Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants

EPA Response to Peer Review and External Comments

I. Comments from External Peer Review panel commissioned by EPA via contractor, Versar, Inc. Winter, 2003-2004.

The EPA contracted with Versar, Inc., to conduct a letter review of the draft document: "Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants" using a panel of technical experts in relevant disciplines. A panel of 12 experts was assembled from schools of public health and environmental science, State Health Departments, and private environmental firms. This document summarizes the Agency's response to the comments received, and how changes are reflected in the final version of the Guidance. The external peer reviewers generally agreed with the age groups selected in the Guidance. Reviewers recommended that fetal and premature infant exposure should be included, and EPA agreed but noted that at this time methodologies are not adequate to address those age groups (see comments by Science Advisory Board on Children's Supplemental Cancer Guidance, 12/2004). The references were improved and expanded and the purpose of the guidance was clarified, based on the comments. The reviewers also recommended that examples be provided on how to implement the age groups; practical issues are discussed in the final document, and future case studies will be posted first on the EPA intranet, reviewed, and finally to the internet.

NOTE: In the peer review comments, the chairperson's summary covers many of the points made individually. Therefore these are addressed first, then individual comments only where they differ from the summary.

GENERAL COMMENTS	
Comment	EPA Response
1. 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.	**Preface, Executive Summary** and **Section 1.0 Introduction**: The description of the purpose and rationale for this document have been greatly expanded and clarified in the text, including relation to other guidance and science policy. The purpose is first stated in the Preface on pager vii. Other exposure assessment guidance are categorically listed on page 1; the relation to the Children's Risk Framework is mentioned on page xiv; the Child Specific Exposure Factors Handbook on page xii.
2. 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.	**Executive Summary**: The revised document addresses how and when to apply this guidance in relation to existing guidance and technical reports. Various other frameworks are also mentioned including the proposed Children's Risk Assessment Framework and the Framework for Cumulative Risk Assessment, as stated in (1).
3. Clarification of the intended audience was also requested.	A **Preface** providing perspective on impetus and intended audience has been added. **Executive summary**: The document is addressed to EPA scientists, in particular exposure and risk assessors, who are encouraged (several times) to work together with toxicologists.
4. 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.	The Guidance acknowledges there are excellent rationales for considering exposure during the prenatal development period. The **Executive Summary** refers to other existing and developing guidance to address this lifestage. It is also stated in **Section 2** that currently available methods are not adequate to address fetal exposure, but should be developed (see pages xiv, 8, 16).
5. 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	**Executive Summary, and throughout**: The scope of this guidance is limited to the impact of age and development on exposure and dose. However, it should be emphasized that other factors can also have a significant impact on exposure and dose, and are addressed in other documents, such as the

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.	Exposure Factors Handbook, Cancer Guidelines and the Framework for Cumulative Risk Assessment (see pages xiv, 1, 4, 15, and **Appendix**). It is noted in the Appendix that additional research is noted in these areas.
6. 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.	In **Section 2.0**, guidance and examples are provided for dealing with limited data. **Section 3** provides a discussion of screening level assessments, integration with toxicity adjustment factors, and the use of binning in models. Scenario-specific **case studies** are being developed for EPA intranet users.
7. 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.	Additional **references** and links have been added, including those provided by reviewers. Further references are provided in the source documents. Table 5 and Figure 2 were added showing integration of age groups with the Early Lifestage Supplemental Guidance for Carcinogens and over various time average exposures.
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?*	
Most of the reviewers requested additional clarification of the rationale for selection of the age groupings and rationale for not including others. *Related:* Reviewers stated that current statements justifying age groupings 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."	**Tables 2 and 3** provide details as to some of the key variables distinguishing age groups physiologically, anatomically, and behaviorally. The July 2000 Workshop and related references and subsequent analyses are identified as sources. The **Appendix** provides a summary of the data supporting the age groupings and the current data gaps.
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.	The value of standardizing age groupings for comparable risk assessment is more fully explained in the **Introduction**. The language was changed to accommodate varying degrees of data completeness for exposure and toxicity, and gives examples of exceptions such as cases as exposure-

	effect relationships (pages 4-5, Table 1). Decisions in selecting age *bins* for exposure modeling are discussed in **Section 3.3**.
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.	Specific examples and references are provided in **Section 2**, screening assessments in **Section 3**, and the **Appendix** recommends age groups for further analysis and research. The future **Case Studies** will give specific application examples.
Reviewers suggested that the document clarify at the beginning of the guidance that the groupings are based upon exposure pathways only, with toxicokinetic and toxicodynamic factors not always 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.	**The Executive Summary** clearly states: "*It is important to note that the recommended age groups are based on exposure considerations and as such are not intended to take into account chemical-specific toxicological variability that can also impact risk* – such considerations, as discussed later, should occur through an iterative dialogue between exposure assessors and toxicologists." (p. xi; italics in document)
There was general agreement among most of the reviewers that prenatal considerations are very much needed in this document. Several reviewers provided excellent detailed discussions with examples as to why consideration of exposures during the gestational period are essential. In addition, it is suggested that EPA review the vast literature, contact specific investigators, or convene a group to address this topic in more detail.	The **Executive Summary** states that consideration of fetal exposure is important, "However at the time of this writing, Agency methodologies have not been developed to separately evaluate fetal exposure (SAB 2004)"p. xiv.
Reviewers noted that the decision to start the age bins at birth without consideration of the timing of birth was contrary to workshop recommendations. In addition, 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.	The need to address special susceptibility of additional lifestages, such as premature infants, is recognized in the **Executive Summary,** and the first month of life is considered a separate age group. Like fetal exposure, the Agency is not able to address premature infant exposure at this time (page xiv). **Section 2** mentions premature birth as an additional consideration (p. 15).
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.	The **Appendix** recommends: "Collect data that would allow estimation of the effect of a mother's nutrient status on the fat/lipid content of breast milk (both before and during lactation). Data are needed on the types of lipids that may change

	because of these variables and the mobility of such lipids in the milk during lactation." (p. 37)
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 did not have specific recommendations about these age groupings, but suggested that EPA describe their rationale for creating the two groups for 16 to < 18 years and 18 to < 21 years. Reviewers also 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.	In other peer review comments (above) it was recommended that the perinatal period be considered separately due to various immature systems in the infant. This is justification for the additional birth to <1 month lifestage. (p. 15) The additional late teen/early adult split has been rejoined in the final recommendations; the original rationale was primarily behavior related (driving and other activity milestones). **Section 2** describes the deliberations of the behavioral and anatomical/physiological groups and the selection of the 6<10 and 10<21 age groups.
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.	In the **Executive Summary and Appendix,** the Guidance states that gender and other factors, were identified as important to consider in exposure assessment, but are beyond the scope of this document and further research is needed.
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 if 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. *Related comment*: 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 affected by gender. The guidance document needs to discuss these points.	Qualitative and quantitative approaches to evaluating age group heterogeneity are described in several locations in the Guidance, in particular addressing uncertainties in selecting different age groups. The Agency acknowledges here and in the Guidance that, ideally, exposure and development should both be considered as a continuum. Although discrete age groups may be used for practical reasons, the variability in the underlying distributions should be documented; the Appendix describes these efforts.
Reviewers encouraged the Agency not to neglect the philosophy expressed during the EPA Risk Assessment Forum workshop of July 2000 where the ideal situation for considering	In Section 3.3, it is stated that: "Data-specific bins used in the models should follow the

development was discussed as a continuum of exposure values. Since age groupings must be considered, then it should be emphasized 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, it was 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.	following principles: (1) bins should express representative and relevant metrics for the range of individuals grouped with each bin, and (2) the selected bins should not mask any truly unique profile within the bin (i.e., don't hide a significant peak). If this data binning process is done well for each database, then the values sampled from each database should be representative for each age group."
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?	
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 few data were available. Reviewers suggested that adding some examples with references would be useful for demonstrating how to be flexible and generally stay within the context of 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.	Guidance for situations when no data or very few data are available in **Sections 2 and 3** and the future **Case Studies**. The **Case Studies** are being developed to meet this need and will be posted on the EPA intranet until they can be tested by the EPA assessors; they can be edited and updated before posting on the intranet. The need for flexibility is laid out several times in the Guidance. It is emphasized that fully characterizing the dataset and its uncertainties is very important. The data gaps and recommendations for further analysis and research are delineated in the **Appendix**.
2B. 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?	

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.	The advice for combining or otherwise changing age groups has been made more specific in **Sections 2 and 3**, and in the future **Case Studies**.
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.	See statement above.
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.	Efforts were made to increase the clarity of the discussion of the data available, particularly in the **Appendix**, and **references** were upgraded, including suggestions from the peer reviewers.
2C. 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?	
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 than evaluating the uncertainties associated with such data gaps. Reviewers felt there was a need for the assessor to evaluate the impact of this course of action on exposure assessments.	The need to address the use, or not, of age groups and resulting uncertainty has been further explained in the **Executive Summary**, **Sections 2 and 3**, and the **Appendix**.
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 no recommendation can be made at this time regarding any additional points to be considered in making age-grouping decisions	The examples of age bins used by various offices in EPA are only illustrative (Table 1). "The case-by-case consideration of vulnerable periods and/or the availability of exposure data have led to variations in the specific age groups considered by different Program Offices" (p. 4) To understand the rationale for each bin, various programs' regulations, guidelines and procedures would have to be
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.	considered. Inter-individual variability is addressed more fully in the referenced Exposure Factors Handbook.
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.***	
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... Reviewers noted that the guidance document should address the importance of using NHANES III data to update age-specific exposure factors.	In the Appendix, analysis of NHANES III data is recommended for several exposure factors. (pp. 19, 42, 43)
B. The priorities and recommendations for further data collection activities (Table E-3 in Guidance document).	
In general, reviewers agreed with the document recommendations for further data analysis and collection…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… 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. 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. The document did not provide details on whether there were adequate data on children 5-10 years old.	A discussion of the various research efforts, including the NCS and NLCS, were added to the introduction to the **Appendix**. The need for data on usage and exposure to consumer products has also been included in the **Appendix.** The Guidance clearly states that more data are needed for children 5-10 years old. (see Table A-1).

C. Whether any critical exposure factors have been overlooked in these recommendations?	
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 is needed 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.	See above – The **Appendix** focuses on exposure factors data needs (not chemical specific). The discussion is about the need for data on breast milk ingestion and fat content in breast milk. The soil ingestion example **Case Study** is being developed to be fairly simple and straightforward, but references are made to other guidance for exposure assessment, such as RAGS. The discussion in the A**ppendix** on soil ingestion includes this as a data need**.**
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.	
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 Research and Prevention Centers.	The introduction to the **Appendix** and the expanded **References** have included many suggested sources. The NHANES data are also mentioned throughout the discussion on research needs.
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.	A discussion of the effects on timing on exposure and dose is contained in **Section 3**. Averaging time used and duration of exposure are critical to risk assessments. Uncertainty and variability due to temporal issues are discussed.
The document needs to capture the recommendations from the workshops that models be validated using direct measures, including measures of both exposure and biomarkers.	Application of the Guidance to models is addressed generally; but most comments about specific models were removed. Validation of models is highly recommended

	in **Section 3**.
Clarity of uncertainty and interindividual 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.	(See Above) These issues are specifically addressed in **Section 3** of the guidance.
CORRECTIONS: GENERAL	
*__NOTE__: Comments and corrections relating to LifeLine™ software have been omitted as all references to LifeLine™ have been removed from the EPA document.	
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".	These suggestions have been implemented in the document to the fullest extent practicable. The terms "behavior related" and "physiology related" are illustrated by example throughout the document, as appropriate to the context (e.g., Introduction, p. xi).
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.	References have been expanded and citations standardized.
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 lifestages. 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.	Tables and figures have been changed, simplified, clarified, and footnoted to be stand-alone. Table 5 was added to demonstrate implementation of exposure-based age groups and toxicity-based age adjustment factors in risk assessment. Figure 2 illustrates variation in exposure over time, and effects of time averaging of exposure.

II. *EPA Response to External Comments (received during the public comment period, September-December 2003, on the 2003 draft external review version of "Guidance on Selecting Appropriate Age Groups for Children's Exposure Assessment")*

The following organizations submitted comments to the EPA:
American Chemical Council;
Crop Life America;
International Life Sciences Institute; and
Implementation Working Group

1. Comments were received concerning the accuracy of the breast milk intake data used for the Guidance. The principal point related to the age groupings was that the breast milk intake does not show a rapid decrease until the 9 to 12 month age range

   RESPONSE: The **Appendix** states: "The issue paper (EPA 2001) noted that the 6 through 11 month age group captures a period of rapidly decreasing breast milk intake. This observation is consistent with the July 2000 workshop discussion, which noted the expanding variety of foods consumed during this time period. Therefore, future breast milk intake data collection efforts should consider that it may be appropriate to further divide the 6 through 11 month age group into two or three separate groups."

2. Comments were received regarding the language surrounding the use and characterization of the recommended age groups.

   RESPONSE: As for similar comments from the peer reviewers, the flexibility in implementation was emphasized in the Introduction, and practical examples of implementation issues and how to address them were included in **Section 3.3**. Practical case studies are being developed that address regulatory and program-specific needs.

3. It was suggested that EPA maintain the Guidance as an "evolving document on the NCEA web site, with regular updates as further research is conducted and new data are provided."

   RESPONSE: The Guidance states it is the intent of the Agency that this document be a "living document," updated as new information and practice is introduced. The planned case studies will also be updated as needed, independent of the Guidance.

4. A number of comments were generally supportive of the recommended age groups. Some suggested additional characterization of uncertainty inherent in the selection of age groups and use of those groups to estimate children's exposure. The interaction between the health scientist investigating the chemical hazard level and the scientist estimating the exposure parameters was also reiterated. An there were references to the ILSI framework for assessing risks to children from exposure to environmental agents.

   RESPONSE: Additional characterization was incorporated in the guidance on the uncertainty in selecting age bins for any assessment, versus the impracticality at this time of addressing lifestages as a continuum. The ILSI workshop and the report and ensuing discussions with the EPA have been referenced and incorporated in the Guidance.

5. Some commenters recommended other existing systems of age grouping over the recommended groups in the Guidance for evaluating childhood exposure. Concern was expressed that risk assessments using the recommended age groups would result in

inappropriate, inadequate, or, at the opposite end, labor-intensive exposure estimates due to rigid conformance with a single standard set of age groups. The viewpoint that too many age groups were recommended by the Agency was supported by the current lack of exposure and behavior/activity pattern data, according to the commenters.

RESPONSE: The Agency points out in the final guidance that the age groups are based on current understanding of physiological, anatomical, and behavioral (e.g., dietary intake; hand-to-mouth activities) differences in growing children. The document is an attempt to apply generalized milestones to changes in children's exposure, so that the differences in different ages' exposures might not be missed, resulting in over- or under-estimation of risk. The EPA establishes early on that there *are* data gaps in the exposure fields that need to be filled before all or even most of these age groups may be well implemented in exposure assessments. That is the second principal purpose of this document, after a consistent, scientific set of age groups: informing the research agenda for children's exposure factors.

6. Comment was received that EPA should have presented the cost-benefits which would accrue from the use of the age groupings recommended in the Guidance. Related comments questioned the scientific advantage to using the additional age groupings and harmonizing the children's exposure assessments across the Agency.

   RESPONSE: The Guidance document has been revised and edited to reflect internal and external comments, particularly focusing on the purpose, the scientific rationale, and implementation of the age groups. The age groups, or lifestages, were selected using the best available information about physical and behavioral changes occurring in children over time. It is clear that it is not necessary to address all age groups for all exposure assessments. In many cases, screening level assessments may be appropriate which represent the highest exposure for children for a stressor and scenario, as stated in **Section 3.1.**