



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JAN 16, 2001

THE ADMINISTRATOR

Dr. Morton Lippmann
Acting Chair
Science Advisory Board Executive Committee
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W., MC-1400A
Washington, DC 20460

Re: SAB Report-Review of Revised Sections of the Proposed Guidelines for Carcinogen Risk Assessment, EPA-SAB EC-99-015, July 29, 1999 and SAB Report-Review of EPA's Draft Revised Cancer Risk Assessment Guidelines Pertaining to Children, EPA-SAB-EC-00-016, September 11, 2000

Dear Dr. Lippmann:

The Agency appreciates the efforts of the Science Advisory Board (SAB) in conducting the recent reviews in January 1999 and July 1999 of the draft revised Guidelines for Carcinogen Risk Assessment. The Technical Panel of the Risk Assessment Forum is in the process of addressing the many recommendations contained in the Environmental Health Committee's reports and will be discussing them in the near future with the Agency's Science Policy Council.

The continuing involvement of the Environmental Health Committee has been extremely helpful in shaping the revisions to the Agency's Guidelines for Carcinogen Risk Assessment. Having now conducted one advisory and three related reviews of the Guidelines, the extent and depth of the SAB's involvement has been unprecedented and I applaud the SAB's efforts to include members of the pediatric community in the recent reviews. I note the recommendation of the majority of the SAB reviewers that the Agency consolidate the progress made to date and issue the Guidelines as soon as judiciously possible and then undertake a program of research and risk assessment improvement to more completely address the childhood susceptibility issue in future revisions of the Guidelines. However, I also recognize that other members believe that the Agency should address fully the needed research regarding children's risk before finalizing the Guidelines.

Although the Science Advisory Board members could not reach consensus on a number of controversial issues, the diversity of opinions expressed by the members provides a range of

options for the Agency to consider. As the SAB points out, it is only through the continual involvement of the risk assessment and pediatric communities that a consensus will develop around some of the more controversial issues. To facilitate this process, the Agency has increased its efforts to actively seek the input of the scientific and stakeholder communities as we move forward toward finalization of the Guidelines. For instance, the Agency has conducted three scientific workshops dealing with children's risk issues during the past year. The first workshop (September 1999) reviewed the available data on preconceptual, prenatal, and postnatal developmental exposures and outcomes, including cancer, and examined the state-of-the-science regarding children's critical windows of vulnerability. The second workshop (March 2000), organized jointly with the National Institute of Environmental Health Sciences, dealt with how best to utilize existing testing schemes and how future improvements in testing could further the Agency's ability to assess children's cancer risk. The Agency will be exploring the recommendations of this panel regarding additional laboratory protocols that may be incorporated into testing guidelines to address risks unique to children. The third workshop (July 2000) focused on issues associated with considering developmental changes in behavior and physiology in order to improve the Agency's ability to conduct exposure assessments for children. In addition, the Agency received a very positive review by an external panel of pediatricians and researchers of its Strategy for Research on Environmental Risks to Children (EPA/600/R-00/068), and the strategy has now been finalized based on the results of that review. The strategy highlights many of the issues raised by the SAB members in the review of the Guidelines. Finally during this period, the Agency's risk assessments for chloroform and atrazine were reviewed by the Science Advisory Board and the FIFRA Scientific Advisory Panel, respectively. These reviews produced several worthwhile recommendations for clarifying aspects of the Guidelines. In total, the SAB reviews, stakeholder involvement, and workshops have produced a range of strongly held opinions, but not a consensus. The Agency's Science Policy Council will discuss and sort through these different, and sometimes disparate, recommendations as the Guidelines are finalized.

The enclosed summary addresses the SAB's major overall findings and recommendations from the two recent reviews. In examining the SAB's recommendations, it is clear that some can be addressed straightforwardly by the Risk Assessment Forum Technical Panel through revisions to the current text; others pose policy issues that will need to be addressed by the Agency's Science Policy Council before final revisions can be made; and others will be the subject of research activities that will lead to future supplemental guidance. The enclosed summary provides a cross-walk between the identified research issues and ORD's Research Strategy for Children.

In conclusion, the Agency appreciates the SAB's assistance in revising the Guidelines for Carcinogenic Risk Assessment. In finalizing the Guidelines, the Agency will ensure that the

Guidelines are health protective, particularly to children, and scientifically valid, while making sure the document allows for the application of new knowledge, thought, and technology.

Sincerely,

/S/

Carol M. Browner

Enclosures (2)

ENCLOSURE 1

Response to Science Advisory Board Recommendations

I. Background

In January 1999 the Environmental Health Committee of the Science Advisory Board met to consider selected sections of the draft Guidelines that were revised to address recommendations from the public and the earlier SAB review (1997) of the Guidelines as proposed in May 1996. The Agency requested that the Environmental Health Committee review the revised hazard descriptors and example narrative summaries; the expanded guidance on the use of Mode of Action information; the use of departure points for the dose-response analysis; and the approach to the Margin of Exposure analysis. An additional review by the Environmental Health Committee was conducted in July 1999 that focused on new sections of the Guidelines developed to address children as a sensitive subpopulation. Specifically, the Committee was asked to review the adequacy of the general guidance contained in various sections of the revised Guidelines (i.e., the supplementary information section of the introduction, and the hazard assessment, dose response assessment, exposure assessment and risk characterization chapters) on how to incorporate relevant data into the evaluation of carcinogenic risk to special subpopulations, in particular children. The Committee was unable to reach consensus on many of the issues and provided its recommendations as a range of views rather than a consensus.

II. Major Issues - January 1999 Review

- 1.) **Primacy of public health protection:** It is essential that the Guidelines state at the outset that “.. The primary goal of EPA actions is public health protection and that, accordingly, as an Agency policy, the defaults used in the absence of scientific data to the contrary should be health protective. These defaults should be clearly explained..... The basis for various default uncertainty factors should be clearly described.”

EPA adopts the recommendation of the SAB. In the July 1999 draft of the Guidelines, the Introduction contains a detailed description (Section 1.3) of the major default assumptions underlying EPA’s approach to carcinogen risk assessment. As part of this introductory discussion, the Guidelines state that the primary goal of EPA actions is public health protection. Because the issue of the primacy of public health protection has continued to arise, the revised Guidelines will contain additional text that acknowledges, explicitly and prominently, that EPA’s chief goal in assessing chemical carcinogens is the protection of public health, including the health of children and other vulnerable populations.

- 2.) **Loss of flexibility:** The Subcommittee is concerned that EPA, in responding to the SAB’s earlier request for more definition in several areas, actually reduced, rather than increased, flexibility in moving from the 1996 version.

It is not the intent of the Agency to reduce the flexibility embodied in the Guidelines. As the SAB correctly points out there is a fine line between providing adequate guidance as recommended by the public and the SAB in response to the Agency's 1996 proposal and being overly prescriptive. In the July 1999 version, the Agency removed much of the prescriptive description of the Margin of Exposure Analysis in response to the sense of the SAB recommendations on this issue. The Agency is continuing to explore the development of further guidance on points to be addressed when performing a Margin of Exposure analysis for cancer risk where a nonlinear or threshold mode of action is indicated. Efforts are being made to harmonize these considerations across cancer and noncancer health endpoints. In addition, the Agency is preparing guidance material for the curve-fitting procedure referred to in the Guidelines and will be organizing a peer review on this topic in the near future. This effort is part of the Agency's overall effort to develop guidance and user-friendly software for calculating benchmark doses for cancer and noncancer assessments. A guidance document on this topic was recently peer reviewed.

- 3.) **Sensitive subpopulations:** EPA should include a discussion of sensitive subpopulations for all agents to which the general public (as opposed to healthy workers) is exposed. Specifically, this discussion should include consideration of pregnant females, the fetus, young children and adolescents, the ill and the elderly. The basis for the uncertainty factor or alternative modeling procedure used to account for susceptibility of the young should be clearly stated. EPA should also discuss other known or likely sensitive populations due to susceptibility factors in addition to young age: nutritional deficits, preexisting disease, ethnicity, gender, pregnancy - which occur simultaneously (in combination) in various subsets of the population. The Agency should conduct systematic reviews to explore quantitatively the extent of variability among individuals in the human population.

In July 1999 the Agency provided the Environmental Health Committee with revisions to the Guidelines that address sensitive populations, including fetuses and children. The Guidelines recognize that qualitative as well as quantitative differences in response are possible. The revisions addressed the major default positions of the Guidelines vis-a-vis children and the need to include any subpopulations believed to be more susceptible than the general population. The Guidelines especially address attending to fetuses, infants and children as part of the hazard characterization, applying the framework for Mode of Action analysis in determining whether children are at disproportionate risk, adjusting inhalation and ingestion doses from adults to children, adjusting unit risks when early life-stage exposure indicates increased sensitivity, and performing separate exposure assessments for highly exposed or susceptible subgroups in the population. As discussed in the July 1999 draft Guidelines, the National Research Council 1994 report "Science and Judgment in Risk Assessment" reviewed studies estimating potential variation in susceptibility to cancer and found them to generally indicate that "predisposed" people may be a factor of 10 more susceptible than "normal" ones. The studies were in part of cancer mortality data that cover sources of variability including, diet, personal habits, nutrition, inborn metabolism factors and genetic disease, infections, exposure to radiation or chemicals, medical care, and all sources of exposure. The SAB Subcommittee stated that it is quite difficult to determine how the most sensitive members of a large population differ from the average and that with regard to carcinogenesis there are relatively few systemic data of good quality that shed light on this issue,

although data are emerging to further explore this issue. The Subcommittee concluded in their report of the January 1999 review that the evidence from radiation epidemiology suggests a 10-fold factor for susceptibility would be a health-conservative factor, however, the radiation experience may not be representative of some chemical carcinogens. The Subcommittee recommended that flexibility should exist to use uncertainty factors other than 10 (higher or lower than 10) should scientific data exist to support some other value. In carrying out a Margin of Exposure Analysis, the current draft Guidelines recommend a default factor of 10-fold to account for the variability in cancer responsiveness in the general population, unless case-specific information indicates that a greater factor is appropriate. This issue will be considered further by the Science Policy Council before finalizing the Guidelines (see additional discussion below regarding children).

- 4.) **Background and multiple exposures:** EPA should discuss the need for the risk assessment to consider background exposures/processes and concurrent exposures with which the chemical (mixture) of interest may display additivity or interact multiplicatively.

The Agency has recognized that exogenous chemical exposures may add to those associated with background and additional discussion will be added. The Agency applies the Carcinogen Risk Assessment Guidelines in conjunction with the 1986 Mixtures Guidelines when assessing the risk from a mixture of carcinogenic chemicals. The Mixtures Guidelines (and supplementary guidance) provide guidance on using whole mixtures data or data on individual components and provides approaches for incorporating information on toxicologic interactions when available. Currently, the Agency in implementing the Food Quality Protection Act is developing guidance and methodologies for assessing chemicals which work through a common mode of action. The implications of exposure to chemical mixtures is an area that the Agency will be giving greater emphasis to in its strategy for human health research and in conducting cumulative risk assessments in the future.

- 5.) **Framework for Evaluating a Postulated Carcinogenic Mode of Action:** The Subcommittee strongly supports the proposed “Framework” as a means for providing a working model for incorporating and interpreting mode of action data in a clear and transparent manner. The Subcommittee suggested that an additional element be added to the Framework that specifically addresses the relevance of the mode of action to human populations and whether any subpopulation is expected to qualitatively respond to the mode of action differently than the general population.

The Agency in the July 1999 draft Guidelines included an additional element that addressed this recommendation and revised the case examples to further illustrate this element. In addition, the draft Guidelines call for a separate analysis of the relevance of the mode of action to children (see further discussion below).

- 6.) **Narrative Summaries and the Five Hazard Descriptors:** As with the 1997 review, the Subcommittee did not reach consensus on the descriptor “Known to be Carcinogenic to Humans.” The Members did not agree on whether to restrict use of this category to scenarios in which there was conclusive epidemiological data for causality. Most Members favored this

position. However, some Members recommended that, even with less sufficient epidemiological data, an agent with strong animal evidence plus evidence (in exposed humans) that the chemical is causing measurable changes that are on the causal pathway to cancer in humans, should be considered to be carcinogenic to humans.

The July 1999 draft Guidelines contain revised language for the five descriptors. In particular, the descriptor “Carcinogenic to Humans” is defined to be appropriate in situations where there is convincing epidemiologic evidence demonstrating causality between human exposure and cancer. The descriptor is also used in situations where there is an absence of conclusive epidemiologic evidence to clearly establish causality but there is compelling evidence of carcinogenicity in animals and mechanistic information in animals and humans demonstrating similar mode(s) of action. A set of four conditions are described which must be met in applying this descriptor. The Agency’s Science Policy Council considered the options discussed by the SAB in arriving at this new language. The revised language is felt to be consistent with the current approaches of the National Toxicology Program and the International Agency for Research on Cancer and is internally consistent with the concept of the use of mode of action information which is central to the revised Guidelines.

- 7). **Departure from Defaults:** The current guidance allows for departure from the linear default when supported by mode of action information in favor of a non-linear or combined linear/non-linear approach. The Subcommittee recommended that the Guidelines incorporate additional clarification on this issue. Some Members expressed their view that the Guidelines should require a much higher threshold of evidence for departure defaults than the “more likely than not” concept.

The revisions provided to the Subcommittee in July 1999 contain further discussion of this issue. The text emphasizes that departure from defaults requires a *data rich* situation and that the alternative may replace the default when it is supported by *clear and convincing evidence* and is accepted in peer review. There is no one set of rules making the judgment of whether a data analysis is both biologically plausible and persuasive. There are two criteria set out in the Guidelines: first, that the underlying scientific principle has been generally accepted within the scientific community and second, that supportive experiments are available that test the hypothesis. The Guidelines emphasize the need for extensive experimentation to support a hypothesis as to mode of action, including coverage of the issue whether other modes of action are plausible. The recent reviews of the chloroform and atrazine assessments have provided the Agency with real world experience in applying these principles and subjecting the conclusions to peer review. The Agency recognizes that this is a controversial area and final revisions to the Guidelines will address the recommendations of the SAB and SAP reviewers, as well as public comments.

- 8) **Margin of Exposure Approach (MOE):** The Subcommittee was concerned about the linkage between the selected risk level and the incorporation of adjustment and uncertainty factors. The Agency is encouraged to develop explicit guidance regarding the selection of uncertainty factors or MOE guidelines for points of departure other than 10%. The Agency

should strive to use the standard point of departure whenever possible.

The Agency intends to develop additional supplementary guidance on this issue that will be approved by the Science Policy Council. The revised document provided to the SAB in July 1999 removed the more prescriptive language that was of concern to the SAB and replaced it with more flexible language which described a set of considerations that should be addressed in the analysis of the point of departure and the margin of exposure.

II. Major Issues - July 1999 Review

- 1) **Soundness of the Default Science Policy Position:** The SAB report states that, despite a number of important caveats that are subsequently examined, most of the Subcommittee endorsed EPA's position that the existing linear default process of estimating human doses associated with low levels of lifetime cancer risk generally provides adequate protection for sensitive subpopulations.

Various Subcommittee members raised concerns about the issue of human variability and that, in any particular instance, children may be more susceptible than adults. Some Members felt that the degree to which the current default procedure used for estimating risk at low doses adequately predicts risk is a matter of speculation. A number of improvements were recommended to be explored that could improve the risk estimates. For example, age at time of exposure could be taken into account in the exposure assessments and the cancer slope factors can be stratified by age. Other recommendations were made to further research in the area of population heterogeneity and genetic polymorphisms and to incorporate this information explicitly into risk management decisions, as it becomes available. In response to the SAB's recommendation concerning incorporation of age at time of exposure, the Agency held a workshop in July 2000 to explore how children's activity patterns and physiology can be incorporated explicitly into exposure assessments and what age groupings would most appropriately reflect critical periods of development. The Agency intends to develop supplementary guidance on this issue during the next year. Regarding stratifying cancer slope factors by age, the draft Guidelines contain an example of how this might be done. Regarding the various research recommendations, a cross-walk with ORD's Research Strategy for Children is provided.

- 2) **Mode of Action Framework:** The Subcommittee stated that the Mode of Action Framework for analysis of data should be relevant for most subpopulations of concern. However, in the case of children, and other subpopulations of concern, it would be important to consider a special evaluation which would determine whether all assumptions based on the "typical" adult "mode of action" would apply across the entire time-span in children, and others factors in other subpopulations.

The SAB suggested relevant considerations that the Agency should address when an agent produces a carcinogenic effect in standard bioassays using adult laboratory animals by a non-linear

threshold mode of action as to its relevance to comparing adult and childhood carcinogenic potential. These include: a) whether the target tissue and key events are the same in the developing human compared to the adult; b) the appropriate dose to the target tissue of the child compared to the adult; c) the latency period for development of the cancer; d) the sequencing of sensitizing and subsequent potentiating events; and e) the possible increase or decrease in the actual risk from the exposure. The recommendations offered by the SAB in this report, as well as the experiences gained from the reviews of the chloroform and atrazine assessments, will aid the Agency in providing additional guidance as to what constitutes a cogent biological rationale, supported by data. This issue requires further discussion with the Agency's Science Policy Council.

- 3) **Protective Factors in Margin of Exposure Analysis:** The Subcommittee was unable to reach a consensus on the issue of whether an additional protective factor for children should be applied in a Margin of Exposure Analysis. The Subcommittee did agree that the population threshold for children could be lower than for adults for some carcinogens acting through a non-linear mode of action.

Various members had differing perceptions about how often increased sensitivity of children actually occurs and whether EPA should routinely apply a separate factor. There was consensus that if such a factor were to be used, it should be dependent on the state of the database and not necessarily a single default number. The subcommittee supported EPA's intent to evaluate the acceptability of a Margin of Exposure on a case-by-case basis. This issue will need to be further addressed by the Science Policy Council before finalizing the Guidelines. Currently, a Technical Panel of the Risk Assessment Forum is reexamining the Agency's overall methodology for setting Reference Doses/Reference Concentrations with the goal of making improvements in how children's risk is addressed in non-cancer assessments. The Panel's recommendations will be provided to the Science Policy Council.

- 4) **Use of Default Options to Convert An Adult Dose to a Children's Dose:** The Subcommittee agrees that the default approach for converting an adult dose to a childhood dose should examine the relevant characteristics of children before simply converting the dose using a standard default option.

The Subcommittee noted that EPA's default approach for converting an equivalent dose for adults to an equivalent dose for children is unclear and needs better definition. The SAB Members suggested approaches that the Agency might take. The Agency will revisit the default approaches described in the Guidelines, bearing in mind the SAB's concerns and recommendations. Improvements to the approaches will be discussed with the Science Policy Council.

- 5) **Adjustment of Slope Factors to Reflect Data on Early-Life Sensitivity:** In general the Subcommittee found the methods used to handle the specified adjustments were appropriate. However, the Members also felt that there was considerable room for improving clarity of the presentation in the Guidelines document.

The SAB Members made a number of recommendations on how to improve the discussion in the Guidelines as well as the example that is used to illustrate the concepts. The Technical Panel will revise this section to reflect the SAB's recommendations. Research may illuminate matters and suggest other means of addressing this issue in the future.

ENCLOSURE 2

III. **Research Needs / Data Gaps / Uncertainties Identified by SAB Report** *Review of the EPA's Draft Revised Cancer Risk Assessment Guidelines Pertaining to Children September 11, 2000.*

Note: the section numbers correspond to the actual numbers appearing in the SAB report and the Research Strategy. The letters presented within each section (e.g., 3.6.9 a)) of the SAB report have been added for convenience and do not appear in the report.

§3.6.9 Research to Evaluate Unique Susceptibility of Children and High-risk Populations

§3.6.9 a) “The Subcommittee sees the need for a large (hopefully coordinated across the government and private sector), ongoing effort to document the many differences in physiological/ biochemical/ metabolic processes between children and adults, and understand how these differences impact human health and disease process,” noting that this also needs to reflect continuing changes during childhood “since all the different molecular & cellular processes do not mature at the same time or rate during human development...”

Relevant ORD Research Strategy Sections: [§4.3.1.1](#), [§4.3.2.1](#)

§3.6.9 b) Research should be undertaken so that dosimetry better reflects changes in development, taking into account “changes in physiology and biochemistry that mediate the response of the fetus, the nursing child, the toddler, and later developmental stages, to exposure.” This will involve, in part, “understanding the nature and expression of enzymes responsible for metabolic clearance that activate and inactivate given compounds” and incorporating this information into toxicokinetic models.

Relevant ORD Research Strategy Sections: [§4.3.1.1](#), [§4.3.2.1](#)

§3.6.9 c) Report indicates that regarding animals studies that have a perinatal exposure component to better understand cancer risks in the young, EPA needs to:

- “encourage or commit to the development of data in the chronic bioassay to contribute knowledge,” i.e. change or expand current chronic bioassays.
- “quantitatively review the existing data and apply more realistic approaches to the analysis of risks from age varying exposures.”

Relevant ORD Research Strategy Sections: [§4.3.3.1](#)

§3.6.9 d) Report notes that understanding apoptosis “could be of particular importance in understanding the true sensitivity of the young to cancer,” given that “suppression of apoptosis could give rise to increased risk of cancer...”

Relevant ORD Research Strategy Sections: none apparent

§3.6.9 e) “Quantitatively analyzing the available experimental and epidemiological literature on age dependence in carcinogenesis, in a comprehensive and systematic review, would be very helpful.” [EPA’s qualitative review of perinatal rodent carcinogenicity was limited.]

Relevant ORD Research Strategy Sections: [A review paper on this topic \(Critical Windows of](#)

Exposure for Children's Health: Cancer in Human Epidemiological Studies and Neoplasms in Experimental Animal Models, L. M. Anderson et al., EHP Supplements, 108, pp. 573-594, June 2000) was developed for the EPA workshop on Identifying Critical Windows of Exposure for Children's Health (September 1999).

§3.6.9 f) Regarding questions “as to whether observed cancer rates for children are in fact increasing or decreasing,” the report urges EPA “to track carefully the data on this issue to help gauge the actual status of the problem.”

Relevant ORD Research Strategy Sections: §4.3.1.2

§3.1 Soundness of the Default Science Policy Positions

§3.1 a) Concern/issue: upper bound of the linear default may not reflect full uncertainty in the risk estimate.

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.5.1

§3.1 b) Concern/issue: more broadly, lab tests use genetically homogenous animals that do not reflect the heterogeneity of the human population, and thus risk assessments do not account for heterogeneity (some Members disagree). “Some Subcommittee Members found that because human variability is likely to be the rule rather than the exception, it should be explicitly addressed in risk assessments...”

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.3.1, §4.3.5.1

§3.1 c) Concern/issue: defaults from animal tests may not involve protective assumptions because of these under-predictive assumptions: exposure to other substances not important; transplacental exposures not important; age of postnatal exposure not important; risks from intermittent, high exposure do not exceed average exposure risks; occupational exposure risks are representative. Additional factors are the assumption of site concordance in pharmacokinetic analyses; failure to address intercurrent mortality; saturable pharmacokinetics of the activation pathway in the bioassay; lack of early life exposure; and cessation of studies at two years.

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.5.2

§3.1 d) Concern/issue: some Members felt that standard defaults can be improved by taking into account age in the exposure assessment, by stratifying slope factors by age, and by varying pharmacokinetics by age and sex.

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.1.2, §4.3.1.3, §4.3.1.4, §4.3.2.1

§3.1 e) Recommendation: Agency should begin thinking about implications of the growing data on genetic polymorphisms and age-/sex-related differences in risk.

Relevant ORD Research Strategy Sections: §4.3.1.2, §4.3.5.1

§3.2 Mode of Carcinogenic Action in the Human Population

§3.2 a) Concern/issue: “Although children and adults may respond with the same ‘mode of action’ when exposed to an agent, it is also possible that they would not.”

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.1.2, §4.3.2.1, §4.3.2.2, §4.3.3.1, §4.3.3.2, §4.3.5.1

§3.2 b) Recommendation: “Since childhood includes the period from preconception through adolescence, the Agency needs to consider not only the changes in development during that time period, but the potential for different exposure scenarios.”

Relevant ORD Research Strategy Sections: §4.3.1.3, §4.3.1.4, §4.3.2.2

§3.2 c) Recommendation: “both fetal[/newborn] and maternal metabolism must be considered in determining prenatal and lactational exposures.”

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.2.1

§3.2 d) Concern/issue: some Members felt that for genotoxic carcinogens, the linear default (based on adults) may not be sufficiently protective because children may be more sensitive.

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.2.1

§3.2 e) Recommendation: the Agency should consider the possibility of concentrated, high-dose exposure to carcinogens by children, given their behaviors and narrow diets.

Relevant ORD Research Strategy Sections: §4.3.1.3, §4.3.1.4, §4.3.2.2, §4.3.5.1

§3.2 f) Recommendation: ideally, in the future the Agency should consider significant immune system changes that take place in early childhood and effects of events such as vaccination on immunity.

Relevant ORD Research Strategy Sections: none apparent

§3.2 g) Concern/issue: more data are needed on cell type involvement (rather than simply cancer by organ site) in humans so that this information can be used in examining MOAs for children.

Relevant ORD Research Strategy Sections: none apparent

§3.2 h) Recommendation: evaluating MOA in children “should involve a consideration of reproductive and developmental factors.”

Relevant ORD Research Strategy Sections: §4.3.1.1

§3.2 i) Concern/issue: “Some Members noted the need to extend the body of scientific information to improve our ability to evaluate multi-generational carcinogenesis through the conduct of transplacental and multi generational bioassays and mechanistic studies on a selected series of chemicals.”

Relevant ORD Research Strategy Sections: not directly addressed in the strategy but EPA’s recent workshop (March 2000), organized jointly with the National Institute of Environmental Health Sciences, dealt with how best to utilize existing testing schemes and how future improvements in testing could further the Agency’s ability to assess children’s cancer risk.

§3.2 j) Recommendation: “the Subcommittee suggests that the Agency develop a list of ...factors that might result in quantitative differences in dosimetry or responses [by children] and search for appropriate information in the basic biomedical literature as it would apply to the agent under consideration.”

Relevant ORD Research Strategy Sections: none apparent

§3.4 The Use of Default Options to Convert an Adult Dose to a Children’s Dose

§3.4 a) Recommendation: in converting dose from an adult to child, EPA should go beyond the simple body weight/surface area scaling factor, such as by taking into account rate of xenobiotic metabolism.

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.2.1, §4.3.3.1

§3.4 b) Research recommendation: additional studies are needed in age dependent carcinogenesis, which involves at least three contributions:

- inherent differences in susceptibility at different ages
- timing of exposure
- sequencing of exposure with other agents or disease states that affect the cancer process.

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.2.1, §4.3.3.1

c) Recommendation: when more data are available (per previous recommendation), EPA should “evaluate mathematical modeling approaches to take into account age dependencies.”

Relevant ORD Research Strategy Sections: §4.3.2.1

§3.6 Responses to CHPAC Questions

§3.6.2 Modes of Action for Chemical Agents in Children and Adults

Research recommendation: “How environmental chemicals interact with the altered cancer biology during development and how the chemicals interact with the familial and genetic linked disorders associated with malignancies of childhood...is an area where additional studies are needed.”

Relevant ORD Research Strategy Sections: §4.3.2.1, §4.3.5.1

§3.6.8 New Models for Acute or Combinations of Acute and Chronic Exposures

Recommendation: In taking into account dose timing and intensity, EPA should review and consider “age dependent models which produce more satisfactory results than analyses based on lifetime average dose.”

Relevant ORD Research Strategy Sections: §4.3.1.1, §4.3.3.1

Table 2. Summary of Research Areas

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Biology of Toxicant-Induced Tissue and Organ Damage in the Developing Organism (§4.3.1.1) High Priority		
<p>Investigate absorption, metabolic pathways and rates, distribution and storage in the body, and elimination in sensitive age groups. Investigate biologic basis for age-related differences in target organ development, detoxification, repair, and compensation. Link effects at tissue, organ, and system level with underlying effects at cellular and molecular levels. Identify common modes of action for multiple developmental endpoints and chemicals.</p>	<p>Identification of more appropriate animal models for critical ages and endpoints. Improved extrapolation from animals to children. Improved risk assessment models relying less on data from whole animal toxicity testing and able to incorporate biologic data specific to children. Identification of classes of chemicals with the same modes of action.</p>	<p>The necessary data to develop biologically based dose-response models (§4.3.2.1) will be developed under this research area. Mode-of-action studies will help identify pollutants that are good candidates for human studies and may develop biomarkers that could be used in human studies (§4.3.1.2). Development, validation, and application of new test methods (§4.3.3.1) will be needed to conduct mode-of action research. This research also provides some of the basic science that will be necessary to understand the complicated issues of variability within susceptible age groups (§4.3.5.1) and cumulative risk resulting from exposure to multiple pollutants (§4.3.5.2).</p>
SAB Cross-walk: §3.6.9 a), §3.6.9 b), §3.1 a), §3.1 b), §3.1 c), §3.1 d), §3.2 a), §3.2 c), §3.2 d), §3.2 h), §3.4 a), §3.4 b), §3.6.8		
Relationship Between Exposure to Environmental Agents and Adverse Health Effects in Human Populations (§4.3.1.2) High Priority		
<p>Conduct studies of the relationship between exposure and effects in human populations. Explore feasibility of interagency longitudinal birth cohort enrolling children at birth and continuing through childhood or adolescence. Conduct hypothesis-based analysis of existing data sets to investigate relationship between exposure and effects in children.</p>	<p>Identification of hazards and important sources and pathways of exposure. Opportunities to test hypotheses related to human exposure and effects and the ability of animal testing and risk assessment methods to predict exposure and effects in children. Testing of intervention and risk reduction techniques. Collection of data for dose-response assessments.</p>	<p>Studies in humans will be indicated by results of research into the biological bases of adverse effects (§4.3.1.1) in order to verify predictions of response in children and to aid in developing models to extrapolate between animals and children (§4.3.2.1). Epidemiology studies and exposure field studies (§4.3.1.3) are closely related, and ORD should explore opportunities to combine these studies in such a way that the objectives of both types of studies are met. Methods of studying effects and exposure in humans (§4.3.3) will be used in human studies and often developed in the context of these studies. Investigators will need to work with communities and participants in conducting studies in human populations and will need communication methods (§4.3.4.3) and practical intervention methods to offer to individuals and local public health departments to deal with problems that may be uncovered (§4.3.4.2). Human studies designed to consider multiple chemicals have the potential to provide information on variability within age groups (§4.3.5.1) and responses to complex mixtures (§4.3.5.2).</p>
SAB Cross-walk: §3.1 d), §3.2 a), possibly §3.6.9 e)		

Table 2. Summary of Research Areas (continued)

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Multimedia, Multipathway Exposures in Human Populations (§4.3.1.3) High Priority		
<p>Measure exposure in various age groups in the national population and selected subgroups hypothesized to be more highly exposed. Collect environmental concentration data, personal exposure data, biological samples, and questionnaire data.</p>	<p>Determination of when children are exposed and which age groups are more highly exposed and should be subjects of further study and assessment. Development of baseline data and data on distributions of exposure in the general population and highly exposed subgroups. Development of data for risk assessment of chemicals in study and data on activity patterns and other exposure variables for direct use in EPA risk assessments. Identification of important sources and pathways of exposure for risk management decisions. Collection of data for use in model development and predictions of exposure.</p>	<p>Information on the most highly exposed age groups and their patterns of exposure is useful in selecting relevant chemicals for pharmacokinetic and mode-of-action studies (§4.3.1.1), designing biological models compatible with actual exposure patterns (§4.3.2.1.), and designing human studies of the relationship between exposure and effect (§4.3.1.2). Ideally, epidemiologic and complex exposure studies would be combined in cases where it is possible to do so without sacrificing the ability to obtain the studies' objectives. Multimedia, multipathway measurement studies can often be designed to collect information on exposure variables (§4.3.1.4) and for use in designing and testing exposure models (§4.3.2.2) suitable for use in many risk assessments. The strategy recommends that methods of measuring exposure applicable to infants and toddlers (§4.3.3.2) be developed in the course of conducting these studies. Investigators will need to work with communities and respondents to conduct exposure studies and will need both communication methods (§4.3.4.3) and practical methods to offer help to individuals and local public health departments to deal with problems that may be uncovered (§4.3.4.2). Studies designed to consider multiple chemicals have the potential to provide information on variability in exposure within age groups (§4.3.5.1) and exposures to complex mixtures (§4.3.5.2).</p>
<p>SAB Cross-walk: §3.1 d), §3.2 b), §3.2 e)</p>		
Analysis of Factors Contributing to Exposure (§4.3.1.4) High Priority		
<p>Develop data on distributions of values of key exposure variables within critical age groups, including activity pattern data, intake rates, and other factors that may cause higher exposures for children.</p>	<p>Development of data on exposure variables that introduce the greatest uncertainty into EPA risk assessments as identified by EPA Program Offices and Regions and ORD analysis.</p>	<p>Multipathway studies (§4.3.1.3) often collect data that can be used directly in risk assessment to evaluate exposure factors. However, this is usually a secondary objective of such studies. Data on exposure factors and how factors influence each other is key to developing exposure models (§4.3.2.2). Measurement methods are often developed (§4.3.3.2) in the context of studying particular exposure pathways and variables. Studies of critical exposure variables, such as food intake and ingestion of soil and dust, can provide insight into variability in exposures within age groups (§4.3.5.1).</p>
<p>SAB Cross-walk: §3.1 d), §3.2 b), §3.2 e)</p>		

Table 2. Summary of Research Areas (continued)

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Methods and Models for Using Biological Data in Risk Assessment (§4.3.2.1) High Priority		
<p>Develop integrated biological models of the exposure-dose-response continuum that routinely use pharmacokinetic and mode-of-action data in risk assessments for children. Develop models incorporating biological data to aid in extrapolation between animals and children.</p>	<p>Risk assessment models that take into account age-related differences in size, absorption, metabolism, distribution, and storage, and response to exposure at the cellular and molecular level. Improved ability to identify age-appropriate animal models and extrapolate from animals to children.</p>	<p>Data for model development are generated through mode-of-action research (§§4.3.1.1, 4.3.3.1). Human studies also provide relevant data for model validation and extrapolation between animals and humans (§4.3.1.2). Exposure studies (§4.3.1.3) often provide relevant data on uptake, body burden, and elimination. Exposure models (§4.3.2.2) and biological models are connected through PBPK modeling. It should be an objective of chemical-specific modeling to develop exposure, PBPK, and BBDR models that can be linked to connect effects with exposures through the PBPK model. With a sufficient input database, probabilistic models will be useful in predicting distributions of exposure, dose, and risk within an age range, allowing for estimates of variability (§4.3.5.1).</p>
<p><u>SAB Cross-walk: §3.6.9 a), §3.6.9 b), §3.1 d), §3.2 a), §3.2 c), §3.2 d), §3.4 a), §3.4 b), §3.4 c), §3.6.2</u></p>		
Exposure Modeling and Use of Exposure Data in Risk Assessment (§4.3.2.2) High Priority		
<p>Develop models for important pathways of childhood exposure, models of total dose via multiple pathways, and probabilistic assessments combining exposure data on multiple pathways.</p>	<p>Identification and quantification of exposure and dose in the risk assessment. Identification and quantification of sources and pathways in order to develop appropriate risk management options. Estimation of child-specific exposures and aggregate exposures for children in EPA assessments where measurements must be supplemented with modeling approaches to fill data gaps.</p>	<p>Data for model development are provided through studies of exposure variables (§4.3.1.4). Human studies (§§4.3.1.2 and 4.3.1.3) may provide data to evaluate model variables and to develop and test exposure models. Exposure models and biological models (§4.3.2.1) are connected through PBPK modeling. It should be an objective of chemical-specific modeling to develop exposure, PBPK, and BBDR models that can be linked to connect effects with exposures through the PBPK model. With a sufficient input database, probabilistic models will be useful in predicting distributions of exposure within an age range, allowing for estimates of variability (§4.3.5.1). Probabilistic models will also be helpful in predicting distributions of dose from multiple chemicals via multiple pathways (§4.3.5.2)</p>
<p><u>SAB Cross-walk: §3.2a), §3.2 b), §3.2 e)</u></p>		

Table 2. Summary of Research Areas (continued)

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
In Vivo/In Vitro Methods for Hazard Identification (§4.3.3.1) High Priority		
Develop methods for identifying and modeling mechanisms of toxic action in children.	Development of animal models and protocols that will provide information on mode of action to be used in risk assessment.	Predictive tests will be developed as part of a program investigating the biological basis of risk (§4.3.1.1) and provide data for extrapolation between animals and children (§4.3.2.1).
<u>SAB Cross-walk: §3.6.9 c), §3.1 c), §3.2 a), §3.4 a), §3.4 b), §3.6.8</u>		
Methods for Measuring Exposures and Effects in Infants and Children and to Aid in Extrapolations between Animals and Children (§4.3.3.2) Medium Priority		
Develop measurement methods suitable for use in infants and toddlers, such as biological sampling methods and cognitive testing methods. Develop biomarkers of effect and exposure in young subjects.	Improved methods for collecting data on children that, when applied in a study, contribute to better data for risk assessment.	Some of these methods are likely to be developed in the context of laboratory studies and other human studies (§§4.3.1.1., 4.3.1.2, 4.3.1.3, and 4.3.1.4)
<u>SAB Cross-walk: §3.2a)</u>		
Multimedia Control Technologies (§4.3.4.1) Low Priority		
Develop control technologies for releases of substances to which children are believed to be exposed, including drinking water treatment for <i>Cryptosporidium</i> , control of air emissions, bioremediation of chemicals at waste sites, and control of pesticide releases in point sources and nonpoint source runoff.	Reduced risks to children and adults through control of a substance at its source.	Risk assessments based on the results of research described in other research areas help identify substances for which control methods are needed. Risk assessments also help set numerical targets for cleanup, effluent control, and other risk management options, and are used to assess the efficacy and benefits of the options.
<u>SAB Cross-walk N/A</u>		
Methods for Reducing Exposure Buildup of Contaminants in Indoor Environments (§4.3.4.2) High Priority		
Cleanup and remediate children's environments that have unacceptable environmental concentrations. Engineer consumer and building products to reduce release of environmental agents to the indoor environment.	Reduced risks to children in their homes and schools through remediation and pollution prevention.	Risk assessments based on the results of research described in other research areas will help identify substances for which control methods are needed. Risk assessments also help identify and evaluate remediation and pollution prevention options and their efficacy. Intervention methods can be used in conjunction with human studies (§§4.3.1.2 and 4.3.1.3) to assist residents and local public health departments when high exposure levels are found.
<u>SAB Cross-walk N/A</u>		

Table 2. Summary of Research Areas (continued)

Description	Contribution to Risk Assessment or Management	Links to Other Research Areas
Communication of Risks and Development of Risk Reduction Techniques Through Community Participation (§4.3.4.3) High Priority		
Investigate intervention and education methods that enlist members of the community to work together to reduce risks to their children.	Reduced risks to children through intervention by parents, schools, medical personnel, and others in the community.	Risk assessments based on the results of research described in other research areas help identify substances for which intervention methods are needed. Risk assessments also help evaluate efficacy of community-based intervention. Intervention methods can be used in conjunction with human studies (§§4.3.1.2 and 4.3.1.3) to assist residents and local public health departments when high exposure levels are found.
SAB Cross-walk: N/A		
Variability in Susceptibility and Exposure in Children (§4.3.5.1) Medium Priority		
Investigate impact of factors on variability in response or exposure within the critical age range. Factors include preexisting disease, lifestyle and nutrition, genetic characteristics, sex, and ethnicity.	Identification and quantification of risk in susceptible and highly exposed subpopulations.	Many factors that influence variability within a critical age range will be assessed as part of studies to identify the age range and determine why that age range is critical. Studies of mode of action (§4.3.1.1) will often consider genetic and other susceptibility factors. Human studies as well as risk assessments often focus on special groups that are expected to be more susceptible or more highly exposed (§§4.3.1.2, 4.3.1.3, and 4.3.1.4).
SAB Cross-walk: §3.1 a), §3.1 b), §3.1 e), §3.6.2		
Cumulative Risks to Children (§4.3.5.2) Medium Priority		
Investigate simultaneous exposures to multiple environmental agents and other stressors in a child's environment.	Data for assessment of risk of simultaneous exposures, including chemicals by the same route, chemicals with common modes of action by multiple routes, and all environmental agents and other stressors found in the child's environment.	The results of mode-of-action studies (§4.3.1.1) will be important in understanding effects of mixtures. Epidemiology and exposure studies (§4.3.1.2 and §4.3.1.3) often provide data on the multiple chemicals (although only a small fraction of all chemicals) to which infants and children are exposed. Dose-response methods for assessing toxicity of simultaneous exposures are critical to development of models and assessment methods for summing multichemical exposures and risks.
SAB Cross-walk: §3.1 c)		