.

Activity Patterns: While CHADS is a useful database, the guidance document should flag the limitations of the data. There are very few children in this database and they do not represent the general US population. By design, there are ZERO children of tribal communities.

Page 1—Introduction

The FQPA and Executive Order 13045 are important foundations of the issue at hand. Accordingly, the guidance document should provide:
- Clear reference to each of these, with access information --- url addresses or comprehensive instruction as to how complete copies may be obtained. Agency interpretations of these mandates may also be useful and access to such should be clearly provided.
- A paragraph for each with a clear overview of the theme of each mandate and the specific relationship to the issue at hand should be written to put each into perspective.

These are important mandates and deserve a better introduction.

Page 2, paragraph 1
"An EPA workgroup convened (??when) under the auspices of the Risk Assessment Forum (?? url citation)."

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The relationship of the Risk Assessment Forum to the various program offices of the Agency should be discussed. For example, where does the Forum reside in the EPA structure? Are program offices bound by these recommendations? How will this guidance impact the risk assessments of the various program offices? It is nice to say that "this issue is critical for scientists…" but how will these scientists be related to the risk Assessment Forum's thinking?

_____


Re: Page 28, Section 4.1 "Existing Models for Aggregate and Cumulative Risk Assessment"


This section suffers from several major misunderstandings and inaccuracies. The information is outdated, but the major problem is a basic disconnect between the realities of the modeling approach and the points being illustrated in the discussion. This section must be corrected before the document is finalized. It is wrong.

First a few relatively minor points.

(page 28) Para 1 of Section 4.1
        The current version of LifeLine is 2.0, with new versions being prepared for release in the near future. The reference to and extensive discussion of this (and other models) should be included along with all other references, and access to the LifeLine model (which is distributed freely) noted. It is available via www.TheLifeLineGroup.org . The Tribal LifeLine models will be coming online in the very near future also. The Tribal version carries data relevant to the diets and environmental exposure parameters of tribal (Native American Tribal) communities, a population group included in the legal mandates of the US EPA. The document fails to adequately reference the model and its extensive technical documentation that addresses these very principles and many of the details involved in the points within the guidance document.


Second, correction of the discussion points in this section

(page 29)
        While I agree with the spirit of the discussion in paragraph 1 on this page, Figure 3 does NOT illustrate the point of "criteria for matching data from multiple survey instruments or for using data within a model". (Note: The discussion in paragraph 3 of page 29 and Figure 3 is from the LifeLine™ model. I recognize the description and none of the other models fit this description.) The criteria for the binning of the data used in different databases within the LifeLine™ model is described in great detail in the LifeLine Technical Document which is available online at www.TheLifeLineGroup.org and accompanies each free software copy.
        The brief descriptions of the metrics utilized in the LifeLine™ model approach, which is obviously the underpinnings of the Figure 3 illustration, is terribly confused. Granted, it would be hard to reduce to a paragraph the dozens of pages in the technical document on this topic. But this interpretation of the model approach is wrong.

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(Page 30, 31 and Table 5)

Paragraphs on page 30 and 31 of Section 4.1 discuss the modeling approach used in LifeLine™. For starters, the comments are in error. Many other data bases are utilized in the workings of the model (including CSFII and NHAPS), but this guidance document is supposed to be about the age groupings, not the model functions. The entire conversation around Table 5 is a discussion about needs in modeling and a possible approach. It does not belong in the conversation about age groups. If the EPA wishes to consider the debate on the approach suggested here for "assigning values to each exposure factor) such as suggested in Table 5, I can write volumes about the pros and cons of that suggestion…but it adds little to the conversation about age groups. As I'll discuss below, we have skipped over some very relevant issues about exposure metrics that can be presented by the models that are relevant to age groupings (maximums versus averages). Rather than introduce another concept about model development, the guidance document should focus on points such as that.

Table 5 should be completely removed, along with the discussions on page 30 and 31 in section 4.1. Discussions on page 29 should be corrected and the points about data metrics versus exposure metrics should be untangled. The authors missed the point here completely and are providing misdirected guidance.

The final paragraph of page 31 contains an important point, "It is important to understand the sampling approaches used in aggregate/cumulative models…" VERY TRUE!! But the conversation about Figure 3 suggests the authors have confused the issues about data binning and age group binning.

It is true that, "In the example portrayed in Figure 3, the majority of food consumption observations in the 5 to <15 year old bin are actually from surveys of 10 to <15 year olds…" BUT I take great issue to the rest of that statement, "these data may not be adequately representative of the 5 to <6 year olds."

The CSFII records gave the consumption information for each person, including the age, season, and many demographics. The task of binning was achieved by testing many possible grouping according to the criteria developed for the dietary information. That process is described in great detail in the technical documentation to the model. The technical documentation is publicly available and could be valuable to this conversation. That document should be cited in this guidance document and the availability made known. It can be freely accessed easily on the web at www.TheLifeLineGroup.com.

The criteria for binning the dietary data WILL BE DIFFERENT FROM criteria for activity profiles or for growth metrics or other databases. The criteria chosen for such binning must be clearly articulated by the model developers, and the criteria rejected should be discussed also. There may be no perfect way to do this, but the criteria should be transparent and relevant.

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I will briefly explain the criteria for the CSFII data binning in the LifeLine™ model. The criteria were based on factors related to food choice or factors related to technical processes that alter the concentration of contaminants in foods as eaten.

> Consider, for example a child of one and a child of ten. Both may consume the same amount of "apple", but the one-year-old consumes it as highly processed applesauce and juices (pasteurized, single apple variety, pulp only) and the 10-year-old consumes it as fresh apple (with skin, multiple varieties) and in baked goods.

So, various binning options considered if there where significant "break points" between age groups based on: amount of the food eaten: per eating occasion or across the whole day, the form(s) of the food eaten, the number of eating occasions per day (eating three "squares" per day versus grazing through the day implies a different choice of foods and forms of those foods), the number of different foods eaten, the number of different forms of food eaten, etc. This was done for males only, females only or male/female combinations within all age groups. The search was for the "break points" that would define the "edges" of age bins, using these criteria. The results were not necessarily intuitive. Less difference was found between the sexes at early ages than I would have expected from my own experience with children. If such difference really exists, it wasn't expressed in the CSFII data. (Maybe it just exists with my kids.) When kids start school, they seem to take on a different pattern of eating—number of eating occasion's decrease, more forms of food are encountered, amounts per eating occasion increases, etc. The process of binning here has to make sense of the kind of data being considered and the robustness of the database itself. If the CSFII had not recorded so many different parameters, the binning criteria would have been different, and perhaps the binning decisions would have been different.

Considering NHAPS, the activities of a child do not necessarily follow the patterns of dietary change. The criteria for binning these data should be based on relevant criteria for these kinds of data—not on the features of the dietary data and not on physiological characteristics relevant to toxicological significance. The binning criteria should seek the edges of the bins for activity scenarios related to non-dietary exposure opportunities. When are the kids spending more time in their yard, in the public places (school yards, parks, playgrounds)? When are they exploring the whole house—on their knees versus walking? How much time are they sleeping/awake? When are they in their own house versus another indoor environment? When are they expanding their activities to new exposure opportunities (swimming, soccer, gymnastics, etc.)? The bins here must follow the same principles:

- bins should express representative AND relevant metrics for all the individuals grouped within each bin, and
- The binning process should not mask any truly unique profile within the bin (don't hide the significant peak).

The NHAP age bins may differ from the CSFII age bins, however, and that is to be expected.

This process is undertaken for each database. If done well, the data will "be adequately representative" for any age under consideration as you select "representative data" for that age from each of the databases.

For a 5 year-old, the dietary intake value should be representative of a 5 year-old from the dietary database, and the time spent in the bedroom sleeping should be representative of a 5 year-old from the NHAPS database and the weight and height of that child should be representative of a 5 year old from the NHANES database.

<u>Finally, discussion of the relevance of Figure 3 (and its discussion) to the point of this guidance document:</u>

The issue at hand seems to be "what age categories of EXPOSURE metrics should be considered in an exposure and risk assessment?" So we can consider a year-by-year (or season-by-season) analysis such as one portrayed in Figure 3. The original line in this figure is close to the idealized "continuum" recommended by the participants of the July 2000 workshop. In fact, the LifeLine model can describe aggregate exposure (route and source specific) for each season of each year of life. It can present the average exposure across a season or the highest exposure and the full distribution of exposures within a season for an age group. Which of these exposure estimates (average or maximum) should be considered IS an important consideration and the importance IS age dependent.

Consider for example, the aggregate exposure of diet and indoor ambient air and residue of detergent to an infant of 3 to 6 months of ages as compared to a child of 6 to 11 years of age. The variations in the aggregate exposure (or source or route) amongst infants (3 to 6 months of age) will have little relevance to season. These infants eat the same food, spend most of their time in the same rooms and will have their clothes treated in much the same way no matter the season. The child (age 6 to 11) could see a vastly different array of exposure scenarios as the seasons change. They do eat different foods, change their indoor/outdoor time, and play on different surfaces doing different things for different durations of time. Their clothes may be treated for grass stain removal, be decorated with different materials, etc. Variations (hence max versus average) may be more relevant for one age group over another.

The guidance document misses the point completely, and thus does not offer guidance on what kind of exposure estimates might be desired for different age groups. It does not consider these points, even though the exposure models are now capable of responding to such guidance. Guidance on these points will be critical also for data generators. Should they report their data as maximums, distributions, averages, etc. for different parameters? This would be critical guidance, driven by the question at hand—differences in the scenarios of exposure for different age groups.

Another note about the models. Several models, including the LifeLine™ models are developing exposure continuums that demonstrate exposure across hours, not just days and seasons and years. These models can consider every day of every year, but the function discussed in the third paragraph portrays the model as incapable. That is not a point that is relevant to this guidance document…and is an inaccurate portrayal of modeling capability. This is not a discussion of

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modeling capability (already outdated in this document) but a discussion of what the modeled should be doing!

So, the models CAN already portray year-by-year descriptions of exposure (maximum, average, etc.). Now, if one wants to express the information as a function of age groups, the question is what ages to "group".

There are two ways to approach this:

First there is a discussion of what the exposure assessment suggests are good groupings. One can look at the peak exposures described for the aggregate exposure (combination of dermal, oral, inhalation by all sources) OR look at this same figure for each of the routes (just oral, just dermal, just inhalation by all sources). Depending on the chemical being considered, one of these routes may be more pertinent to the toxicology issue. The existing models allow this choice of exposure assessment with just the push of a button. Likewise, individual sources of exposure can be independently considered with another button push. Consider the example described above. The relative contributions from different routes and different sources will differ by age group.

In any case, age bins can be derived from a sketch like Figure 3 by considering:
- what groupings of years will present a representative exposure assessment for each age within the grouping, AND
- What grouping will not dilute out any truly unique and important exposure profile for a given year. (hiding the peaks)

To do this, we can calculate a time-weighted average (t.w.a.) across different bins to see where the t.w.a. begins to differ significantly. We can also consider where a peak value within a bin is significantly different from the t.w.a. of that bin. In the hypothetical Figure 3 I suspect that the t.w.a for the 10 to 20 year old bin would not be significantly different from the 11 to 16 year old bin, or a 13 to 17 year old bin. But, the 6 to 12 year old bin might well differ significantly from the 7 to 8 year old bin. And, the two year olds in this example might be worth looking at individually. They seem very different from the one year old group in this hypothetical example.

There is a problem with this approach. The year-by-year and season-by-season continuum exposure line will be different for every chemical situation considered. The highest exposure peaks may fall into different ages depending on the sources of the chemical and circumstances of the exposure scenario.

Consider how the hypothetical exposure line would look for a chemical used only as a disinfectant in public pools. For this analysis, a very few infants, a few young children and more school aged youth would be exposed. Within these "bins" some kids may be highly exposed on a regular basis (the infants in swimming programs and the competitive swimmers) but most will not be in a swimming pool at all. Perhaps it would be wise to

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see a profile of the maximum exposures within each "bin" as well as the average value for the age group. They are going to differ greatly.

If our chemical of interest is a pesticide used on many crops, the exposure may look very much like the hypothetical line in Figure 3 and the maximums may not differ greatly from averages for any age bin.

The second way to approach the issue is to follow the philosophy expressed during the EPA Risk Assessment Forum of July 2000. The ideal situation is a continuum of exposure values (which models can now achieve), but if age groupings must be considered (for whatever reason), those groupings should express representative AND relevant exposure metrics for all the individuals grouped within each bin, and the binning process should not mask any truly unique profile within the bin (don't hide the significant peak). The forum expressed views on the parameters to be considered when deriving those exposure bins—changes in anatomical dimensions, changes in immunological competence, changes in behaviors that change or expand exposure opportunities and the conditions of those exposure scenarios.

The question of how to bin the exposure answers should not be confused with how to bin the DATA, but how to bin the exposure (source specific or aggregate) profiles across age groups. The principles for binning may be the same, however—

- bins should express representative AND relevant metrics for all the individuals grouped within each bin, and
- the binning process should not mask any truly unique profile within the bin (don't hide the significant peak).

What is relevant and representative will differ for each type of database. Parameters for relevance and representativeness for exposure answers have been articulated by the discussants in the Risk Assessment Forum.

**Review by**
**Jeffrey H. Driver, Dr.P.H., D.A.B.T., M.T., C.L.S.**

**Peer Review of EPA's Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Chemicals**

Reviewer:     Dr. Jeffrey Driver
Date:         February 6, 2004


GENERAL IMPRESSIONS

The guidance document is an important contribution towards the improvement of the scientific basis for evaluating potential environmental exposures to children.  It requires editing prior to public release.  The need for explicit evaluation of children's exposure by addressing potentially relevant stages of physiological and behavioral development has become recognized as necessary and the document, along with underlying technical support documents (which should be distributed with the guidance) help to fill this void.  The document should clearly emphasize in an introduction that it represents a guide for assessors (not a cookbook) and means of identifying future exposure data collection.  The guidance should not imply that the recommended age bins must be routinely addressed.  Rather, the assessor should initially consider the recommended age bins and justify the selection they made; this justification may include conventions currently used by specific EPA Offices (e.g., OPP) until those Offices formally adopt changes resultant from the guidance.  In general, the document is lacking enough references to underlying technical support; this should include primary sources (scientific literature citations), as well as secondary (e.g., Versar 2000, EPA' CSEFH).  The absence of pre-natal-related factors should be addressed in an introduction.


RESPONSE TO CHARGE QUESTIONS

1.  As discussed above,  the use of the information presented at the peer involvement workshop ( "Summary Report of the Technical Workshop on Issues Associated With Considering Developmental Changes in Behavior and Anatomy When Assessing Exposure to Children http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=20680) coupled with a subsequent analysis of exposure factors data (http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=237196) formed the basis for the guidance. Please comment on whether the guidance appropriately reflects the recommendations of these expert deliberations and whether the process of selecting the age groupings is adequately described?


The guidance reflects the expert deliberations; however, it lacks reference to important underlying technical support documents.

2.  Section 2 of the guidance concludes by presenting three recommended points for discussion by the assessor when combining or eliminating age groups in a particular exposure assessment. These points include: (1) the basis for the determination; (2) description of uncertainties and biases; and (3) discussion of the types of data and information, if available, which would allow combined groups to be separated in future analyses. Please comment on:

A. Whether the guidance adequately reflects the need for flexibility in using these age groupings?

   The flexibility should be emphasized via an introduction.

B. What more specific guidance regarding application of the 3 points identified above might be provided to risk assessors; for example, discussions of statistical considerations, or temporal and inter-individual variability?

   Statistical considerations and other issues, such as temporal data (or lack thereof), intra- and inter-individual variability and uncertainty should discussed in more detail in Section 4 and its associated subsections.  Further, publications [e.g., EPA guidance such as: USEPA (U.S. Environmental Protection Agency). 1997a. Guiding Principles for Monte Carlo Analysis. Risk Assessment Forum. USEPA, Washington, D.C.; USEPA (U.S. Environmental Protection Agency). 1997c. POLICY FOR USE OF PROBABILISTIC ANALYSIS IN RISK ASSESSMENT at the U.S. Environmental Protection Agency. May 15, 1997. (USEPA Document No. EPA/630/R-97/001)] on these topics, albeit general discussions in some cases, should be cited as part of the expanded discussion. ILSI will be releasing guidance re: a subset of child-specific exposure factors in the Spring of 2004 and this document should also be useful in this regard.

C.  Are there additional points beyond the 3 identified that should be highlighted in making the decision to use an age grouping for a particular exposure scenario and data set?

   Perhaps policies and procedures currently in place with EPA Offices (e.g., OPP)

3.  Section 3 of the guidance contains recommendations for a set of critical exposure factors pertaining to further analysis and research. Subject to EPA approval and finalization of this guidance, the Agency anticipates re-compiling its Child-Specific Exposure Factors Handbook – Interim Final Report ( EPA-6006P-00-002B, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145 ).  As a preliminary exercise along these lines, the guidance includes recommendations for further analysis/research on child specific exposure factors.  Please comment on:

A. The accuracy of the statements about our current knowledge regarding each of these exposure factors.

   This underlying technical support documents (Versar 2000 and the CSEFH) are critical for this purpose and should accompany the guidance document when released to the public).

B. The priorities and recommendations for further data collection activities (Table E-3 in Guidance document).

See specific comments below re: characterization of child hand size distributions and the surface area of hands involved in mouthing events.

C. Whether any critical exposure factors have been overlooked in these recommendations?

Mass transfer factor distributional data, e.g., contact rates or transfer coefficients are not explicitly addressed in Table E-3 (future research needs). Discussion of this metric in the context of macro and micro dermal exposure modeling is discussed on Page 25, and characterized as "an area that is ripe for research." Thus, it should have its own discussion as a factor in Table E-3.

D. Whether there are any additional or developing sources of information that could be used to improve or fill exposure factors data gaps related to the recommended set of age groupings?

ILSI / HESI Ram Project – contact: Syril Petit, ILSI, Washington, DC

European Exposure Factor Project – contact: Rosemary T. Zaleski, ExxonMobil Biomedical Sciences, Inc.

4. Section 4 of the guidance is intended to alert assessors to uncertainties and biases that can be introduced through the use of models, time weighted doses and the like. Please comment on the utility of this discussion and what additional points, if any, should be highlighted.

See response to question 2B above

SPECIFIC OBSERVATIONS

1. Page ii – Add Table of Contents

2. Page iii – "A consistent set of childhood age groups"…this statement is not the appropriate premise, i.e., consistency across EPA Offices may not be possible given different statutory requirements and purposes for evaluating potential health risks …the correct premise is that technical guidance regarding childhood age groupings provides exposure factor information for science-based selection of and transparent explanation for the selection of groupings that meet the purpose of a given human health risk assessment. Further, it is recognized that integrated, multi-source (e.g., food and drinking water-related, products used in and around residences, ambient air), pathway (fate of residential-related surface residues and ingestion via mouthing behavior), and route (oral, dermal, inhalation) exposure assessments require consideration of the available data for differentiating child-specific age-groupings in the context of aggregate and cumulative analyses. Therefore, this guidance and the underlying technical reports provide assessors with an accounting of the strengths and limitations of the existing data.

3. Page iii – Table E-1, footnotes a) additional explanation should be provided

4.  Pages v to vii – Table E-2, references should be provided to support this Table, e.g., "high skin permeability" this statement (associated with birth to < 1 month) should be supported by referenced and explained further (e.g., premature infants and integrity of the stratum corneum); e.g., "mouthing of hands and objects increases" – add reference, e.g., Tulve et. al. 2002; e.g., NHANES and other sources can be cited to support physiological changes as a function of age

5.  page vii – Table E2 "Note" at end of table…a statement is made re: "the rate of change in these characteristics" being a key factor…while this is an appropriate finding, the analysis should be referenced.

6.  Page viii – another bullet should be added re: a discussion of the underlying data limitations regarding the assessor's selected binning procedures for a given exposure factor or characteristic (if these discussions can be collated as they are collected across EPA Offices, it will provide feedback to the RAF re: existing data limitations and needs)

7.  Page ix – Table E-3 – Non-Dietary Ingestion – this should be expanded and explained in more detail, e.g., relevant mass-transfer-related processes should be better characterized such as the sequential or temporal sequence of contact (surface/object to hand vs hand to surface/object mass loading/unloading), the hand/finger surface area distributions involved in environmental surface contact, and in mouthing.  Studies to evaluate incidental oral contribution to total absorbed dose (e.g., differential oral versus dermal metabolite profiles in urine)

8.   Page ix – Table E-3 – ventilatory equivalence should be defined via footnote (see Page 20)

9.  Page 1 – Table E-3 – internet web site url should be provided for CHAD

10. Page 1 – Table E-3 – add review of available data regarding child-specific hand surface area distributions

11. Page 2 – References should be added to statements where appropriate (e.g., mouthing hands and objects during the 1 to < 2 year old life stage – Add Reference such as Tulve et al. 2002; age-related differences in iron deficiency – Add Reference)

12. Page 2 – An expanded explanation re: why pre-natal was not included in this effort and the efforts that are ongoing or planned that will address pre-natal; this is mentioned on page 4, but should be explained earlier in the document, perhaps in the Executive Summary

13. Page 3 – "…dermal and oral potential doses are appreciably higher than those of adults." Add references, such as biological monitoring studies as evidence supporting this statement.

14. Page 4 – "Internal Dose - …amount of chemical contained…"  What is "contained"…should this be contaminant?

15. Page 5 – The footnote is important and should be part of the text, rather than a footnote.

16. Page 7 – "The age groups listed in Table 2 were derived largely from considering the rate of change…" A reference should be cited to support this analysis / consideration.

17. Page 7 – "The Agency is currently considering childhood development and it's relationship to dose and effects through other efforts." Example efforts should be cited.

18. Page 8 – Table 1 – References, such as the Versar 2000 technical report should be cited in support of this Table.

19. Page 9 – Tables 2 and 3 - References, such as the Versar 2000 technical report should be cited in support of these Tables.

20. Page 12 – "…presented above in Table 3." Should this be Table 4?

21. Page 15 – add reference to the new Food Consumption Intake Database developed by EPA/OPP.

22. Page 17 – "The preliminary reevaluation of mass balance soil intake data..." Add reference.

23. Page 21 – "Daily estimates of E derived from this method…" Explain further, this is an excellent idea and illustrates the value of how to improve the basis for integrating disparate exposure factor data sources due to their different designs and resulting age-related binning.

24. Page 25 – "The EPA Office of Pesticide Programs (OPP) has proposed an interim value of 10,000 cm2/hour…" this value has been updated – see EPA/OPP Policy 12.

25. Page 26 – Section 3.4.1 – useful discussion…should add need to characterize child hand surface area distributions and hand surface area involved in mouthing.

26. Page 28 – Edit as follows: "…, the Cumulative and Aggregate Risk Evaluation System (CARES™) developed by member companies of CropLife America, and now under the stewardship of the International Life Sciences Institute (ILSI), and the Residential Exposure Assessment Model (REx) developed by infoscientific.com, Inc."

27. Page 29 – Delete sentence: "It should be noted that, although the existing models estimate day exposures, they may not…" The majority of existing temporal models can provide graphic depiction of temporal profiles, defined by day, relevant moving average period, or annual average.

28. ADD TABLE to Section 4.1 regarding "Exemplary exposure factor data sources and their respective time domains" that includes the following: Data Source (name, e.g., CSFII), Exposure Factor (e.g., food consumption), Child Age Groups Addressed (e.g., CSFII has

included survey instrument that have over-sampled infants and children allowing differentiation of <1 month, 1 – 2 months, etc.), Time Domain (e.g., CSFII is a nationally representative diary surface of food consumption that was collected for either 1 or 2 days for an individual; diary collection across the surveyed population occurred throughout the calendar year and geographic regions in the U.S.)…other example data sources could include U.S. Depart of Agriculture's Pesticide Data Program (PDP), CHAD, NHEXAS, NHANES, National Home and Garden Pesticide Use Survey, Child Videography/Observations Studies (e.g., Tulve et al. 2000). This table would illustrate disparate data source data collection designs and highlight differences that may limit "break point" or binning opportunities for different child age groups…this would also relate to Table 1 in the Versar 2000 document.

29. Page 31 – Table 5 – "fixed deterministic value from residential SOPs"…typically, for purposes of probabilistic residential simulations, this variable is represented as a distribution for children, 1 – 6 yrs old.

30. Page 32 – Section 4.2 discussion should include a statement recognizing that for certain acute or short-term toxicological endpoints (e.g., transient CNS-related neurotoxicity), physiologically-based toxicokinetic modeling requires time horizons less than 24 hrs (or less than 1 day).

31. Page 37 – Check all references for citation in the document; several references are missing, e.., Allan and Richardson 1998; Layton 1993; McCurdy 2000.

32. Figures 1, 3 and 4 require color (not a problem for the PDF version).

**Review by**
**Robert J. Fares**

**Peer Review Workgroup Comments on** *Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants*

**by Robert J. Fares**

**General Comments:**

Overall, this document presents a good summary of the data gaps and recommendations presented at the Risk Assessment Forum July 2000 workshop and the 2001 expert review and reevaluation of data available in the Child-Specific Exposure Factors Handbook. However, the document falls short of guiding risk assessors in the process of selecting age groupings. Although the authors of this document have done a pretty good job of summarizing the behavioral, anatomical, and physiologic characteristics that should be considered in deriving appropriate sets of childhood age groups for risk assessments (Table E-2), the recommendations may be moot, especially for children less than 2 years of age for which critical exposure factors are extremely limited or non-existent. Additionally, the authors have included an ambitious list of recommendations for further short-term analysis and long-term research on exposure factors data for children (Table E-3). These recommendations stemmed from the workshop held in 2000 and the reevaluation of available child-specific exposure factors data that was submitted to the Risk Assessment Forum in October 2001. Apparently there has been no progress in resolving some of the data gaps that were identified more than two years ago. That begs the question – what is meant by the terms "short-term analysis" and "long-term research"? This reviewer did not find anything in the document that indicated long-term research is currently underway. The authors only stated that "the longer term research identified in Table E-3 **can** be accomplished through the EPA Office of Research and Development Strategy for Research on Environmental Risks to Children [accent added by reviewer]". With regard to short-term analysis, the authors indicated that "some of the short term analyses described in Table E-3 **are likely to be** incorporated in an update to the Child Specific Exposure Factors Handbook (expected to be completed within the next year) [accent added by reviewer]", which implies that those analyses are currently underway. At minimum, the authors need to present a time line for completion of each of the analysis and research needs listed in Table E-3. Without those data, this document may be premature. This document would be better served to present a section summarizing what age-specific exposure factor data is available, and how to address those age groups that might be important to a particular program when data are not available. If the exposure factors for a particular age group are not available, that does not mean that there is no risk for that age group. Additionally, making rough estimates of exposure that are based on other age groups (see Response to Charge no. 1) may be capricious.

**Response to Charge no. 1** - *Does the guidance appropriately reflect the recommendations of the expert deliberations, and is the process of selecting the age groupings adequately described?*

The recommendations in this document are, for the most part, reflective of the recommendations from the Risk Assessment Forum July 2000 workshop and 2001 expert review and reevaluation

of data available in the Child-Specific Exposure Factors Handbook. However, the document falls short of guiding risk assessors in the process of selecting age groupings. For example, in Section 1 of the document the authors suggest that in instances where exposure data for a particular age group of potential importance is lacking, an assessment could include a "rough estimate based on exposures of other age groups and consideration of how these age groups differ". This reviewer does not understand how this can be accomplished in a scientifically defensible manner, especially if the age group of potential importance is less than 2 years, considering the differences in behavioral, anatomical, and physiologic characteristics presented in Tables 1 and 2. Although, based on those differences, a risk assessor may be able to qualitatively compare exposures with other age groups, this reviewer does not understand how exposures for those age groups could be quantified, even roughly, when many of the critical exposure factors are non-existent. Perhaps the authors can elaborate on how this might be achieved and provide an example.

**Response to Charge no. 2 -**

> *A. Does the guidance adequately reflect the need for flexibility in using these age groupings?*

The document adequately reflects the need for flexibility in using the different age groupings.

> *B. What more specific guidance regarding application of the three points (i.e., basis for determination, description of uncertainties and biases, discussion of the types of data and information that would allow combined groups to be separated in future analyses) might be provided to risk assessors?*

This question is somewhat ambiguous, especially with regard to the third point (i.e., "a discussion of the types of data and information that, if available, would allow combined age groups to be separated (or omitted age groups to be addressed) in future analyses"). This reviewer feels that the information presented by the authors in Tables 1 and 2 of the document is a good step in addressing that point. However, it might be helpful for the authors to expand the textual discussion with a few practical examples that show how such a determination might be made by risk assessors. The authors also need to provide guidance on what to do with regard to the younger age groups (<2 years) until the data needs presented in Table E-3 are resolved..

> *C. Are there additional points beyond the three identified that should be highlighted in making the decision to use an age grouping for a particular exposure scenario and data set?*

In the Introduction (Section 1) of this document the authors have discussed the problem of cross-program differences in age groups. However, it would help if the authors could expand the introduction to explain the rationale used by the different program offices to select specific age groups for their assessments. Without that information this reviewer can make no recommendation at this time regarding any additional points to be considered in making age-grouping decisions.

**Response to Charge no. 3 -**

> *A. Comment on the accuracy of the statements about our current knowledge regarding each of the exposure factors.*

Most of the statements in this document accurately reflect what was reported in the Risk Assessment Forum July 2000 workshop report and 2001 expert review and reevaluation of data available in the Child-Specific Exposure Factors Handbook. However, from a "guidance" perspective, it appears that some of the information from those reports has not been addressed in this document. For example, this document should address the importance of using NHANES III data to update age-specific exposure factors. The 2001 issue paper cautioned the use of the two-decade old NHANES II data to derive total body surface area values for current age groups. The issue paper stated that since NHANES II data were collected, there has been an upward shift in the prevalence of overweight among children and adolescents. From the 1960s to 1980, overweight in children and adolescents was relatively stable. However, from NHANES II (1976-80) to NHANES III (1988-94), the prevalence of overweight nearly doubled among those age groups. During that time period, the prevalence of overweight among children ages 6 to 11 years increased from 7 percent to 11 percent, and adolescents ages 12 to 19 years increased from 5 percent to 11 percent. The issue paper indicated that a review of NHANES 1999 data suggested that overweight in children and adolescents may be increasing to even higher levels than in 1994. Subsequently, the issue paper concluded that age-specific total surface area values based on NHANES II data may not be representative of the current population. This may be true for other exposure factors as well, and should, as a matter of guidance, be addressed in this document.

> *B. Comment on the priorities and recommendations for further data collection activities (Table E-3).*

Table E-3 appears to be all inclusive regarding recommendations for further data collection activities, but no inference can be made regarding any priorities for the data collection activities. Please see this reviewer's General Comments for a more detailed comment.

> *C. Have any critical exposure factors been overlooked in the recommendations?*

The authors should address the effects of dermal reloading on exposure. This was one of the issues raised in the recent SAP review of the Draft Preliminary Probabilistic Exposure and Risk Assessment for Children Who Contact CCA-Treated Wood on Playsets and Decks and CCA-Containing Soil Around These Structures. That study was based on the Stochastic Human Exposure and Dose Simulation Model (SHEDS) mentioned in Section 4.1 of this document.

> *D. Are there any additional or developing sources of information that could be used to improve or fill exposure factor data gaps related to the recommended set of age groupings?*

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This reviewer is not aware of any ongoing research that the Risk Assessment Forum should be aware of for future updates to the document.

*Response to Charge no. 4 - Comment on the utility of the discussion in Section 4 and what additional points, if any, should be highlighted.*

This section appears to have been thrown together as an afterthought. The authors mention five models, all of which were developed to address aggregate exposure/cumulative risk mandates for pesticides under the Food Quality Protection Act (FQPA) of 1996. The authors state further that all of the models:

- combine exposures to an individual or population of individuals across sources, pathways, and routes
- present exposure results at a given time or time profiles
- use well established algorithms along with probabilistic sampling techniques and survey instruments to estimate daily exposure and simulated longitudinal exposure patterns

The authors present an example to illustrate the importance of fully understanding the sampling algorithms used by each model in order to interpret the model outputs in light of the recommended childhood age groups and allow for a more complete characterization of uncertainties. The authors state that "there may be sound statistical reasons for the age bins used in the exposure model", such as the approach used to achieve a particular sample size within each age bin. The authors also state that "aggregate and cumulative exposure models will need to assign values to most (if not all) the exposure factors discussed in Section 3" of this document. The authors allude to the use of random sampling of empirical distributions, random sampling of theoretical probability models, and selection of fixed deterministic values to assign values to the exposure factors used in the different models. The example is somewhat vague in that the authors do not identify the model from which the graph was generated. The example and discussion of the sampling algorithms beg several questions. How do each of the models mentioned by the authors differ? Do they all use the same algorithms? Do each of the models have the same probabilistic sampling abilities and survey instruments? Can random sampling be accomplished with truncation in order to avoid overlap of age groups and still achieve the required sample size within each age bin? The authors also need to make a distinction between uncertainty (which seems to be the overlying theme of this section) and interindividual variability inherent in both the empirical distributions and theoretical probability models that generally are based on the result of goodness of fit tests of empirical data.

*Specific Comments:*

| Page | ¶ | Line(s) | Comment |
|------|---|---------|---------|
| *4* | *2* | *5* | *Change "EPA 1992" to "U.S. EPA 1992".* |
| *4* | *3* | *4* | *Change "(EPA, 1992)" to "(U.S. EPA, 1992)".* |
| *4* | *4* | *2* | *Change "(EPA, 1992)" to "(U.S. EPA, 1992)".* |
| *4* | *5* | *2* | *Change "(EPA, 1992)" to "(U.S. EPA, 1992)".* |
| *13* | *2* | *4* | *Change "ISAPI" to "U.S. EPA".* |
| *17* | *2* | *1* | *Align equal sign for $TE_{mouth}$.* |
| *17* | *5* | *1* | *Align equal sign for $t_{mi}$.* |
| *19* | *1* | *1* | *Align equal sign for $D_{pot(inh)}$.* |
| *19* | *4* | *2* | *Change "(hours/day" to "(hours/day)".* |
| *19* | *5* | *3* | *Add period at end of sentence.* |
| *26* | *2* | *3* | *Change "(add reference)" to "(U.S. EPA, 2001)".* |
| *37* | *-* | *-* | *Add bibliographic references for Allan and Richardson (1998), Boyd (1935), Layton (1993), and McCurdy (2000).* |

**Review by**
**Elaine M. Faustman, Ph.D.**

Comments on: U.S. Environmental Protection Agency, Risk Assessment Forum, External Review Draft (February 2003) Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposure to Environmental Contaminants

Elaine M. Faustman, PhD, DABT

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Introduction:

It is extremely important that the US EPA has prioritized Children's Health and has produced a guidance document for selecting age groups for assessing children's exposures to environmental contaminants. This guidance is timely and will be widely used. This approach recognizes the dynamic changes both in children's physiological development but also in their behaviors which can significantly impact both their potential for and amount of exposure but also the likelihood that such exposures can have a health impact. Towards these goals, the EPA deserves significant credit.

Because of the complexities of these considerations and because of the myriad of EPA program activities on children, this reviewer recommends that additional context is need for this specific guidance document. In order to provide context for this guidance and to ensure that it is used along with and not instead of existing supporting technical documents, a programmatic and decision diagram is needed that illustrates several things. For example, this context diagram

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should emphasize that this is relevant guidance across media specific programs.  Second, the context should also emphasize where additional details can be obtained if the reader needs detailed information (for example on physiology or behaviors).  Third, expansion of the context for this document should occur.

The initial phone call between reviewers identified that in utero exposure considerations were not included in this document.   As detailed in the responses to the specific charge questions, this reviewer strongly supports the inclusion of the prenatal exposure period.

Charge Question 1:

The information presented at the peer involvement workshop and summarized in technical documents available to this review committee are in general captured and summarized in this guidance report.  (Please note that this reviewer did not attend these workshops so the following comments are based only on a review of the workshop proceedings and the guidance document.) As indicated in the first conference call among the reviewers, the recommendations of the 2000 Workshop to include fetal exposures was not taken in the guidance document.   This is a serious shortcoming.   First, EPA's definition of children is inclusive of the prenatal period of development.  Second, many researchers feel that these early prenatal developmental periods represent significant "windows of susceptibility" and hence consideration of exposures during these times of significant physiological changes is essential for understanding and evaluating the significance of children's exposures to environmental contaminants.  Third, new research is suggesting that these early exposures do not only lead to adverse impacts at birth and in early childhood but also may represent times of sensitivity for impacts of adult disease and hence new

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research is under way to evaluate the fetal origins of adult disease. Research has also shown that significant storage of lipid soluble compounds can occur prenatally, thus the fetus can be born with a significant toxicant load. This is important to evaluate as this "background" exposure at birth would not be evaluated if exposures during the pre and post-natal exposure periods are separated and not thought of as a continuum. A similar phenomenon would occur if the mother is exposed during pregnancy and lipid soluble compounds build up in her milk and only post-natal exposures are considered. Therefore, it is difficult to separate the continuum and mother-conceptal unit when considering children's exposures. Thus, for these reasons and many more, exposures that occur during prenatal developmental are believed to represent very significant timepoints. Because the guidance document did not act on the recommendation to be inclusive of these prenatal timepoints and because there is not context established for the risk assessor using this document, the lack of discussion implies that this is not an important age group to consider. It is important to address this significant omission.

The guidance document also needs to examine the issue of premature infants. Having recently served on the NTP CEHR panel for phthalates, I am aware of significant unique exposure pathways that can occur for premature infants that would require special considerations for this "age-group" and for these compounds. (Kavlock et al, 2002, Reproductive Toxicology 16: 453-719). I feel the guidance document should provide approaches for evaluating exposures during this special post-natal period and include the recommendations from the 2000 workshop participants on this issue.

Charge Question 2:

The guidance document adequately reflects the need for flexibility in using age groupings. However, perhaps additional more specific guidance is needed.

In many places the guidance document lacked sufficient details for the user to make specific decisions. In the case of data insufficiencies the reader was left wondering if specific defaults are recommended or if criteria is available in a related technical document. Some of this lack of detail could be addressed with enhanced use of links to documents that provide this detail. It could be useful to provide the context for this detailed information in the context diagram that will be developed for the introduction to this document. The user would benefit from a table or "flow diagram" that details a decision map when information is missing.

Criteria for determining when data are sufficient would also be useful. For example page 22 of the document states " ..'the current database on children's macroactivities is sparse and data are insufficient to adequately assess exposures to environmental contaminants. However, the results of the Hubal et al. (2000) evaluation of CHAD data for children less than 12 years of age are sufficient…". What criteria were used to determine when such data were sufficient? Such information would be useful for the reader to understand implications of data insufficiencies. It was surprising that minimal discussion of gender related differences in age group characteristics were given. Such differences would be significant for both physiological as well as behavior characteristics. This document should expand discussion of these characteristics.

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This reviewer was very pleased to see the document give encouragement for exposure assessors, toxicologist and risk assessors to work together. This document reflects integration of expertise, data evaluation and data assessment from all three of these disciplines.

Charge Question 3:

The document identifies many significant data needs. However as mentioned above in my response to charge question 2, no criteria for inadequate data is given hence the identification of critical data needs fails this same test. Criteria for prioritization of these data need should be given.

Table E3 Summary of recommendations—This table did not include any discussion of research needs to determine internal dose. Also, nothing on age related differences in bioavailability were listed. It would appear that research needs in these two areas may have fallen between exposure and physiological considerations. This reviewer would encourage inclusion of such data needs.

There are several on-going activities that can inform this guidance. First, WHO is developing a criteria document on Children's Health. Of interest to this report is the use of a standard set of age definitions. Drs. Carole Kimmel and Teri Damstra are the leads on this "in progress" document.

The ILSI children's environmental health framework document has just been published in Environmental Health Perspectives and that is now available on the web as Daston et al 2003.

Charge Question 4:

This reviewer felt that two things were missing from section 4 of the guidance document. First, although a variety of equations were given to illustrate quantitative differences in the approaches taken for time averaged doses, very few examples were given to illustrate the significance of these issues or even the application of these issues to specific problems. There are many good examples in the literature, for example methyl mercury exposure during pregnancy and segmental hair analysis. Also, good examples exist for calculating seasonal differences in pesticide usage and the implications for exposure estimates.

Secondly, also this section highlighted example approaches, minimal to no discussion was given to approaches for validating these calculations. Since there is extensive bio sampling data available, some discussion should be given for either current or proposed approaches to characterize and validate model predictions. This should also be added as a critical data need.

Editorial Comments:
Ensure that all abbreviations are defined when they are first used in the text. (For example, see page 29 lines 20-21 abbreviations are defined here yet they were used extensively before in the text.)

Important ILSI review to include:   Daston et al 2003, Environmental Health Perspectives.

Figures 2 and 4 as presented are not helpful and in fact are confusing. Document should contain detailed figure legends for each figure.

More extensive use of references is needed throughout the document. For example, see the section on dietary exposures (section 3.2.1). In other places, references are given but do not appear in Section 4 References. For example see page 21 missing references for Layton (1993) and McCurdy (2000).

Equations used in the document need better definition and documentation. Most of these definitions are not original. Ensure that all have documentation. Also, typos in this section are especially confusing. For example, page 17, see EF mi and Efmii?

Review by
Natalie C. G. Freeman, Ph.D.

**Natalie Freeman Response to Charge Questions for Peer Review of EPA's "Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants"**

EPA's Risk Assessment Forum is seeking review of the scientific soundness of the proposed guidance. The purpose of the document is to provide guidance to Agency scientists on the appropriate age groups to consider as a starting point when assessing childhood exposure and potential dose to environmental contaminants. The guidance recognizes that the selection of appropriate childhood age groupings for a specific situation will be governed by a number of factors, however, a consistent set of childhood age groups for initial consideration will, over the long run, improve Agency exposure and risk assessments for children and help guide future data collection activities.

In July 2000, the Forum sponsored an external consultation workshop on determining appropriate age groupings for children's exposure issues. This was followed by an expert analysis of existing exposure factors data (Versar, 2001). From these efforts, a cross-Agency workgroup on childhood exposure, coordinated by the Risk Assessment Forum, has recommended age groups for initial consideration in Agency exposure assessments for children, and for use as a guide for future exposure data collection. These age groups reflect consideration of developmental changes in various behavioral and anatomical characteristics that impact exposure and potential dose, and physiological characteristics that impact potential dose, internal dose and effects.

General comments.

a. As mentioned by several people on the conference call (1/16/04) it is essential that something be said about prenatal exposure and risk. There is an abundance of evidence that *in utero* exposures can produce risks to the fetus and/or risks to the postnatal child. While we understand the difficulties the agency has incorporating prenatal exposure and risk into the guidance document, it is necessary that it be included.

b. References reported in the text need to be properly presented and cited in the reference section.

c. It should be noted that gender specific differences are not addressed in the guidance document although they were discussed during the workshop and in the Child-specific Exposure Factors Handbook.

d. Section 3 needs some reorganization. In some areas there are bullets for identified data needs, while in other areas (Dietary exposure 3.2.1, Water 3.2.1.3, Dermal Exposure 3.4) the bullets for data needs are lacking. If issues are identified in Table E-3, they also need to be in the corresponding areas of Section 3.

Specific questions to be addressed.

1.  Please comment on whether the guidance appropriately reflects the recommendations of these expert deliberations and whether the process of selecting the age groupings is adequately described?

The expert deliberations from the workshop July 26-27,2000 are reported in the following document: 'The summary report of the technical workshop on issues associated with considering developmental changes in behavior and anatomy when assessing exposure to children' (EPA/630/R-00/005) December 2000. The technical workshop was divided into two subgroups, one dealing with behavioral development and the other dealing with anatomical/physiological development. Each subgroup presented recommendations, and then the workshop as a whole produced a set of recommendations with a number of caveats. The subgroup age bins recommendations are reported in the workshop report on Tables   and in the guidance document on Tables 1 and 2 (EPA/630/P-03/003A NCEA-F-1449, February 2003).

Several age groupings are presented in the guidance document on tables E-1, E-2, and Table 4. Table E-1 and Table 4 present the recommended set of childhood age groups being considered by the Risk Assessment Forum, Table E-2 provides some of the behavioral and anatomical characteristics that may differential children within the age groups. Also presented in the guidance document in Tables 1, 2 are age categories representing either behavioral or anatomical developmental categories developed by the workshop subgroups, and on Table 3, the Risk Assessment Forum initial set of childhood age groups. The presentation of the various age groupings was apparently to show the evolution of the groupings from the workshop to Risk Assessment Forum to final guidance document. The flow of the document in presenting the evolution of the age groupings is somewhat rough and hard to follow. It would have worked better had there been more supporting documentation.

The final age groups proposed are presented on E-1, E-2, and Table 4. They broadly are associated with the summary recommendations of the expert deliberations at the workshop, but do show some variation based on subgroup discussions and specific age groups. The behavior workgroup initially lumped children between birth and <3 months rather than dividing it into two groups as in the guidance document.  In addition, the behavior workgroup had combined children from 2 to <6 years rather than subdividing it into 2 to <3 and 3 to <6 years. In addition the behavior work group combined children between 16 to < 18 years and 18 to < 21 years.  It is unclear from the guidance document why these are separated, since the two teen-aged groups were not recommended by either workshop group.

Table E-2 (page v) contains descriptors drawn from the workshop for age 2-5 years for oral and dermal exposure pathways. These are somewhat inaccurate and/or may be irrelevant to exposure, i.e. it implies that 2-3 year old 'hand to mouth activities begin to approximate adult patterns' and 'children begin wearing adult-style clothing'. It is inaccurate to imply that 2-3 year old hand to mouth activities begin to approximate adult patterns. Two to 3 year olds are more like 1-2 year olds in mouthing behaviors than they are like 5-6 year olds or older individuals. The main change in clothing habits for 2-3 year olds is a shift out of diapers which is related to toilet

training. When toilet training occurs is a result of the child's physiological and cognitive development, and the behavior of the caretaker. It is unclear how either toilet training or the shift from diapers to trainers to underpants influences exposure to environmental contaminants.

At the workshop, both sub-groups, while appreciating the agency's desire to create age bins, raised concerns with attempts to create age bins based on behavioral or physiologic changes which are continuous variables with sometimes very different age distributions. In addition, the workshop participants raised concerns that the agency should not consider the age bins as discrete entities, but had to keep in mind that each bin was based on underlying distributions, and that the distributions were driven by a range of behavioral and anatomical developmental factors, and effected by gender. The workshop gave the caveat that should age bins be used by the agency, that they should be considered preliminary, a work in progress subject to change as more information is obtained about development issues. The guidance document briefly addressed the concern about development being considered a continuous function (p. 4), with no discussion as to how that might be incorporated in the future.

The process for selecting the final age groupings is inadequately described on pages 3-9 in the Risk Assessment Forum (RAF) guidance document under review. On page 9, after having presented several age categories based on the discussions at the work shop, the RAF states 'As a result of continuing deliberations and reviews of available exposure factors data, the Risk Assessment Forum workgroup concluded that it may be appropriate to further divide the 1 to <3 years age group. An appropriate division would consider 1 to <2 years and 2 to <3 years as separate groups.' The document cites table 1 which does not reflect this division and 'existing exposure factors information' without any citations. While I personally agree with this separation and know of data to support it, some documentation is needed particularly since it is not in agreement with the workshop. In addition, there is no discussion in the guidance document as to why 16 to <18 years and 18 to < 21 years are considered separate age groups. The endocrine changes in males and females occur in both age groups, and the assumption (Table E-2) that children may move away from home environment in age group 18 to < 21 years makes the assumption that children don't graduate from high school until 18 and that younger children (16 to < 18 years) don't go away to school or shift between institutions during this age group. In terms of using epiphysial closure at age 18, the guidance document needs to add some documentation since most clinical citations use age 21 years as a rough estimate of when closure occurs. It should also be noted that epiphysial closure is linked to a termination of linear growth, but not body mass, bone density, or endocrine changes. In section 3.5 Human Body Weight, the brief discussion on page 28, bullet 2 alludes to these other body metrics without a linkage to the variables presented in Table E-2.

2. Section 2 of the guidance concludes by presenting three recommended points for discussion by the assessor when combining or eliminating age groups in a particular exposure assessment. These points include: (1) the basis for the determination; (2) description of uncertainties and biases; and (3) discussion of the types of data and information, if available, which would allow combined groups to be separated in future analyses. Please comment on:

Whether the guidance adequately reflects the need for flexibility in using these age groupings?

The discussion of the need for flexibility in using the age groupings is minimal and needs to be expanded.  The discussion is presented on page vii of the executive summary: 'there may be instances where combining some of the age groups….' And 'there may be instances where it is not necessary to address every age group…' It is suggested that the underlying scientific rationale be provided if age groups are combined or excluded.  In the guidance document body, on page 11, there is very little more said on this issue than what was reported in the executive summary. The most important guidance on this issue is that 'the exposure assessors 'engage in an iterative dialogue with toxicologists and other health scientists to determine the age groups that will be the focus of any particular assessment'. There is more space spent discussing three points for justifying combining or eliminated age groups in an exposure/risk assessment (p.11-12) than in actually discussing the need for flexibility. Perhaps some examples with references would be useful for demonstrating how to be flexible without completely ignoring the recommended age groups.

<u>What more specific guidance regarding application of the 3 points identified above might be provided to risk assessors; for example, discussions of statistical considerations, or temporal and interindividual variability</u>?

It might be worthwhile suggesting that exposure/risk assessors look at how exposure factors in the Child-specific Exposure Factors Handbook are evaluated for data quality when they are determining what age groups to use. What is not addressed is how to deal with groupings when there is an abundance of data lacking.

As pointed out previously by the workshop on page 2.5, the age bins are an artificial construct trying to merge many very different physiological and behavioral distributions. It is essential that those using the age categories have a good understanding of the distributions, uncertainties, and potential conflicting data that are imbedded in the age categories.  This can be done either by providing supporting documentation and/or references in the guidance document. At present the documentation is inadequate.

<u>Are there additional points beyond the 3 identified  that should be highlighted in making the decision to use an age grouping for a particular exposure scenario and data set</u>?

The need for a means of setting up age groupings when a significant amount of data is lacking was addressed in point B. My concern is that assessors will omit age groups or exposure factors associated with specific age groups for lack of data rather evaluating the uncertainties associated with data issues.  There needs to be an evaluation of the impact of this course of action on exposure assessments.

3.  Section 3 of the guidance contains recommendations for a set of critical exposure factors pertaining to further analysis and research. Subject to EPA approval and finalization of this guidance, the Agency anticipates re-compiling its Child-Specific Exposure Factors Handbook – Interim Final Report (EPA-6006P-00-002B, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145 ).  As a preliminary exercise

along these lines, the guidance includes recommendations for further analysis/research on child specific exposure factors.  Please comment on:

A.  The accuracy of the statements about our current knowledge regarding each of these exposure factors.

The Children's Exposure Factors Handbook contains roughly between 11 and 48 exposure factors, depending on how fine one wants to cut the factors, which EPA believes are important for assessing children's exposure. For example, at least 4 factors are related to breast milk, each of which has a distribution with measured or estimated mean and 95%ile values – daily milk intake rates, duration of feeding, fat and nutrient content of milk, demographics factors such as maternal age, race, ethnicity, and region of country. Most of these are not addressed specifically in the guidance document, yet the data gaps in all the above areas are noted in the Child-specific Exposure Factors Handbook. What the guidance document does point out is the deficiency of data on ethnic distributions of breast feeding, milk intake and effect of a mother's nutrient status on the fat/lipid content of milk (p.14).

Statements on current knowledge need to be supported with documentation from publicly available materials. For example, on page 27 in discussing water intake, there is a quotation from Current which came from the workshop proceedings.  The guidance document that states 'this observation is supported by discussions on the physiology subgroup'. I was not able to find that discussion in the workshop summary document. One could have more confidence in the statement if there were supporting citations.


B.  The priorities and recommendations for further data collection activities (Table E-3 in Guidance document).

Nine broad categories of exposure factors are listed in the guidance document (Table E-3) as needing further analysis and research.  The only one not included from the Child-specific Exposure Factors Handbook is consumer products.  To some extent there is consistency between these recommendations and those in the CSEFH. Where they differ, there needs to be some explanation.

In the Child-Specific Exposure Factors Handbook, chapter 10 deals with consumer products. EPA in this situation concludes that because 'the range and variation of consumer products and their exposure pathways' is so great (p. 10-2), the Agency can't develop exposure values. There is no recommendation for further work in the consumer products area as it pertains to children's exposure in the CSEFH (other than the bullet on p. 1-22 'further data are needed on the frequency and duration of use and kinds of consumer products used by children') or in the guidance document. It is no simply consumer products used by children to which children are exposed, but also consumer products used in the areas where children spend time. It is almost as though the agency has written off consumer products as an exposure issue because they are challenging to work with.  This is not an adequate justification.

The focus on no-dietary ingestion for age groups <6 years of age is based on a priori assumptions about the behavior of little kids, a small amount of data which according to the CSEFH has an overall rating of 'low', and even less amounts of comparable data on children between 6 and 21 years of age. Some justification needs to be made to focus on the younger kids.

It is unclear by the focus on activity patterns should be for children 'less and 4 years and children aged 11 years and older' (p.1, Table E-3: Activity Patterns). Is there adequate data on children 5-10 years old?

C.  <u>Whether any critical exposure factors have been overlooked in these recommendations</u>?

The breast milk intake exposure factor focuses primarily on lipids in the milk which is important for lipophilic contaminants. However, one contaminant still of concern for inner city mothers is mobilization of maternal body lead which is transferred to the infant in mother's milk.  (Again, this is also an area that points to the need to include prenatal exposure and dose – maternal body lead from pregnant woman to fetus.) Since the guidance document is for the entire agency and not just OPP, it has to be broad enough to meet the needs of all sections of the agency.  Therefore, for the issue of breast milk, other components besides lipids need to be addressed.  Indeed, one of the recommendations from the workshop was for research into lipophilic and nonlipophilic substances in breast milk (p. 4-31).

The CSEFH suggests that information on consumption of fish and ethnic foods is needed for children.  This is not addressed in the guidance document.  It is unclear if the Continuing Survey of Food Intake by Individuals (CSFII) can adequately provide the information of fish and ethnic foods.

The area on soil ingestion needs to specifically include house dust ingestion. Children spend the majority of their time indoors. House dust contains a wide range of contaminants from both indoor consumer product uses and from infiltration/track-in. Most of children's mouthing and food consumption occurs indoors. Therefore, the potentials for exposures from indoor contaminants may be as great or greater as from outdoor soils.

D.  <u>Whether there are any additional or developing sources of information that could be used to improve or fill exposure factors data gaps related to the recommended set of age groupings</u>?

a. There are two EPA STAR grants (O'Rourke - U Az and Shalat - EOHSI) in which activity pattern data are being obtained via parent questionnaires and videotaped observations that will provide additional information about indoor/outdoor activities and non-dietary ingestion factors for children ranging from 6 months to 60 months old.  The limitation of these studies is that they focus on Hispanic border communities and therefore may not be representative of all US children.

b. Actual measured hand surface area measurements for infants and toddlers are available from the O'Rourke and Shalat studies, as well from the Children's Dietary Lead Study (Pellizzari, Sheldon, Freeman, and Melnyk). These values are quite different from those extrapolated from total body surface estimates found in the CEFH and currently used by Agency exposure modelers.  Hand surface areas are of particular importance for calculating exposure from hand to mouth activities and ingestion of dust/soil contaminants.

c. Freeman and Adgate presentation at ISEA 2003.  (N. Freeman and J. Adgate: Estimates of dust loadings on the hands of children and daily dust ingestion.) The daily dust ingestion calculated in this study is very similar to dust ingestion reported by Stanek and Calabrese, even though the method for obtaining dust ingestion measures was very different.

d. Leckie study presented at ISEA2003 measured proportion of hand that actually contacts a variety of surfaces and will provide a better measure for hand surface contacts. (A. Kitwana et al. Quantification of contact-specific surface areas for dermal exposure.) While the poster presented data on adults, Kitwana et al also have data on an unspecified number of children.

e. Raymer et al (RTI) has been conducting EPA funded studies on food handling behaviors of children and pesticide exposure in day care settings and homes. The limitations of these studies are sample size and narrow age range.  The a priori assumption by the Agency is that toddlers and pre-school children is where the exposure will be greatest.  There is not an adequate amount of data to either support or refute this assumption.

4. Section 4 of the guidance is intended to alert assessors to uncertainties and biases that can be introduced through the use of models, time weighted doses and the like. Please comment on the utility of this discussion and what additional points, if any, should be highlighted.

Citations for the models discussed would be desirable. What is not pointed out is that some of these models do not use age bins, but include age as a continuous variable (Lifeline). The figure is very enlightening in that it shows the problem that exists by having inadequate numbers for the different age categories in CSFII and NHAPS. What might be even more informative is providing data on the uncertainty associated with using data that is not age category specific.

One of the statements on page 30 is that assigning values to the models 'involves random sampling of empirical distributions, random sampling of theoretical probability models, and selection of fixed deterministic values.' One of the criticisms the agency receives frequently has to do with selection of fixed deterministic values which are often based on 'professional judgment' with little documentation of how the judgment was developed. This should not be encouraged.  In the example given on Table 5, the fixed deterministic values were obtained from the Child-specific Exposure Factors Handbook and from Residential SOPs.  Reliance on these values needs some calculation of the uncertainty associated with them.  In addition, concerns about the excessive use of uniform distributions when data is minimal have been raised at various science advisory panels (SAPs) by Dale Hattis, Steve Heeringa, and others. Having these two factors in the guidance document without any caveats is a concern.

<u>Specific changes, additions or modifications</u>.

a. On table 1, page 8, characteristics relevant to oral and dermal exposure, age group 16-<21 'high rate of food consumption begins'. This may be seen in partial conflict to the statement on page 15 'the intake per unit body weight is greater for children than for adults'. The intake per unit body weight is typically discussed for infants, whereas the total amount of food consumed is a factor especially for adolescent males. Are they equally crucial for dietary exposure?

b. Page 17-18 discussion of non-dietary exposure model, text on page 18 states that SA $_{h/o}$ "must be presented per unit time (i.e. $cm^2$/minute), not per event". This section needs to be rewritten. There are actually two formulae for non-dietary exposure models. It is unclear from the way the guidance document is written that the authors understood this. This may be due to the inaccurate presentation of the model. Equation 3 might better be expressed as Equation 3a and Equation 3b.

$$D_{pot(non-diet)} = CL_{h/o} * TE_{mouth} * SA_{h/oE} * EF_{mi} \qquad \text{Equation 3a}$$

$$D_{pot(non-diet)} = CL_{h/o} * TE_{mouth} * SA_{h/oT} * t_{mi} \qquad \text{Equation 3b}$$

The differences in these two equations are in the last two variables, where $SA_{h/oE}$ is Surface area of hand or object that is mouthed ($cm^2$/event) and $SA_{h/oT}$ is Surface area of hand or object that is mouthed ($cm^2$/minute); $EF_{mi}$ is the frequency of the micro-activity (e.g. number of mouthing events over a 24 hour period, i.e. events/day) and $t_{mi}$ is total time spent engaged in the micro-activity over a 24-hour period (minutes/day). Both calculations end up with a mg/day measurement of dose ($D_{pot(non-diet)}$). These formula are similar to the macroactivity and microactivity dermal exposure equations listed on page 23 and 24.

As shown in the examples below, both equations end up with the same results. However, when given the scenario where a child keeps his fingers in the mouth for extended periods of time, it is unclear when incorporated into equation 3b, whether the exposure 'meaning' is the same as in equation 3a. If a child placed 20 $cm^2$ of fingers in the mouth (3 fingers) for 10 minutes, according to the formula in equation 3b, it would be equivalent to the child having placed 2 $cm^2$ of fingers in the mouth for 1 minute. It discounts the fact that if a child has the fingers in the mouth for a prolonged period of time, that the non-dietary exposure is only attributed to the environmental contacts that preceded that mouthing event. What differentiates the two scenarios is that in the first, a child has frequent mouthing events interspersed with contacts with contaminants while in the second scenario, the child has a prolonged mouthing event with exposure only preceding that event.

Examples.
Scenario 1      10 events, 1 minute duration each
Scenario 2      1 event, 10 minute duration
Assumptions CL = 1 mg/$cm^2$, TE=0.5, SA mouthed= 3 fingers= 20 $cm^2$

Using Equation 3a      $D_{pot(non-diet)} = CL_{h/o} * TE_{mouth} * SA_{h/oE} * EF_{mi}$
Scenario 1                              1 mg/$cm^2$ * 0.5 * 20 $cm^2$/event * 10 events/day = 100 mg/day

Scenario 2                        $1 \text{ mg/cm}^2 * 0.5 * 20 \text{ cm}^2/\text{event} * 1 \text{ event/day} = 10 \text{ mg/day}$

Using Equation 3b     $D_{pot(non\text{-}diet)} = CL_{h/o} * TE_{mouth} * SA_{h/oT} * t_{mi}$

Scenario 1                       $1 \text{ mg/cm}^2 * 0.5 * 20 \text{ cm}^2/\text{minute} * 10 \text{ minutes/day} = 100 \text{ mg/day}$

Scenario 2                       $1 \text{ mg/cm}^2 * 0.5 * 2 \text{ cm}^2/\text{minute} * 10 \text{ minutes/day} = 10 \text{ mg/day}$

       Assuming that $20 \text{ cm}^2$ over 10 minutes = $2 \text{ cm}^2$ over one minute

If a child sucks 3 fingers for 10 minutes, most of the contaminant would have come off during the first minute of sucking so that a variant for Scenario 2 using equation 3b should be

                    $1 \text{ mg/cm}^2 * 0.5 * 20 \text{ cm}^2/\text{minute} * 1 \text{ minutes/day} = 10 \text{ mg/day}$

with the extra 9 minutes not contributing anything to the dose.

c. Page 17 reference needed for the preliminary reevaluation of mass balance soil intake data. The recommendations for age bins 1 to < 3, 3 to <6 and 6 to < 11 are based on this reevaluation, yet in the next paragraph, the report states that there is a paucity of data for estimating childhood soil ingestion rates.  There seems to be a discrepancy in these two statements. According to the Child-Specific Exposure Factors Handbook there is moderately good data for children 1-2 and 3-5 years old, but data is lacking for children less than 1 year old and for children older than 11 years.  The data quality for children 6-10 is considered low.

d. Page 18 paragraph starting 'Children contact potentially contaminated surfaces…' should be rewritten.  The third sentence states how sparse the data is for the strongly asserted first two sentences. Perhaps it might be rewritten as 'Based on a few microactivity studies of few children, children may contact potential contaminated surfaces….'.  One needs to keep in mind that similar microactivity studies have not been conducted on children over 12 years of age or on adults.

d. There is need for consistency in the citations reported in the text and those in the references. Page 13 reference for the EPA Guidelines for Exposure Assessment should be (EPA, 1992). On pages 21, 22, 26, 27 all references that are cited need to be listed in the reference section.

e. Consistency in use and definition of abbreviations in needed.
Abbreviation for the Child-Specific Exposure Factors Handbook (CSEFH) should be introduced the first time it is used on page 12.

f. Abbreviation for the Continuing Survey of Food Intake by Individuals (CSFII) should be introduced the first time it is used on page 15. Abbreviation not presented until page 29.

g. Abbreviation for the National Human Activity Pattern 'Studies'(sic) (NHAPS) should be on page 22.  This is the National Human Activity Pattern Survey. Abbreviation not presented until page 29.

**Review by**
**Gary L. Ginsberg, Ph.D.**

**Peer Review of EPA's Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants**


REVIEWER: Gary Ginsberg, Connecticut Dept. of Public Health
DATE:             February 6, 2004


This review provides overall and specific comments on the document and then specifically addresses the charge questions at the end.


<u>Overall Comments</u>


1)  This guidance represents a significant effort by USEPA to attempt to harmonize the manner in which children's exposure assessments are organized.  Developing age categories which do not obscure important developmental phases in the areas of behavior, anatomy, physiology, and toxicokinetics is a challenge.  The approach taken in this guidance, of a large number of relatively finely divided age categories, is prudent from the perspective that it is unlikely that one would miss any key developmental stages.  However, this approach creates a large burden on the analyst to separately consider many age groups.  Therefore, it is essential for the document to provide the risk analyst with guidance on how to prioritize specific age groups for detailed analysis while omitting other age groups, or how to condense age groups based upon the likelihood for similar exposure (e.g., exposure rate for population that would be unimodally distributed with s.d. or g.s.d. within reasonable parameters).  If such advice can be brought into the current framework, the value of this guidance to children's risk assessment would be significantly enhanced.


2) The document should clarify what type of risk assessor is the intended user.  Is the document intended for use by EPA scientists in the regions for site-specific risk assessments?  If so, then the recommended age categories should be compared to the age groups typically used in default exposure scenarios so that these assessors can see exactly

what are the intended changes to their baseline scenarios (e.g., instead of calculating a default exposure dose from soil ingestion for the 1-6 year old age group as is now done, is this guidance telling the field risk assessors to calculate doses for all of the subgroups up to and beyond 6 years of age?). Alternatively, the guidance may be more suited to chemical managers in program offices or who are responsible for IRIS files; the new guidance on age groups may be useful for them as they try to make their chemical-specific (rather than site-specific) assessments as inclusive of high exposure life stages as possible (and where they may be less structured by standardized exposure scenarios). One gets the impression from a statement in Section 4 that the guidance is meant for "program specific assessments". The targeted audience and potential utility of the document should be more clearly stated and this statement should come at the beginning of the document.

3) The document should set up its age group recommendations based upon criteria for what constitutes a definitive age group. Without such criteria, the establishment of age categories can appear arbitrary and non-specific, based primarily on the deliberations of a panel of behavioral and anatomy/physiology experts from 4 years ago. A set of criteria would allow for an objective evaluation of whether the age groups are in fact suitable for any key parameter in an exposure assessment. The only thing in this document that comes close to stating the criteria used to create age categories is on Page 7 where it offers a short statement from the 2000 workshop discussions on how age groups were developed: "derived largely from considering the rate of change in the listed characteristics." Possible language regarding criteria for age groupings could include quantitative and qualitative descriptors such as: a) Quantitative Criterion: when data are statistically combined across the individual ages within the proposed age category, variability should be characterized as a coefficient of variation that is no greater than xx% for the key behavioral, physiological, or anatomical parameters that govern potential dose. b) Qualitative Criterion: the age range must not contain stages of development that are clearly distinct from one another in terms of behavior, food consumption pattern, or maturation of physiological systems. It would be beneficial for such a set of criteria to come nearer

to the beginning of the document and then have the various parameters reviewed in light of these criteria to ensure that the proposed age bins do not represent so much heterogeneity that they should be broken into subgroups for the purpose of analyzing a given exposure pathway. Current statements justifying age grouping are too general and uninformative -e.g., "As a result of continuing deliberations and reviews of available exposure factors data, the RAF workgroup concluded that it may be appropriate to further divide the 1 to < 3yr age group." - Pg 9, bottom para. At a bare minimum, the goal of keeping age groups narrow where rapid developmental changes occur should be stated up front.

4) Ideally, a guidance document would provide some of the supporting data justifying the age groupings. Tables 1 and 2 could be enhanced in this regard by showing some of the key data that distinguishes one age groups vs another. For example, if one showed data for the following parameters for each age group, the rationale for the many-fold groupings would likely become clearer: food ingestion rate/bwt, water ingestion rate/bwt, breast milk ingestion rate/body wt, inhalation rate per body weight under resting conditions, soil ingestion rate/body weight. This information together with defined criteria would very possibly make the age group recommendations more transparent and defensible.

5) It should be made clear at the beginning of the guidance that these groupings are based upon exposure pathways only, with toxicodynamic factors not taken into consideration. Thus, if a particular age group is of special concern due to vulnerability, this window may need to be evaluated even if the current age group framework does not specify that age group.

6) The guidance focuses upon "potential dose" more so than "internal dose." However, potential dose does not consider toxicokinetic factors that will affect systemic dose across age groups. For a given potential dose, the internal dose may be very different for a neonate than a 6 month old due to a host of ADME differences across these ages. This is part of the reason to keep these ages in a separate bin. Keeping a focus

on internal dose will make sure these TK factors help govern how age groups are constructed and analyzed. On Page 7, when discussing deliberations of the 2000 workshop, the importance of internal dose in constructing age groups is recognized. This should be described sooner and more completely in this guidance document. Further, Section 3 could readily be augmented to describe (or at least reference) the databases/reviews showing the time frame for maturation of key toxicokinetic systems and how this could affect internal dosimetry.

7) While the age groups recommended in this document are generally inclusive and finely divided, the document fails to mention 3 developmental stages that at times can be important to exposure and risk assessment: 1) The in utero period - this document should mention the importance of evaluating this life stage and refer the reader to other agency guidance for how to incorporate it into risk assessments; 2) Premature infants - this subpopulation has particularly immature stratum corneum allowing high uptake rates of many dermally applied chemicals, as well as very immature metabolic systems. For these reasons, risk assessors may want to consider this as a separate age group, even though premature infants often spend significant amounts of time in hospitals and thus away from the general indoor/outdoor environment. 3) First week of life - this is also a particularly immature time for numerous metabolic and renal functions, and with respect to the availability of serum proteins for drug/chemical binding; also the blood-brain barrier is particularly immature at this time. There tends to be substantial amounts of data in neonates. While it may not be necessary to create a separate age group for the first week of life, it would be beneficial for the risk analyst to be informed that this period can be particularly immature relative to the rest of the first month and thus to make sure that parameter inputs include data from this period.

8) The document should tackle the question of continuous vs. age group category exposure modeling. Continuous modeling is feasible for many anatomical, physiological, and even metabolic factors as documented in recent reviews and

analyses ( Alcorn and McNamara, Clin. Pharmacokinet. Ther. 41: 1077-1094, 2002; Clewell, et al., Crit. Rev. Toxicol. 32: 329-389, 2002; Gentry, et al., Tox. Sci. 66: 1-2, Abstract No. 251, 2002).  Such parameters include: body weight, skin surface area, cardiac output, inhalation volumes, respiratory tract surface areas, development of hepatic enzymes and renal function.  Given that these examples have been published, EPA scientists may wonder why age groups are necessary rather than using a continuous exposure model for early life.  Continuous modeling is attractive because it allows all ages and their unique exposure/behavioral issues to be given equal focus, leading to a graphical representation of the peaks and valleys of exposure.  However, it is data intensive and may not be needed or always accurate for each age grouping given limitations in the underlying chemical-specific or age-specific data.  Risk assessors may be confused about the different approaches and need a logical argument as to the relative value of age bins vs. continuous modeling.

9)  The main body of document, Section 3, is an evaluation of data needed to parameterize children's exposure models and whether such data are available for children in the recommended age groupings.  This is an important exercise, serving as a resource as assessors try to implement the guidance.   These sections could be made more practical and useable by providing assessors with the basic data on parameter recommendations from the Child-Specific Exposure Factors Handbook (CSEFH), organized into the age groups recommended in this guidance.  The CSEFH provides a summary of recommended values for a wide range of age groups for many parameters, which for now, it may make sense for risk assessors to use.  The limitations and data needs associated with these recommended parameter values should be noted (as Section 3 does).  However, the current Section 3 is a little too abstract because the discussion is not centered on a set of age group-specific parameter values, such as could be gleaned from CSEFH.  Discussion of specific data would make the issues raised in Section 3 more concrete and point assessors to parameter values that would help them construct a children's age group- specific assessment.

Not stated in the guidance but stated in the Charge Questions, is the intention to reorganize the CSEFH which is not necessarily organized by the age groups recommended in this guidance. It would be good for the document to point out any differences between the recommended groupings and how data are presented in the CSEFH and that the CSEFH may be reorganized in the future to conform with these recommended groupings.

10) Need to discuss treatment of inter-individual variability: Exposure assessment needs to consider the degree of inter-subject variability regardless of whether the assessment is focused upon children or adults. With children this issue can be more important due to rapid physiological and behavioral changes such that even within a relatively narrow age group, variability may be particularly large. This variability affects our understanding of the upper percentiles of exposure and risk and so can be critical to children's risk assessment. An relevant example is in the case of childhood lead exposure. Current risk assessment practice utilizes a modeling framework developed by USEPA, the Integrated Exposure Uptake Biokinetic Model. This model takes into account the variability in blood lead response from a variety of environmental and in utero exposures and predicts the population distribution of blood lead for specific children's age bins (e.g., 0-1, 1-2, 2-3, etc.). The key risk descriptor is the $95^{th}$ percentile blood lead concentration, with the goal to keep this percentile below 10 ug/dl. This is not an example of incorporating exposure variability into the assessment (e.g., the variability in mouthing behavior, soil ingestion rate, water intake rate within an age group is not included), but rather of incorporating variability in terms of the biokinetic (toxicokinetic) response. Nevertheless, it does provide an important example of the need to take variability into consideration in conducting risk assessments for children. This guidance document would do well to include this example.

Specific Comments

Table E-2 - Maybe should change title to include "Exposure Characteristics" rather than just "Characteristics" because this age grouping is based upon exposure assessment only. A categorization scheme based upon toxicodynamic factors would have a whole host of additional parameters to consider. Differences between TK and TD age grouping approaches should be mentioned in text.

Birth to < 1month: Table E-2 implies that this group spends all its time spent sleeping or being sedentary; I'm - not sure that I would call crying sedentary; it likely involves a heightened ventilation rate and muscle usage.
The notation about high skin permeability for this age group is not true except for premature infants - see (USEPA, 1992 Dermal Exposure Assessment, Principles and Applications, EPA/600/8-91/011B, and the references contained therein).
Table E-2 for some reason includes immature immune system. How does this factor affect exposure? It would seem to be more of a TD factor that does not belong in this guidance.
More factors for this age group: low serum protein binding; immature BBB

For older age groups: 1 year and up – Table E-2 should include children's higher intake of food and liquids per body weight.

Table E-3 - Research Needs

Soil ingestion - a data need is to better define how much of a child's daily exposure dose is likely to come from outdoor soil ingestion vs. indoor housedust. This is important given that pesticide and household chemicals may be in housedust while a different array of contaminants may predominate outdoors in soil.

Figure 2 could be enhanced in several ways:

1. Include the terminology developed in text regarding potential dose and internal dose for lower half of chart;

2. Include the ages where the exposure or dose factors become important; in fact an exposure factors matrix would be helpful to identify which factors could have important effects on dosimetry at which developmental stages.

Table 1- pgs 7-8:

Section 3 Parameters Discussion – beginning on pg 13: this presentation could benefit from a summary table showing the recommended age grouping (from Table ES-1) but indicating for each age group whether sufficient data are available to quantify this exposure pathway at that age group, the source of the data, and what the exposure data tend to show relative to the need to further subdivide or condense groups.

The exposure equations in Section 3 do not have a denominator such as body weight for the normalization of chemical intake. Given that exposure assessment typically needs to derive a dose estimate in mg/kg body wt/d to match up with the output from toxicity dose response assessment (also in mg/kg/d), this guidance should show exposure equations with this denominator.

There should be some discussion of whether across-age scaling could be used to help fill in the various data gaps identified in Section 3.

Page 19: The inhalation rate parameter value has considerably more data for children at various stages of development and activity levels than what is shown here - see ICRP, 1994 (ICRP Pub. No. 66) and ICRP, 2002 (Pub. No. 89) for specific data.

Page 25: The reference to dermal transfer coefficients in the last para is unclear - does the value of 10000 cm2/hr mean that children will take up chemicals from 10000cm2 surface area of flooring per hr? If so, for what age group is that factor intended to apply? This paragraph is too vague, although it is clear that this factor represents a data need.

Charge Questions

1. The draft document adequately reflects the age group recommendations from these previous documents. However, as mentioned above, the manner in which age groups are delineated is not well defined in this draft guidance. This may be due to the fact that criteria for age group determinations were not formally stipulated in the prior documents. Further, there does not appear to have been any quantitative analysis of whether there is a high degree of variability within the proposed age groups. It would be helpful to have the current document develop criteria for evaluating age group heterogeneity based upon the information provided in these prior documents and elsewhere. If it is not feasible for the current guidance to provide a statistical evaluation of variability within the proposed age groups, this could be mentioned as a data gap, and the document should be clear that the groupings are based upon a process that involves mostly qualitative judgement.

2. Page 11 of the draft guidance adequately presents the need for flexibility in using the age grouping framework. However, the advice for age group combining is somewhat vague. This is an important part of the document given the challenge presented by separately analyzing all age groups. One possibility for more specific advice is to offer a protocol for organizing/evaluating age group-specific data and then prioritizing age groups for subsequent more detailed analysis. In this mode, qualitative consideration could be given to the factors affecting potential/internal dose for each age group in relation to the exposure scenario(s) being considered and the toxicokinetic properties of the chemical. The qualitative assessment could identify which age groups are likely to have unusually high exposure due to behavioral, dietary, anatomic/physiological, or toxicokinetic factors and then these groups could be prioritized for more detailed analysis (e.g., if chemical is excreted into breast milk, would want to prioritize the first 6 months of life for analysis while if the exposure scenario involves crawling on pesticide-sprayed indoor surfaces, then the 6 month to 1 year group may be specifically prioritized and other groups combined or eliminated).

Thus, a 3 phase approach to using these age groups might be helpful – Phase I - a data gathering/organizing step to take in and consider all the pertinent age group-specific data relevant to the scenario and chemical; Phase II being a prioritization stage where judgements are made about which age groups to analyze in detail; and Phase III being the detailed analysis phase, only done for select age groups. In this way the 3 bullet points (page 11 bottom to pg 12 top) could be systematically addressed.

Regarding Charge Question 2.B., the criteria discussion from above is relevant here as well for risk analysts working with this guidance. Any age group combining/eliminating should be done in light of both qualitative and quantitative (e.g., unimodal distribution, reasonably small coefficient of variation) considerations. Regarding Charge Question 2.C., it may be beneficial to add a 4th bullet point regarding the need to consider each of the factors that constitutes dose and susceptibility (contact rate, toxicokinetics, windows of vulnerability) so that an age group which is significant in one of these 3 areas is not lost from the analysis through combining.

3. A. Comments regarding Section 3 have already been listed above under both general and specific comments.

3. B. Add to soil/dust ingestion, the percentage coming from indoors vs. out. For Food Intake, it should be stipulated that dietary preferences as well as amount of food consumed need to be researched across the proposed age groups. For Activity Patterns: should state the need for scenario specific hand-to-mouth frequency data (e.g., how much of this activity occurs while playing outdoors vs. while watching tv?).

3. C. Once again, the exposure factors highlighted in Table E-3 focus upon potential dose rather than internal dose. It should be expanded to include a list of data needs for toxicokinetic parameters in these age groups. Additionally, one might consider

adding premature neonate exposure to contaminants in hospital settings (e.g., phthalates in tubing) as a data gap.

3.  D.  The recommendation for utilizing ICRP data for children's respiratory parameters was made above under specific comments.

4.  Section 4.1 illustrates an important problem with using pre-determined age categories: the available datasets may be organized differently thus not allowing one to directly extract the data from the underlying sources to conduct the desired age group-specific analysis. This illustration raises the question but the solution to the problem is not clearly laid out. It would be preferable to have numbered or bulleted options for getting around the problem such as: 1) Reorganize the input dataset to conform with the age groupings needed; 2) Use probabilistic sampling techniques to go beyond the categorical limits of the underlying database to utilize all the data and then reformat the probabilistic model output into the desired age groupings to represent exposure doses; 3) Develop a weighting scheme for the underlying dataset to make it more aligned with the desired age groupings. For example if 10% of the observations for the 6 to 11 year old group come from 6 and 7 year olds and 90% come from 10-11 year olds, the data need to be statistically weighted so that equal weight is given to all ages within the group when estimating the group mean and variability statistics. Except for the 3$^{rd}$ option, this has essentially been stated in Section 4.1, but not as clearly defined analytical options.

Section 4 also raises the specter of continuous modeling. The power of these tools to handle large numbers of parameters and data inputs make such approaches more feasible. Continuous modeling using probabilistic sampling from the empirical population of data points would solve the problem of arbitrary age cutoffs. Perhaps the #2 recommendation above (probabilistic modeling with formatting of model outputs into the desired age groups) could be an attractive combination of continuous and segmented approaches to characterize children's exposure.

Section 4.2 is well conceived and represents an important set of considerations. Some of these issues (relevance of long-term chronic dose vs. short-term acute dose to toxic mechanism and window of susceptibility) are pertinent to prioritization of age groups for detailed analysis and the option of condensing age groups. Therefore, some of this material should be brought into the discussion presented at the end of Section 2.

**Review by**
**Ruth A. Etzel , M.D., Ph.D.**

Peer Review of EPA's "Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants"

**General Impressions**

The February 2003 external review draft of EPA's "Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants" (EPA/630/P-03/003A) is well thought through and clearly written. My only major concern is that the guidance calls for collection of data that would allow for estimation of the variability across the population, but neglects to include American Indian and Alaska Native children. The guidance recommends studies of the major ethnic groups in the U.S. population including Black, Asian and Hispanic. I believe it would be a serious mistake to neglect data collection among American Indian and Alaska Native children. I strongly encourage EPA to revise the guidance to ensure that a call for collection of data in this group is specifically included.

**Responses to Charge Questions**

1. *As discussed above, the use of the information presented at the peer involvement workshop ("Summary Report of the Technical Workshop on Issues Associated With Considering Developmental Changes in Behavior and Anatomy When Assessing Exposure to Children") coupled with a subsequent analysis of exposure factors data formed the basis for the guidance. Please comment on whether the guidance appropriately reflects the recommendations of these expert deliberations and whether the process of selecting the age groupings is adequately described?*

   I believe that the draft guidance appropriately reflects the recommendations of the Technical Workshop on Issues Associated With Considering Developmental Changes in Behavior and Anatomy When Assessing Exposure to Children. Overall, the process of selecting the age groups is adequately described, although I am not sure the justification for including an additional age group spanning from 18 to < 21 years is adequate.

2. *Section 2 of the guidance concludes by presenting three recommended points for discussion by the assessor when combining or eliminating age groups in a particular exposure assessment. These points include: (1) the basis for the determination; (2) description of uncertainties and biases; and (3) discussion of the types of data and information, if available, which would allow combined groups to be separated in future analyses. Please comment on:*

   A. *Whether the guidance adequately reflects the need for flexibility in using these age groupings?*

      Yes, the guidance adequately reflects the need for flexibility in using these age groupings. The guidance stresses that it is important for exposure assessors to engage in an iterative dialogue with toxicologists and other health scientists to determine the age groups (or portions of age groups) that will be the focus of any particular assessment. (p. 11)

   B. *What more specific guidance regarding application of the 3 points identified above might be provided to risk assessors; for example, discussions of statistical considerations, or temporal and interindividual variability?*

      I think it would be useful to include a discussion of interindividual variability.

   C. *Are there additional points beyond the 3 identified that should be highlighted in making the decision to use an age grouping for a particular exposure scenario and data set?*

      The three recommended points appear to be sufficient.

3. *Section 3 of the guidance contains recommendations for a set of critical exposure factors pertaining to further analysis and research. Subject to EPA approval and*

*finalization of this guidance, the Agency anticipates re-compiling its Child-Specific Exposure Factors Handbook – Interim Final Report ( EPA-6006P-00-002B). As a preliminary exercise along these lines, the guidance includes recommendations for further analysis/research on child specific exposure factors. Please comment on:*

A. *The accuracy of the statements about our current knowledge regarding each of these exposure factors.*

The statements about our current knowledge regarding each of these exposure factors appear to be accurate.

B. *The priorities and recommendations for further data collection activities (Table E-3 in Guidance document).*

Overall, the recommendations for further analysis and research on exposure factors data for children are solid. I would add another recommendation to the third recommendation on the list on page 1 for body weight. My recommendation relates to body weight data for American Indian and Alaska Native children. It is true that a more complete understanding of body metrics may have a bearing on exposures, doses and risks. Some studies suggest that American Indian and Alaska Native children may have a higher proportion of fat-free mass than the national reference standards. Therefore I think it is important to gather data on this ethnic group. This is especially critical in view of the fact that their diets may differ dramatically from the diets of other ethnic groups.

C. *Whether any critical exposure factors have been overlooked in these recommendations?*

It does not appear that any critical exposure factors have been overlooked in these recommendations.

D. *Whether there are any additional or developing sources of information that could be used to improve or fill exposure factors data gaps related to the recommended set of age groupings?*

I am not aware of any additional or developing sources of information that could be used to improve or fill exposure factors data gaps related to the recommended set of age groupings.

4. *Section 4 of the guidance is intended to alert assessors to uncertainties and biases that can be introduced through the use of models, time weighted doses and the like. Please comment on the utility of this discussion and what additional points, if any, should be highlighted.*

Those who are unfamiliar with the art and science of exposure assessment may not realize the extent to which the exposure assessment findings change with different inputs. I think this should receive much more emphasis in the guidance.

**Specific Observations**

These are minor errors that need to be corrected:

On page 13, line 10, change "digestion" to "digestive".
On page 26, line 11, the reference is missing.

**Review by**
**Larry L. Needham, Ph.D.**

**EPA's Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Chemicals**

1.  In short the answer to #1 is yes. Of course, one could subdivide even more the early months although I think this is fine. However, I see no real reason to separate the post-puberty years. If one is going to link males and females together, I would probably say the groups should be 6 to <12 and 12 to <21 years, but this is fine.

2.  In regards to the exposure assessment, it really depends on the question. If the question is risk management in nature, then it really matters what the routes and pathways leading to exposure (contact) are; if these are known, then hopefully prevention measures can be taken as an intervention steps. However, if the question centers around the first sentence of the Executive Summary (page iii) "…appropriate age groups to consider when assessing childhood exposure and potential dose to environmental contaminants," then defining these bins should, in addition to the examining developmental changes in various behavioral and anatomical characteristics, consider differences in pharmacokinetics which determines the dose after exposure and pharmacodynamics which determines the effects. Pharmacokinetics consists of absorption, distribution, metabolism, and elimination. The age groups suggested are fine in general although I still prefer those I gave in #1. Since these age group bins are developed for the general population, they cannot include certain things that will affect individual differences in pharmacokinetics, such as sex, race/ethnicity, other genetic differences, nutritional status, etc. However, for most all health related endpoints I see no need to further divide post-puberty years.

3.  I think what has been done is fine, but it is highly academic. A more relevant question really is for large exposure studies, with or without a given health endpoint, what is the rank order of environmental matrices to collect for attempting to assess exposure to individuals in each of these age bins. I see that really no where in the document. We simply cannot afford to measure concentration levels of any given substance in all matrices leading to different routes of exposure. Attempts need to be made to rank these for general population studies and then perhaps list where certain activities (such as indoor spraying of pesticides) would change this ranking.

4.  Models are models. They are needed but it is important to note that they should be calibrated and validated, and if possible, against a biomarker. But biomarkers have limitations as well, especially with nonpersistent chemicals. It would therefore be recommended to test out these models (see Fig 3 and 4) for persistent chemicals using biomarkers to calibrate and validate the model.

Review by
P. Barry Ryan, Ph.D

**Preliminary review of "Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants."**

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*General Comments*

This document is comprised of a nine-page Executive Summary followed by 38 page of text.  The Executive Summary offers a relatively concise presentation of the recommended Childhood Age Groups to be used in Exposure studies, as well as a tabular list of the reasoning behind the selections.  The selected list differs little from that suggested in the 2000 Workshop, the principal difference being a recommendation for splitting off the 1 to <2 age group separately- a recommendation with which I concur.

The main document begins with an Introduction to the problem (two pages) and follows that with a presentation of a section outlining the age groups.  This section includes several working definitions and a very difficult-to- read figure (Page 6).  Pages 7-11 repeat tables presented in the Executive Summary, adding some descriptive prose.  At the end of this section, the RAF gives some guidance on combining multiple age groups arguing that, for many exposures, not all age group divisions will be necessary.

Chapter 3 offers a presentation of numerous models of exposure commonly used in exposure assessment and risk assessment.  Many of these models are quite general—not specific to children.  The presentation includes references to sources of data for many of the parameters, and offers a valuable resource to those examining this document.  However, more complete presentations are available, for example in the Exposure Factors Handbook and in the Children's Exposure Factors Handbook.

Chapter 4, beginning on page 28, delineates models that may offer some utility in addressing temporal variability of exposures.  Again, such models are presented in other forums as well.

What puzzles me about the whole document is its intended purpose.  As mentioned, the Executive Summary, and its near-twins Chapters 1 and 2 offer the insight needed for most researchers.  RFA has given guidance here, as well as given reasoning behind the guidance.  This is quite good and is needed.  Further, they have argued, compellingly I believe, that the Guidance is just that.  Some exposures may not require the full spectrum of age-group divisions.  For example, a study of the injuries associated with teenage driving may chose not to examine the 0-<3 month, 3-<6 month categories, and so on.

What is less clear is the need, or even desirability, of including Chapters 3 and 4.  An annotated bibliography may be of more use.  Most researchers working in the exposure and risk assessment areas are going to be familiar with the type of simple models used to estimate exposure and risk. If they are not, they would be better advised to read the detailed expositions in other guidance, e.g., EPA's Superfund Guidance, the Exposure Factors Handbook, and the Children's Exposure Factors Handbook.  I think the scientific community would be better served through an annotated bibliography rather than page after page of equations relating exposure or

risk to certain factors. Further, many of the parameters need are very poorly known; either only a few data exist or no data exist. This should be stressed in any presentation.

*Charge Questions*

1) *Please comment on whether the guidance appropriately reflects the recommendations of these expert deliberations and whether the process of selecting the age groups is adequately described.*

In general, I believe the document accurate reflects the results of the deliberations cited. However, I do not think the full reasoning was adequately described. The brief descriptions in the Tables in both the Executive Summary and in the early chapters cannot do justice to the deliberations that went on. However, referring to the original documents and summarizing them as has been done is, by and large, adequate.

2) *Three Questions:*
   a. *Whether the guidance adequately reflects the need for flexibility in using these age groupings.*
   The presentation stresses this is a number of places. See earlier comments. This is a positive aspect of the report.

   b. *What more specific guidance on the 3 points identified above might be provided to risk assessors; for example the discussion of statistical considerations, or temporal and interindividual variability?*
   The discussions suggested in this question are certainly important and would be highly desirable to include in this presentation. However, temporal and interindividual variability for many exposures, and certainly exposures in the age group outlined simply do not exist. So we can ask for a better presentation, but without the data to support the guidance we must be content with what is here.

   c. *Are there additional point beyond the 3 identified that should be highlighted in making the decision to use and age group grouping for a particular exposure scenario and data set?*
   I cannot think of any at the moment.

3) *Four Questions: Comment on:*
   a. *The accuracy of the statements about our current knowledge regarding each of the exposure factors.*
   The review adequately described the data available at the time of the Workshop and somewhat later. However, new studies and new data are being collected each day that improve our knowledge of children's exposure.

   b. *The priorities and recommendations for further data collection activities.*

The data analysis suggestions should be done immediately in that they are substantially cheaper to implement than new data collection studies.  Further, they will give us a great deal of useful information..  However, funding should be allocated to fill in the gaps in these data as well. For example, soil ingestion rates for children in the age groups suggested are very poorly known at present.  This is true whether the child is a normal child or suffers from pica.  The information required from these studies is substantially more detailed and stratified than earlier studies.  This suggests a costly data collection procedure.

c. *Whether critical exposure factors have been overlooked in these recommendations.*

I have not perceived any specific shortcoming that I can identify.

d. *Whether any additional or developing sources of information that could be used to improve or fill exposure factors data gaps to the recommended set of age groupings.*

The suggestion made to analyze existing datasets, e.g., CSFII, NHANES, etc., is the way to go.  In addition, numerous new studies under the EPA STAR program are gathering data on exposure factors specific to children.  These will need to be incorporated as results come in.

4) *Please comment of on the utility of the discussion in Section 4 on uncertainties and biases.*

I think that the most important part of this discussion is that on temporal variation in exposures among the different age groups.  This is a most difficult problem to tackle, especially when exposures are episodic and highly variable.  I would urge a more complete discussion in this area.

**Review by**
**Robin M. Whyatt, Dr.P.H.**

**Comments on: U.S. Environmental Protection Agency, Risk Assessment Forum, External Review Draft (February 2003) Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposure to Environmental Contaminants**

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**Introduction:**

The U. S. EPA is to be commended for developing a framework for assessing childhood exposures that will provide a consistent starting point for program-specific risk assessments. As is clear from the Guidance Document (see Figure 1), multiple different approaches have been used within the Agency in the past, resulting in significant variations in childhood age groupings. The proposed guidelines should facilitate much-needed cross-program consistency in risk assessments, particularly for the youngest age levels where susceptibility is likely to be greatest.

The Agency is also to be commended for taking a child-protective approach in developing the guidelines. This is consistent with the recommendation of the May 2000 Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy when Assessing Exposure to Children (the Workshop) that the Agency be as child-protective as possible in developing age-bins. It is also consistent with the intent of the Food Quality Protection Act and Executive Order 13045. In particular, the Agency is applauded for including multiple bins during the first years of life. As discussed at the Workshop, the early postnatal period is characterized by rapid growth and development in many systems (nervous, renal, respiratory, GI), changes in skin permeability and the ratio of skin surface area/body weight, and increases in metabolic capabilities. For these reasons, the neonatal period has been estimated to be more different than any another age group (childhood through adult) in terms of physiologic development (1). The differences are likely to affect both exposure and susceptibility, and, therefore, multiple age bins during this early period are warranted. In addition, our data and other studies (2) (3) have indicated that exposures can also be appreciably higher during the preschooler years (ages 1-3) than later in life, and, thus, separate age bins during these years are also appropriate.

**Charge Question 1:**

In general, the Report reflects the recommendations of the 2000 Workshop and does a nice job of combining the recommendations concerning age bins made by both the

behavior and the anatomy subgroups. However, there are several important areas in which the Guidance deviates from the recommendations at the Workshop. Most notable is the omission of consideration of exposures during the fetal period. While assessment of prenatal exposure was outside the scope of the 2002 Workshop, participants at the Workshop unanimously stressed the importance of including this life-stage in exposure and risk assessment, and "strongly recommended that EPA look closely at maternal-fetal exposures, since in utero development is such a critical and sensitive period" (Workgroup p vii). The reason for this is that most chemicals cross the placenta (1) but detoxifying enzymes are often undetected or found at low levels in the fetus; also organ systems are developing rapidly, rendering fetal development a period of particular susceptibility. Several examples from our research and other studies are cited below to illustrate these points. For example, our research has shown that that levels of the organophosphates chloryrifos and diazinon are identical in paired maternal and newborn blood samples collected at delivery, and are highly correlated (r=0.6-0.8, p<0.001), indicating that these compounds readily cross the placenta (4). However, paraoxonase, the enzyme that hydrolyzes toxic metabolites of organophosphates, is at low levels during fetal development. Similarly, studies have shown that the phthalates diester and monoester cross the placenta (5). While the fetus is able to hydrolyze the parent diester to the more toxic monoester (which is the bioactive agent), the glucuronidation detoxification pathway does not develop until 3 months after birth (6). In a recent small pilot study of phthalate levels in meconium samples collected from newborns from minority communities in New York City, we detected monoester metabolites for 2 phthalates in 100% of the samples. Both experimental and epidemiologic evidence indicates that nicotine levels concentrate in the fetus (7;8). This appears attributable in part to reduced clearance mechanism, as the half-life is longer during fetal development (9). However, the fetus is also likely to be exposed to nicotine from gastrointestinal reabsorption of nicotine in swallowed amniotic fluid, as well as through transfer from the maternal circulation (10). Amniotic fluid may also be a source of fetal exposure to other toxic compounds as well. Finally, a number of lines of evidence indicate that the fetus may be particularly susceptible to certain DNA damaging agents due to rapid cell division and to reduced detoxification and DNA repair capabilities (11;12). Consistent with these hypotheses, we found plasma cotinine and white blood cell aromatic-DNA adduct levels to be significantly higher in newborn compared to paired maternal blood samples collected at birth (13). These examples highlight the importance of including fetal development in any risk assessment guidelines for childhood exposures as recommended by the Workshop.

In addition, the decision to start the age bins at birth without consideration of the timing of birth is contrary to Workshop recommendations. While, ideally, birth occurs at 40±2 weeks gestation, this is often not the case. As illustrated at the Workshop, exposure and susceptibility are likely to be quite different for the infants who falls into the first age bin (birth < 1 month) between 28 and 32 weeks gestation, compared to the infant who falls into this age bin between 40 and 44 weeks gestation. Specifically, premature infants can differ from full-term infants in terms of hepatic capabilities, respiratory rates, skin permeability and immune function. All of these differences are likely to affect exposure and/or susceptibility. Panelists at the Workshop therefore recommended that premature

babies should represent a special subpopulations, and suggested that an age bin for premature infants could go up to the expected date of delivery (p 4-27).

The scope of the discussion on breastfeeding should be expanded to include not only consideration of exposures to lipophilic compounds but also the possibility of exposure to nonlipophilic substances (Workship p 4-31). While data are quite limited, several studies suggest that water soluable compounds may partition into the water fraction of breast milk and be transferred to the infant. These include organophosphates and possible other non-persistent pesticides (14-16).

In regards to whether or not the Guidance appropriately reflects the conclusions of the Risk Assessment Forum Technical Issue Paper (Age Group Recommendations for Assessing Childhood Exposure and the Adequacy of Existing Exposure Factors Data for Children), the purpose of that Forum was principally to determine the availability of data to support the age bins as proposed by the 2000 Workshop. The Guidance does a good job of summarizing the availability and lack of availability of data for assessing exposures by multiple routes (dietary, dermal, non-intentional ingestion, inhalation) for each proposed age bin. The lack of available data for many routes at the younger age levels is quite striking. However, this should not deter the Agency from finalizing the Guidance, as one of its major benefits will be to provide a framework for future research and data collection efforts. Indeed this effort is already ongoing as illustrated by the targeted sampling towards children 9 years and younger by the USDA 1998 Continuing Survey of Food Ingestion for Individual. Results of this sampling are likely to improve dietary and water ingestion rates for the younger age bins (Issue Paper, 2001).

**Charge Question 2:**

The recommended steps that should be taken when combining or eliminating age groups are generally well articulated. In particular, the recommendation that a record of the scientific rationale underlying the risk assessment be developed, and that it address the points outlined on pages 11-12, will be of value both in guiding future risk assessments and also in focusing data gathering efforts. Also, the Guidance has nicely captured the recommendations from the 2000 Workshop regarding the importance of having exposure assessors work in concert with toxicologists and other health scientists. In particular, Workshop panelists stressed the importance of having exposure assessors understand the biologic phenomena and distributions underlying the age bins. Participants further noted that variability is likely to be greatest during periods of rapid change such as occur among the youngest age groups.

However, the Guidance does not provide adequate guidelines for the risk assessors in instances in which no data are available at all, which is clearly going to be the case for the younger age bins, at least in the short run. In particular, I found the following statement vague: "Where there is a lack of exposure data for a particular age group of potential importance, the assessment could still include a rough estimate based on exposures of other age groups and consideration of how those age groups differ". What are the criteria for making the rough estimate? How should the risk assessor determine

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how the particular age group differs from other age groups? If the Guidance is to provide Agency-wide uniformity in approach to risk assessments for childhood exposures (clearly an important goal), it needs to do a more comprehensive job of outlining criteria that can be used when data are not adequate. For example, perhaps the Guidance could recommend specific factors to be used for specific age bins to account for the greater exposure and/or susceptibility in the absence of a complete dataset. This is similar to the approach that was taken by the FQPA in recommending the 10X factor. Specifically, that act provided that "[A]n additional tenfold margin of safety…shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children……[T]he Administrator may use a different margin of safety …only if, on the basis of reliable data, such margin will be safe for infants and children."

**Charge Question 3:**

As stated above, I thought the Guidance did an excellent job of summarizing the availability and lack of availability of exposure factors data as compiled by the Risk Assessment Forum Technical Issue Paper Age Group Recommendations for Assessing Childhood Exposure and the Adequacy of Existing Exposure Factors Data for Children. In particular, Table E-3 provides a compelling list of future research needs. I have already discussed the areas I think were overlooked (the prenatal period and potential exposures to nonlipophilic compounds through breast milk). The Risk Assessment Forum should know that there are two ongoing initiatives that may help to fill some of these data gaps. Specifically, the Chemical Working Group of the National Children's Study is currently preparing a white paper on techniques for assessing childhood exposures to support the National Longitudinal Cohort Study. Among other things, it provides a reasonably extensive review of research on assessing childhood exposures to a broad range of environmental contaminants. In addition, the 12 NIEHS/EPA-funded Children's Environmental Health Centers are currently collectively preparing a series of manuscripts summarizing the lessons learned through their longitudinal cohort studies, including of *in utero* and childhood exposures.

**Charge Question 4:**

The emphasis in Section 4 that exposure assessors develop a full understanding of the model constructs, including uncertainties and biases, is extremely important. As discussed above, risk assessors also need to develop an understanding of the biologic phenomena underlying the age bins. It should be noted that there was considerable concern raised at the 2000 Workshop regarding U. S. EPA's direction of basing children's exposure assessment on indirect exposure factors. Panelists strongly urged that models be validated using direct measures, including measures of both exposure and biomarkers. I concur with these recommendations. In addition to a number of studies that are already ongoing within the Agency, environmental and biologic measures are also being gathered in most of the longitudinal research studies being conducted by the Children's Environmental Health Centers and these may be of significant value to the

validation efforts. In addition, The Minnesota Children's Pesticide Exposure Study is conducting an aggregate exposure assessment and is collecting environmental and biologic data relating to multi-pathways in children (17).

Section 4 of the Guidance also includes a useful discussion of some of the problems associated with averaging exposures in risk assessments. This may be of particular concern when assessing childhood exposure to direct acting carcinogens (those that act at the first stage in the carcinogenic process). It has been estimated that when exposures are constant, nearly 50% of the risk from initiating carcinogens is incurred in the first five to ten years of exposure (18). However, for a number of childhood exposure scenarios, exposures are greatest during the first years of life. For example, using a time-to-tumor model, we, estimated that for carcinogenic residues in fruit juice, 75% of the lifetime cancer risk to an initiating carcinogen might be incurred during the first five years (2). The U.S. EPA cancer risk assessment methodologies currently use lifetime average doses and do not account for timing of exposure.

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**Review by**
**Mary S. Wolff, Ph.D.**

**Comments on "Guidance … age groups … childhood exposures .."**

This is a fundamentally sound and thoughtful document. The peer-review process will benefit the statement by adding further sophistication and by updating information that has become available since its creation. In terms of readability, several suggestions for organization and clarity are made below. For reviewers, it would help to have the lines numbered during the review process. A headline or topic sentence to lead off the major paragraphs would also help. The tables need more extensive labeling; some examples are given below, but in general tables should be interpretable without having to consult the text.

Regarding scientific content, the major critique is that prenatal exposures are omitted, as noted in the Review Panel's phone call. In addition, it would be better to include more explicit mention of urban/built environment mediation of exposure, of geographical variation in environmental toxins, behavior, and climactic effects on exposures, and gender differences. These factors, along with related variables discussed, may have a main effect or may interact with other factors to modify exposure several fold. An issue that deserves mention as a primary factor in children's exposure assessments is multiple or combined exposures, and how these windows might affect that, or if that seems too complex, a mention of the need for this. Finally, whether exposures are persistent or non-persistent may be more important in certain age groups.

With regard to whether the process is adequately described, it is not clear what changes/improvements may have been made at each step; however, this may not alter the impact of this statement.

Another readability suggestion is to more completely entitle and label and footnote the tables. For example Table 3- p 9, this was the starting point from which the current document diverged. It has the same title as a later table. You could also say the final age groups are given in Table X.

P iii and p 2: include some examples of purposes of the exposure assessments, such as use in risk assessment, in identifying exposure sources, etc. Do windows cover/mean to cover exposure risks (opportunity and biology) as well as health risks (i.e. prenatal exposures are thought by

many to be the only relevant window for childhood neurobehavioral deficits but not for adult or late childhood behavior). Will it be useful or just impossible to assess multiple exposures?

Table E2: divide into physical and behavior so that multiple influences can be noted, e.g. gender kicks in at age (3-11y??) and breast milk has less impact from age 8 on. The windows of hepatic activity presented here may not be up-to-date (i.e. at 2-3 yrs the lit does not support that all enzymes reach or ("fall back") to adult activity; at 1-2 yr some are nil; some are reached later, exist not and not later, etc., so that this statement might be misinterpreted. In older ages, the behavior seems oversimplified (and in Table 1); drugs, pregnancy, sexual activity all alter exposure patterns. At 3-6 yr inner city children may not see outdoors (built environment). Gender differences are also marked; e.g. 3-6 yr may mark female puberty and 6-11 male development.

The paragraph on p vii is not easy to follow. Maybe the paragraph should have a header. It doesn't seem specific or straightforward enough. Maybe it would benefit from more examples or specific outcomes, or indicate that in some situations that exposure assessments should be mechanistically based.
P ix, table E3: inhalation rate and other absorption factors neglect built environment, including recent reductions in physical activity especially in urban children; this issue goes to the interactions mentioned in my introduction above. Maybe an interaction section could be added? The parts of Table E3 on p 1 are greatly influenced by urban/suburban/exurban residence (box 1), geography (box 2), and gender (box 3).

P 4, bottom, re: behavioral development, see above where I mention prenatal=early neuro deficits. Also, at the top of this page, last sent 1st para says prenatal DEVELOPMENT outside scope. Again the prenatal contribution to both exposures and development are influential during all of life, and are pronounced for the first 8 years of life. There is some repetition, as in p 4 par 3 and p 7 para 3.

Table 2 – Body proportion figure would be great here. (WAITING FROM FRANK)

Table 4 – not clear what footnote b means.

P 11 para. Is this clear? Give a headline (Ages may be combined for specific topics).

P 12 top, scientific uncertainty = what kind? Statistical? Biol? (specify). Are there others?

P 14, 3.2.1.1 bullet on 'Collect data …. Variability' of what? Fat? Chemicals? Maybe add a bullet, regarding other matrix effects, e.g. molality (ionic capacity of non-lipid portion), things that affect protein levels, that affect more polar chemicals. Last sentence (suggested revision): In addition, for infants older than 12 mo who continue to be breastfed, data are needed to determine……

P 15. Top. Are there data on approximate specific food intakes/kg age-?If so mention here and in the H2O section. Para 3: add that the formula = that for diet.

Organization and labeling of 3.2 could be improved for readability and comprehension. The formulae are clear, but the organization is not. Also, label the 3.2 sections more clearly. It is not immediately clear how Eq 2 and Eq 3 differ from Eq 1. The differences here seem to be due to the IR, so label the sections accordingly; i.e. is 3.2.2 IR for non-dietary?

P 18; what about pulmonary enzymes and how they affect available dose of chemical or metabolite? Could add pulmonary metabolism on p 21 to the bullets up top.
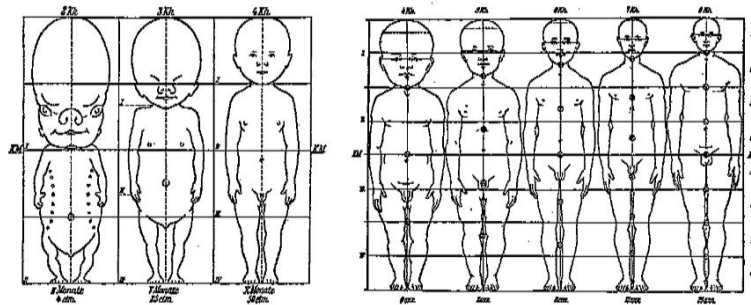
P 21, 3.3.2 does this belong here? It is a key issue, maybe its own section.

P 26. Surface area – also obesity (or ht/wt extremes) are critical.

P 31, Table 5 – define the assigned value sources so table can be read without extensive consultation of the text. "Random" meaning here is not clear.

P 33: Define terms – I did not follow this.

## Stratz's 1909 diagram of change in body proportions during fetal and postnatal growth



J. K. H. Wales, "A brief history of the study of human growth"