**Summary Response to Comments on EPA's Draft Supplemental Guidance**

A notice of availability of EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (Supplemental Guidance) was published in the Federal Register on March 3, 2003, along with notice of a 90-day comment period. The Supplemental Guidance was also provided to the Environmental Health Committee of EPA's Science Advisory Board (SAB). The SAB's comments and EPA's responses can be found on the SAB web site (http:www.epa.gov/sab ). In response to both the SAB's comments and pubic comments, more data were included in the analyses and a more sophisticated analysis was performed. The public comments were diverse, reflecting the different perspectives of the reviewers. Many of the comments were favorable, expressing agreement with the concept of an increased susceptibility from exposure to carcinogens with a mutagenic mode of action (MOA). Some of these commenters requested that EPA apply the approach more broadly than just chemicals with a mutagenic mode of action; namely, any chemical for which early-life data are absent. Other comments addressed the limited data available for quantitative analysis, including some that expressed the view that such an analysis was premature. Some requested clarification of language or concepts, while others pointed out errors, both typographical and mathematical. Several sections of the text have been rewritten, a further literature search has been conducted, the available studies were re-analyzed per recommendations from EPA's Science Advisory Board, more examples of how to apply the Supplemental Guidance have been provided, and corrections have been made. Many of the comments were beyond the scope of this Supplemental Guidance, raising issues that are either (1) more properly addressed to the Cancer Guidelines and general regulatory approaches to carcinogenic risk assessment or (2) requesting guidance on additional modes of action, e.g., for endocrine disruptors. The major issues raised by reviewers are summarized below.

**I. GENERAL COMMENT: EPA received both pro and con comments regarding the issue of whether the proposed age-dependent potency adjustments should apply to all cases where chemical-specific data on age dependence do not exist, or limit it to chemicals with a mutagenic mode of action for carcinogenesis. Some comments recommended that carcinogens with a non-mutagenic mode of action be treated similarly to carcinogens with a mutagenic mode of action, and that similar adjustment factors be applied. Others noted that the current default assumptions were incomplete, do not adequately cover MOA, and are not sufficiently health protective. Many other comments stated that the basis for default adjustments for non-mutagenic carcinogens is weak and not appropriate at this time, and that non-mutagens should be considered on a case by case basis.**

RESPONSE: EPA directly addressed this issue in its September 2004 response to the SAB (Agency Response to the Review of EPA's Draft Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens, EPA-SAB-04-003, available at: http://www.epa.gov/sab/pdf/sab_04003_resp.pdf. The response states that the Agency reconsidered both the advantages and disadvantages to extending the

default potency adjustment factors to all carcinogenic chemicals for which the mode of action remains unknown. EPA is recommending that these factors only for carcinogens acting through a mutagenic mode of action based on a combination of analysis of available data, and that the long-standing science policy position which set out the Agency's overall approach to carcinogen risk assessment be retained. In general, the Agency prefers to rely on analyses of data, rather than general defaults. When data are available for a sensitive lifestage, they should be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. In this analysis, the data for non-mutagenic carcinogens, when the mode of action is unknown, were judged to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied. In this situation, per the Agency's Guidelines for Carcinogen Risk Assessment, a linear low-dose extrapolation methodology is being recommended. It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism *in the absence of chemical-specific data indicating differential early-life sensitivity*. The Agency expects to produce additional supplemental guidance for other modes of action, as data from new research and toxicity testing indicate it is warranted.

**A. COMMENT: Because of the uncertainty in how chemicals might affect children, linear low-dose extrapolation should be used as the default approach for all risk assessments of children, even for chemicals that operate through a non-mutagenic mode of action in adult animals.**

RESPONSE: EPA believes that most of the available evidence points to an expectation that the modes of action should be qualitatively similar in children and adults. The mode of action framework presented in EPA's cancer guidelines (to which this guidance is a supplement) includes consideration of susceptible populations or lifestages. Also, the cancer guidelines and this Supplemental Guidance state that when data are available for a specific chemical regarding the susceptibility of a population or lifestage, those data are considered in the analysis. The Supplemental Guidance takes a first step by addressing quantitative differences for chemicals with a mutagenic mode of action.

**B. COMMENT: Development of similar guidance for nonmutagens was recommended, especially for hormonally active agents. One comment requested a thorough evaluation of non-cancer toxicity for infants and children and the possibility of unique susceptibility due to metabolic differences that could contribute to cancer. One commentor stated that endocrine disruptors should be identified as a class of chemicals to which pregnant women and children are especially susceptible, and that all endocrine disruptors should be classified as likely carcinogens in the absence of data to the contrary. Another commentor stated that *additional* health**

**protective adjustment factors should be applied for all carcinogenic endocrine disruptors, and all carcinogenic PBTs for children aged 0-15 years. Commenter thought that special attention should be given to peri-pubescent exposures, particularly for hormonally active agents.**

RESPONSE: The Agency is interested in evaluating other modes of action. Regarding hormonal agents, EPA's Science Advisory Board said, "In summary, there is reason to believe that hormonal agents can be more potent carcinogens when exposure occurs in early-life stages than in later-life stages alone. This area is important to explore and the Agency may do so in future revisions of the Supplemental Guidance conduct an analysis of the differences in potency by age when data become available. As noted in the Supplemental Guidance, three estrogen active agents are currently in test at the National Toxicology Program (NTP) in multigenerational studies, and the results of those studies should shed light on early-life stage susceptibility. The Review Panel would also encourage the Agency to look at clinical data with secondary tumors arising from primary chemotherapy in children versus adults." The Agency expects to develop additional guidance for other MOAs as the data and risk assessment methodologies are developed.

**II. GENERAL COMMENT: Continued use of LADD assumption is inaccurate and not the best science.**

RESPONSE: This is, in fact, the conclusion that the Supplemental Guidance makes for mutagenic chemicals: that the tumor incidence depends not only on the duration of exposure, but also on the timing of exposure. The analysis of tumor incidence as a function of the number of weeks of dosing (that is, based on duration only) effectively sets up a null hypothesis that timing does not matter. The result that the ratios of early-life to later-life exposure are significantly greater than1.0 is a compelling reason to reject the null hypothesis and conclude that cancer risks are higher for early-life exposure. The inverse variance weighted mean of 10 should be used as a better estimate of the increased susceptibility early in life.

**III. GENERAL COMMENT: The quality of the data used are poor. The experiments did not follow good laboratory practices (GLPs), are old studies with inadequate designs, and were not designed to answer the question asked.**

RESPONSE: The analysis of animal carcinogenicity studies in the Supplemental Guidance relies upon good quality studies that were specifically designed to evaluate whether responses were similar or different due to the exposures at different ages. As described in the document, several different study designs were used and a number of different laboratories have carried out similar studies. Given the multiple lifestages examined, variety of dosing routes used, and range of chemicals with different modes of

action used in these studies, almost any study individually has some limitations that must be considered in their interpretation. There also were studies that had significant study design limitations or such limited reporting of the results that they were not used in the analysis. Concerns of this kind resulted in the deletion of the Neal and Rigdon (1987) study of benzo[a]pyrene carcinogenesis from the revised analysis.

Modern GLP studies, such as the three Chhabra et al. (1992, 1993a, 1993b) studies, are advantageous due to the completeness of the reporting, but good quality research findings published in the peer-reviewed literature by reputable laboratories are appropriate scientific information regardless of their age. A number of these studies, notably those on diethylnitrosamine (Peto et al., 1984 and related publications), vinyl chloride (Maltoni et al., 1984), diphenylhydantoin (Chhabra et al., 1993a), ethylene thiourea (Chhabra et al., 1992), polybrominated biphenyls (Chhabra et al., 1993), and the acute studies on multiple chemicals notably by the laboratory of Vesselinovitch (e.g., Vesselinovitch et al., 1974) represent some of the most sophisticated and pioneering research on chemical carcinogenesis in existence.

**A. COMMENT: The release of the Supplemental Guidance was premature, given the state of the science and the uncertainties associated with the quantitative analyses conducted in the document. Comments included those listed below.**

- **EPA did not demonstrate that early-life exposures typically lead to increased cancer risk so as to justify imposition of universal defaults or assumptions. EPA should assume that risk estimates derived for adults are adequately protective for early-life exposures.**

- **The key public health issue that should be addressed by the Supplemental Guidance was *not* whether children are more or less sensitive, but rather whether they are sufficiently protected under current risk assessment practices that are highly conservative in terms of methodologies and default assumptions and are specifically designed to protective sensitive populations, including children and adolescents.**

- **The data cited and analyzed by EPA are too limited to support the Agency's conclusion that early-life exposure leads to increased lifetime cancer risk (i.e., the cited studies were not designed to examine dose-responses for determining age-related relative susceptibility to carcinogens and have numerous limitations when used for this purpose).**

- **EPA failed to consider evidence that children are not always more sensitive to carcinogens. A more balanced view of the literature on**

**children as a sensitive subpopulation was requested; the guidelines generalize that in all situations children are more sensitive.**

- **The guidance provided in the Supplemental Guidance will significantly and unnecessarily overestimate cancer risks to children.**

- **The list of characteristics of early development (i.e., more frequent cell division, lack of key DNA repair enzymes, not fully functional immune system, hormonal changes during various lifestages, pre-disposing developmental abnormalities) describe why the child is vulnerable to developmental effects but is not compelling evidence for an increased cancer hazard.**

RESPONSE: Universal defaults are not recommended by the Supplemental Guidance for evaluating all cancer risks from early-life exposures. This Supplemental Guidance is applicable only for those carcinogens that have been demonstrated to have a mutagenic MOA. The strengths of the scientific database for humans (e.g., radiation) and animals (e.g., mutagenic MOA for carcinogenicity) were identified in order to develop a scientifically supported approach that would be applied to chemicals with strong similarities to, i.e., the same MOA as, those for which increased early-life susceptibility had been demonstrated. The radiation data were not analyzed in depth, in part because there are recognized differences in toxicokinetics and toxicodynamics between radiation and mutagenic chemicals. Even though the data on A-bomb survivors provide information for many different cancer sites in humans with a single exposure involving all ages, a number of national and international committees of experts have analyzed and modeled these data to develop risk estimates for various specific applications. The targeted approach in the Supplemental Guidance is designed to provide health protective analyses for chemicals causing tumors through a mutagenic MOA that is of particular concern not only because the evidence is clear that there are important early-life susceptibilities, but also because chemicals acting through such mechanisms may represent a large number of known human carcinogenic chemicals. For chemicals with a mutagenic MOA, data that indicated that the chemical or the site were sensitive, refractory, or unchanged by early life stage exposure were considered. All of these data are included in the analysis in the Supplemental Guidance.

While EPA's cancer risk assessment methods based solely on adult information are frequently protective of all lifestages, it would be inappropriate to assume that they are universally protective defaults for all modes of action (NAS, 1994). The National Academy of Sciences has recommended that EPA assess risks to infants and children whenever it appears that their risks might be greater than those of adults. One approach recommended by the NAS would be to choose to incorporate

into the cancer risk estimates for individual risk a "default susceptibility factor" greater than the implicit factor of 1 that results from treating all humans as identical (NAS, 1994).

**B. COMMENT: The current, default methodology for assessment of lifetime cancer risks is sufficiently conservative to protect children. Sufficient data are not available to evaluate if children are at greater risk.**

RESPONSE: Clearly, both of these comments cannot be accurate. If there is insufficient data to evaluate the risks for children, it is not possible to determine if the default procedure protects this age group. The Agency has received comments from its Science Advisory Board (SAB) and all sectors of the public. These have resulted in more complete and sophisticated analyses of the data, and the additional qualitative and quantitative analyses continue to support the analysis in the draft document. These results are also supported by independent analyses of the same or similar data. For example, Hattis et al. (Hattis, D; Goble, R; and Chu, M. (2005) Age-related differences in susceptibility to carcinogenesis II. Approaches for application and uncertainty analyses for individual genetically acting carcinogens. Environ Health Perspect 113:509-516) reported a central estimate ratio for birth to weaning - direct of 11.6 and a birth to weaning - lactational of 21.4. A somewhat smaller increase of about 5-fold for radiation carcinogenesis was reported in this article.

## IV. GENERAL COMMENT: The Supplemental Guidance does not meet the requirements of the Information Quality Act.

RESPONSE: EPA's data quality guidelines recommend that, consistent with the applicable laws and regulations, the analysis be transparent, reproducible, and undergo peer review. The analyses have undergone both peer review and public review; corrections and further analyses were done in response to these reviews. The data and the analyses will be available on our web site, and have been available to other scientists within the Federal government. Moreover, the data and analysis were reviewed by an external expert panel. This analysis is presented in a journal article that has been accepted for publication in *Environmental Health Perspectives*. Therefore, the Agency believes that the Supplemental Guidance adheres to EPA's data quality guidelines.

**A. COMMENT: The Supplemental Guidance is not based on sound science and should be acknowledged as strictly a policy decision.**

RESPONSE: The Supplemental Guidance is based on a thorough scientific analysis of the data that allow comparisons of cancer incidence following exposures early in life with cancer incidence following exposures later in life. The scientific analysis is presented in the first five sections; an approach for

implementing the conclusions of this analysis in risk assessments is presented in Section 6 of the Supplemental Guidance. This scientific analysis was peer-reviewed by a joint committee of the SAB, SAP, and CHPAC in a public meeting. The committee supported the general approach and conclusions and made some recommendations for strengthening the analysis. These recommendations have been incorporated in the final Supplemental Guidance.

**B. COMMENT: Further explanation was requested for how the susceptibility ratio was determined from the two groups (perinatal and adult) where tumor incidence was not statistically significantly above controls. The analysis of the juvenile/adult calculations (i.e., susceptibility ratios) on the six non-mutagenic compounds was said to be flawed.**

RESPONSE: Comments such as the above, along with discussions with EPA's SAB, resulted in a reanalysis of the data, with more data from different tumor sites included. The text of the Supplemental Guidance clearly lays out the rationale for the analyses, and all data and analyses will be available on the web site.

**C. COMMENT: EPA's conclusion that early-life exposure to any mutagenic chemical necessarily poses a greater risk than an equivalent dose absorbed during the adult years is too simplistic and not supported by the literature.**

RESPONSE: The Supplemental Guidance addresses only chemicals with a mutagenic mode of action for carcinogenesis, not all mutagens. The document recognizes that there is limited evidence to inform the mode(s) of action leading to differences in tumor type and tumor incidence following early-life exposure and exposure later in life. However, the available studies support the concept that early-lifestage exposure to carcinogenic chemicals with a mutagenic mode of action would lead to an increased incidence of tumors compared with adult exposures of a similar dose and duration.

**D. COMMENT: EPA failed to distinguish different types of mutagens. It is possible to distinguish chemical mutagens by their modes of action. Some of these cause mutations by mechanisms similar to those that arise spontaneously, while others are more like radiation in their effects. The five compounds that EPA analyzed in the repeated exposure section are all DNA binding agents; some chemicals (i.e., base analogs, and intercalating agents) do not directly bind to DNA.**

RESPONSE: The Agency agrees that there are different mechanisms by which chemicals can form different types of mutations. EPA's cancer guidelines present the mode of action framework. These guidelines also describe some of the types of data that are useful in determining a mutagenic mode of action (section 2.3.5).

This Supplemental Guidance also addresses the issue in sections 2 and 5, providing information on what is meant by mutagenic mode of action for this document.

**E. COMMENT: It is not appropriate to analyze acute-dosing studies without corresponding long-term studies.**

RESPONSE: The analysis of studies involving repeated doses and the acute (generally single dose) studies was carried out separately because they provide somewhat different information. The acute dosing studies absolutely control the exposure dose. Thus, there is no question that both the juvenile and the adults received the same dose and that the differences in response observed at the different ages arise from differential susceptibility to the same, known dose. These acute studies are generally not used for risk assessment because they involve largely injection exposures that are not directly analogous to human exposures. By contrast, the repeated dosing studies involve exposure routes relevant to the human situation (e.g., inhalation, oral via drinking water or diet). Thus, they are less able to rigorously control the exposure dose. Therefore, the two kinds of studies provide different but complementary information that support the same conclusion.

**F. COMMENT: The Supplemental Guidance cites fewer studies than a 1996 analysis by EPA's Office of Pesticide Programs cited.**

RESPONSE: The 1996 analysis (U.S. EPA. 1996. Comparison of the effects of chemicals with combined perinatal and adult exposures vs. adult only exposure in carcinogenesis bioassays. U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC) investigated a different question, that of whether standard (adult-exposure-only) carcinogenesis bioassays are adequate to identify chemicals that might pose a cancer risk from perinatal exposure. The 1996 analysis, therefore, focused on whether those chemicals that induced tumors following perinatal exposure also induced some type of tumor in a standard bioassay. In the 1996 analysis it was not necessary to compare tumor incidence rates between perinatal and adult-only exposure; indeed, it was not even necessary that the same tumor be found in the perinatal-exposure and standard bioassays. For the Supplemental Guidance, quantitative comparisons were made only when the same tumor was observed in the same species, strain, and sex of animal. This insistence on comparability between bioassays is why the quantitative analysis in the Supplemental Guidance is based on a smaller number of studies compared with the 1996 analysis.

**G. COMMENT: For vinyl chloride, the study of Drew et al. (1983) should not be included because the animals were exposed only as adults. Only the study of Maltoni et al. (1984) should be cited.**

RESPONSE: EPA agrees that the study of Maltoni et al. (1984) provides the most compelling evidence that early-life exposure to vinyl chloride poses a higher cancer risk than exposures later in life. This is evident both for hepatocellular carcinomas, which are also caused by later-life exposures, and for hepatomas, which are not caused by later-life exposures. Nonetheless, the study of Drew et al. (1983) provides independent, supporting evidence. Although these animals were not exposed to vinyl chloride before 6 weeks of age, there was a clear tendency toward higher cancer incidence when the 6-month exposure period occurred earlier in life.

**H. COMMENT: It was inappropriate to use data from atomic bomb survivors to demonstrate the greater sensitivity of children.**

RESPONSE: The Agency did not suggest that the radiation data demonstrated that children are more susceptible to cancer induction than adults. As stated in the Supplemental Guidance, "A supporting role was assigned to the available human radiation data" and "Rather, information relevant to comparing cancer risks from juvenile versus adult exposure from UNSCEAR (2000) and U.S. EPA (1994; 1999) are presented as representative findings to determine whether the radiation data are similar qualitatively to the chemical findings." While not stated in the Supplemental Guidance, that the radiation exposure was a single high dose-rate exposure is one more reason to use that information only qualitatively. Tables 9 and 11 clearly show that increases in sensitivity are not observed at all sites. The model developed by Pierce and Mendelsohn (1999) is but one of the many models that have been developed to describe the solid tumor data from the atomic bomb survivors. In "Annex I: Epidemiological Evaluation of Radiation-induced Cancer" of the UNSCEAR (2000) report it is stated that, "Generally speaking, the age-at-exposure and attained-age models describe the Life Span Study data equally well." Further, Pierce and Mendelsohn acknowledged that their reasoning does not apply equally to all types of cancer, and they focused on the major types of solid cancer with similar age patterns.

**I. COMMENT: The data from the atomic bomb survivor cohort provide definitive evidence that early life exposures are important for determining lifetime cancer risks for certain types of leukemia.**

RESPONSE: While the Agency agrees with the comment as it relates to the population of atomic bomb survivors, it does not agree that data derived from an acute exposure to ionizing radiations can be quantitatively extrapolated to chronic low level exposures to environmental chemicals – even those causing cancer by a mutagenic mode of action.

**V. GENERAL COMMENT: There were several comments regarding the form of the Supplemental Guidance and whether it was consistent with other EPA documents. For example, comments were mixed regarding EPA's decision to produce separate documents for the cancer guidelines and the early-life guidance.**

RESPONSE: The main document is a guideline, i.e., a basic document that is meant to form the foundation of the cancer risk assessment process. The early-life document is labeled guidance because it is one of what are assumed will be several, topic-specific supplements to the guidelines. Guidance usually covers a narrower topic, and allows more frequent updating of topics that are still developing. In contrast, guidelines generally cover larger topics and should require less frequent updating.

**A. COMMENT: Several comments noted that the Supplemental Guidance should be revised to be consistent with the draft Carcinogen Guidelines.**

RESPONSE: The observed and noted inconsistencies that arose as these documents were being prepared have been corrected.

**B. COMMENT: The Supplemental Guidance is inconsistent with policy established in setting a maximum contaminant level goal for chloroform.**

RESPONSE: Chloroform was analyzed on a case-by-case basis, using the chemical-specific data, as recommended by both EPA's cancer guidelines and this Supplemental Guidance. Chemical-specific data are generally preferable to either default values or generic, mode of action values. Furthermore, chloroform was determined to have a non-linear mode of action. Therefore, the Supplemental Guidance is not applicable.

**C. COMMENT: The Supplemental Guidance is inconsistent with the precedent established by EPA's Office of Pesticide Programs when they removed the Food Quality Protection Act's default 10x children's factor in the risk assessment of organophosphates.**

RESPONSE: First, the Supplemental Guidance applies to carcinogenic risks evaluated through a mutagenic mode of action. Organophosphate pesticides are not in this group of chemicals. Second, the default 10x children's factor was removed in that case because it was concluded that there were organophosphate-specific data that provided adequate information that children were not more susceptible than adults. Chemical-specific data are to be evaluated whenever they are adequate. Note that there is also a difference between the way defaults are viewed in these two cases: The Food Quality Protection Act starts with a default factor that may be reduced or removed if adequate data are available, while EPA's

cancer guidelines and this Supplemental Guidance start with a critical analysis of the data, and apply a default when the data are either absent or too uncertain.

**D. COMMENT: The Supplemental Guidance should describe how to document and characterize uncertainty and variability.**

RESPONSE: EPA's cancer guidelines, for which this is Supplemental Guidance, are operative regarding the documentation and characterization of uncertainty and variability.

**E. COMMENT: EPA should withdraw the Supplemental Guidance and wait for other government agencies and stakeholders to collect more data on cancer susceptibility following early-life exposure.**

RESPONSE: EPA bases its actions on the best scientific information available. EPA's analysis led to the conclusions that: (1) there are adequate data and mechanistic understanding now to conclude that carcinogens that act by a mutagenic mode of action pose higher lifetime cancer risks when exposure occurs early in life, and (2) EPA should wait for more data on other chemicals that act through non-mutagenic modes of action. External peer review is the standard that EPA uses to judge the soundness of its scientific analyses, and the SAB's recommendation was favorable.

**F. COMMENT: Additional discussion should be provided as to what constitutes sufficient data to establish a non-mutagenic MOA.**

RESPONSE: This falls within the scope of EPA's cancer guidelines (section 2.5), and the Supplemental Guidance references this discussion in several places.

**G. COMMENT: The Supplemental Guidance does not discuss how to incorporate toxicokinetic and toxicodynamic information into the quantitative risk assessment**.

RESPONSE: Again, this question is addressed in more detail in section 2.5 and section 3 of EPA's cancer guidelines where explicit guidance is given to note any differences between children and adults in toxicokinetic processes or toxicodynamic processes.

**H. COMMENT: Figure 3 shows that risk estimates will be developed if there are tumor data from early-life exposures, without considering the data on MOA or its human relevance.**

RESPONSE: One must look at the cancer guidelines in conjunction with the Supplemental Guidance to see when risk estimates would be developed. EPA's cancer guidelines make clear that MOA data are fully considered in determining the relevance of experimental animal data to humans and in the choice of an approach to dose-response assessment. If an animal response is not relevant to humans, than no human risk estimate would be developed for that particular animal response. In cases where risk estimates are developed, the MOA framework (section 2.5 of EPA's cancer guidelines) makes it clear that any data indicating differences between adults and children are used in the subsequent dose-response assessment. The Supplemental Guidance provides defaults for adjusting slope-factor risk estimates in cases where the database on the carcinogen (with a mutagenic mode of action) being assessed does not include studies on early-life exposure.

**I. COMMENT: EPA should highlight the need for additional research and analysis on age-sensitive exposure risks because limited quantitative information on differential sensitivities exists.**

RESPONSE: These research needs are now discussed in the Supplemental Guidance.

**J. COMMENT: The term "mutagen" should be replaced with the more general term "genotoxin."**

RESPONSE: While the Agency agrees that "genotoxin" is a more general term than "mutagen," the use of the general term is not appropriate in the context of the mode of action of carcinogenicity. At the same time it is recognized that the two terms are sometimes used interchangeably. Using mutagenic mode of action in the Supplemental Guidance is consistent with EPA's cancer guidelines.

**VI. GENERAL COMMENT: No information is presented on dose-response curves for either of the life stages. Ratio of responses for a given dose is not predictive of the ratio of doses giving a fixed response, i.e., the concept of relative potency has been incorrectly defined in this document. It is not justifiable to rely on high-dose studies that may be 1000-fold above any likely environmental dose.**

RESPONSE: The use of high-dose studies in experimental animals to make inferences about the toxicity of chemicals to humans is fundamental for regulatory risk assessment and has been addressed in other venues. This question is a generic issue and not an issue for the Supplemental Guidance.

While relative potency is correctly defined as the exposure or dose required to produce the same response, for the limited case considered in this guidance, the analyses of the relative

response from the same dose will produce the same value. This document only considered chemicals for which a mutagenic mode of action has been established and for which a linear, no-threshold dose-response function is assumed for the low-dose range. As described in the Supplemental Guidance, in this situation the relative potency is equivalent whether derived from the ratio of the doses or the ratio of the responses.

**A. COMMENT: Questions were raised about the methods used to evaluate early life susceptibility given the different study designs. Issues raised include the clarity of the discussion of the equations and alternative methods to do the calculations including comparing lifetime exposures to adult only exposures directly.**

RESPONSE: Since the methods have been modified, the methods section of the Supplemental Guidance has been substantially rewritten addressing many of these comments. Further analysis of alternative study designs has also been included in the discussion section. While the comparison of incidence following lifetime exposure versus adult only exposure is informative about whether there is an increased cancer incidence with lifetime (i.e., combined early and adult) exposures, it does not provide information about the magnitude of increased susceptibility from early exposures, so we have improved the application of the approach originally used focusing on the difference in incidence between lifetime and adult only exposures (when that study design is applicable).

**B. COMMENT: The use of a margin of exposure should be retained.**

RESPONSE: Risk characterization of carcinogens is an issue described in EPA's cancer guidelines.

**C. COMMENT: The Supplemental Guidance discusses adjustments to slope factors only, and not to hazard quotients, hazard indices, or margins of exposure.**

RESPONSE: The adjustments recommended in the Supplemental Guidance apply only to carcinogens with a mutagenic mode of action. For these chemicals, cancer risks would be estimated using a slope factor and not a hazard quotient, hazard index, or margin of exposure, all of which are dependant on the RfD/RfC methodology.

**D. COMMENT: The Supplemental Guidance needs to be very clear that the age dependent adjustments are applied only for exposures during the appropriate years of life, and not to an entire lifetime of exposure.**

RESPONSE: Several additional examples and explanations were added to Section 6 to illustrate the application of the age-dependent adjustment factors for a variety of situations, e.g., exposures at different ages, for less than lifetime periods, or throughout the lifetime. The age-dependent adjustment factors apply to exposure during the specified time periods, and the appropriate value for the adjustment needs to be applied for each age at which exposure occurs.

**E. COMMENT: The 3x factor for ages 2<16 is not based on any studies, but is the geometric mean between a 10x adjustment and no adjustment.**

RESPONSE: EPA agrees. The 10 is a direct result from the Agency's analysis of the data. The 3x is a science policy adjustment, i.e., a policy decision informed There is by and based on science information. There are reasons to be concerned about this period (ages 2<16) of rapid development; therefore, it did not seem reasonable to drop down to no adjustment at age 2. EPA asked its Science Advisory Board about this 3x adjustment, and they thought it was a reasonable approach in the absence of direct data on this age group.

**VII. GENERAL COMMENT: Don't double count between exposure and susceptibility. Concerns were raised that, if exposure differences were to be considered in addition to susceptibility issues, there would be "double counting," resulting in overly conservative risk assessments. Therefore, the Agency should provide guidance on how to separate these two factors with regard to pharmacokinetic differences between children and adults (e.g., differences in susceptibility with regard to metabolism verus differences in susceptibility with regard to internal dose due to exposure/dose rate variables).**

RESPONSE: Exposure and susceptibility are two different aspects of risk, and considering both aspects is in no way "double counting." It is possible that a susceptible group can have lower, higher, or similar exposures compared with the general population. EPA risk assessments have always considered both exposure levels and toxicity when estimating cancer risks in an exposed group. Age groupings for various modes of action will depend on the available data as well as the biological and toxicological underpinning for potential susceptibility. These will not necessarily coincide with the age groupings for different activities that might affect exposure rates, durations, or intensities. The age groups that are evaluated separately will depend on both the chemicals and the potential for exposure to various age groups. When the window of vulnerability and increased exposure overlap, both adjustments should be used. When only one is applicable, only that adjustment is used. The revised Supplemental Guidance provides improved examples of applications of these issues.

In risk assessment, the exposure and dose-response assessment steps must be compatible to permit final risk estimation, so it is essential to determine whether age-dependent

differences in cancer response arise from exposure or response to the exposure. The repeated dose studies use inhalation, drinking water, or dietary routes of exposure, so the oral exposure or inhaled dose vary with age. Drinking water and food consumption for rats and mice essentially scale as $BW^{3/4}$ meaning young animals have a higher exposure dose than older animals. Therefore, the repeated dose studies alone provide important indications of whether animals are more susceptible, but do not provide all the necessary information. To analyze these studies and demonstrate early life susceptibility it would be necessary to have modeling to reliably estimate exposure or inhaled doses during the different periods.

An alternative approach was available for compounds acting through mutagenic modes of action. A large literature demonstrates early life susceptibility following acute (e.g,. a single exposure) dosing by injection or oral routes for compounds acting through mutagenic modes of action, though not for a range of other modes of action (e.g., tumor promoters). These studies rigorously control the exposure dose proving that age-dependent differences reflect differences in susceptibility, or conversely, the age-dependent potency of the chemical. In addition, these studies carefully control the period for expression of tumors to demonstrate the effects are age-dependent and not a reflection of differential periods for latency (though it should be noted that decreased latency is reported in a number of studies of early life exposure). The ratios calculated from the acute dosing studies demonstrate that the early life susceptibility was observed in a number of target organs, and if anything, the ratios are larger for liver when exposure dose is rigorously controlled. Thus, the current guidance relies upon both the acute and repeated dosing studies to establish that chemical acting through mutagenic modes of action demonstrate age-dependent changes in potency.

**VIII. GENERAL COMMENT: Data should be preferred over defaults, especially with regard to early life exposure, even for mutagenic MOA.**

RESPONSE: The Supplemental Guidance states a clear preference for analyses based on data, with defaults used if needed to address uncertainty or the absence of critical data. An example would be the IRIS assessment of vinyl chloride, a mutagenic chemical, for which data on animals exposed early in life were used to develop different estimates for adult and childhood exposure. From its analysis of the available data, the Supplemental Guidance concludes that the previous default, i.e., that children and adults are equally susceptible, is not supportable in some cases. Instead, the available data on early-life exposure should be analyzed before invoking either the 10x/3x adjustment (for chemicals where mutagenicity contributes to the MOA) or the default of equal susceptibility of children and adults (currently used for other MOAs).

**IX. GENERAL COMMENT: Human data should be used in preference to extrapolation from animal data.**

RESPONSE: The choice between human and animal data is discussed in EPA's cancer guidelines and is not part of the Supplemental Guidance. Regardless of whether human data or animal data are used to estimate risks, the Supplemental Guidance discusses the need to consider whether risk estimates developed from adult humans or mature animals should be applied with no adjustment to estimate risks in children. The Science Advisory Board in reviewing the Supplemental Guidance discussed the limitations of the available human data.

**X. GENERAL COMMENT: EPA did not justify its age groupings for the purposes of applying different adjustment factors to mutagenic carcinogens. Risks from early-life exposure might be understated because the susceptibility window is too narrow (0-15 years) and does not adequately consider prenatal, parental, pre-pubertal, and pubertal exposures, especially for hormonally active agents. Recommendations included (1) dividing the susceptibility window into three, rather than two, distinct periods; (2) extending the age of sensitivity during puberty to 17 years; (3) adjusting for gender differences in peripubertal windows of susceptibility; and (4) including the prenatal fetal development period as a susceptible exposure window.**

RESPONSE: The age groupings selected for the age-dependent adjustments for carcinogens acting through a mutagenic mode of action were initially selected based on the available data, i.e., for the laboratory animal age range representative of birth to < 2 years in humans. More limited data and information on human biology were used to determine a science-informed policy regarding 2 to < 16 years. Data were not available to refine the latter age group into smaller age grouping(s). Furthermore, a recent analysis (Hattis et al., 2005, op cit) reached similar conclusions regarding age groupings based on analyses of animal growth patterns and data on humans available through the NHANES database. If more data become available regarding carcinogens with a mutagenic mode of action, consideration may be given to further refinement of these age groups. As the Agency examines additional carcinogenic MOAs, the age groupings may differ from those recommended for assessing cancer risks from early-life exposure to chemicals with a mutagenic MOA. The Agency is interested in identifying lifestages that may be particularly sensitive or refractory for carcinogenesis, and believes that the mode of action framework described in the Cancer Guidelines and Supplemental Guidance is an appropriate mechanism for elucidating these lifestages.

**A. COMMENT**: **The prenatal period should be considered a special period of susceptibility with its own safety factor. In the absence of specific data, it was suggested that the default for the 0-2 year age grouping should apply to *in utero* exposures. It was recommended that an adjustment factor of at least 10x be applied in all cases where pregnant women may be exposed.**

RESPONSE: Puberty and its associated biological changes involve many biological processes that could lead to changes in sensitivity to the effects of some

carcinogens, depending on their mode of action. Both EPA and its Science Advisory Board (SAB) are interested in the potential for chemicals to cause differential sensitivity during the prenatal period. As indicated in the SAB's report, however, a procedure for a quantitative analysis of *in utero* exposures is not available at this time .

**B. COMMENT: Multigenerational carcinogenesis needs to receive higher priority, starting with an examination of lessons learned from DES.**

RESPONSE: This is, indeed, an important issue in risk assessment, but it is outside the scope of the issue that the Supplemental Guidance addresses. It may, however, be the topic of future guidance.

**C. COMMENT: The 10x adjustment should be applied throughout childhood, because there may be little practical difference for children who are still growing and developing.**

RESPONSE: The data supporting the 10x adjustment were derived from exposures very early in life, when both toxicokinetic and toxicodynamic processes may be operating at different rates than in adults. The available pharmacokinetic data (Ginsberg, G; Hattis, D; Sonawane, B; et al. (2002) Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 66:185-200) show that after 2 years of age, metabolic processes are substantially similar to those of adults. Consequently, the Supplemental Guidance recommends a reduced 3x factor after that age.

**D. COMMENT: The adjustments recommended in the Supplemental Guidance should be extended to include prenatal exposure and exposure through age 17. In addition, the peripubertal periods should be considered as a period of potentially high susceptibility for reproductive system tumors, for example, breast cancer.**

RESPONSE: The Supplemental Guidance does not address prenatal exposure, as data are not generally available to address this type of exposure. As EPA's Science Advisory Board stated, "The Review Panel cannot recommend at this time a feasible method for incorporating transplacental or *in utero* exposure data." The Supplemental Guidance covers through <16 years of age, chosen to represent middle adolescence, i.e., following the period of rapid developmental changes in puberty and the conclusion of growth in body height according to the NHANES data. The question of windows of susceptibility before and during puberty for reproductive system tumors is an important one, and EPA hopes that data will be generated that will permit additional guidance to be developed in the future.

The current guidance focuses on carcinogens with a mutagenic mode of action. For any mode of action, the Agency is interested in identifying lifestages that may be particularly sensitive or refractory for carcinogenesis, and believes that the mode of action framework as described by EPA's cancer guidelines, is an appropriate mechanism for elucidating these lifestages. In general, our analyses of lifestages that may be sensitive will depend on three factors: (1) establishing the mode of action for carcinogenesis; (2) using knowledge about the biological and toxicological key events in that mode of action that are likely to be affected by lifestages; and (3) the availability, or development, of data that allows analysis of the effects of chemicals acting by that mode of action during the relevant ages. For each mode of action evaluated, therefore, the various age groupings determined to be at a differential risk, which may differ significantly from those proposed for the mutagenic mode of action, is expected be evaluated independently of other modes of action.

With regard to the current guidance, the limitations of the available database would not allow us to breakdown the 2 -15 age grouping into finer increments. The potency adjustments for chemicals that are carcinogenic through a mutagenic mode of action were initially selected based on the available data, i.e., for the laboratory animal equivalent of birth to < 2 years. The SAB Review Panel noted, and the Agency recognizes, the complexity of estimating the human equivalent age(s) to laboratory animal age(s). We are aware that some analyses that attempt to use various biological points of comparison are on-going (e.g., Hattis et al., 2005, op cit), and we expect to evaluate those analyses as they become available, to better define this complex relationship. More limited data and information on biological effects are being used to determine a science-informed policy regarding 2 to < 16 years. The Agency concludes that at this time the data are not available to refine the latter age group. If more data become available regarding carcinogens with a mutagenic mode of action, the age groups may be modified.

**E. COMMENT: There are several pharmacokinetic reasons to expect that there will be age-dependent differences in susceptibility.**

RESPONSE: EPA agrees. When there are data that allow adjustments to be made for the agent being assessed, the Supplemental Guidance says that they should be used.

**XI. GENERAL COMMENT: The adjustment factors estimation uses an over-reliance on liver tumor data from B6C3F1 mice.**

RESPONSE: Among the studies used there are a number of studies that observed liver tumors in multiple strains of mice, but there are also tumors in other tissues and in rats. It is also the case that a large number of chemicals acting through a range of different modes

of action cause liver tumors in rodents, so liver tumors tend to be well represented in any broad analysis of chemical induced rodent carcinogenesis. Some discussion of the target organ specificities of several carcinogens that work through a mutagenic MOA, all of which cause liver tumors, is provided in Vesslinovitch et al. (1979). It is clear that multiple organs show the age dependent sensitivity, at least for chemicals with a mutagenic mode of action. Table 6 has been added showing the ratios by organ for the acute dosing studies, which demonstrates that liver, mammary gland, and nervous system tissues among others show age-dependent susceptibility. Not every tissue shows age-dependent susceptibility. In some cases, notably lung, age dependence may be masked by the high tumor response at all ages, suggesting the studies needed to be done at lower doses. An example of this is reported with urethane by Rogers (1951) (see Table 3) in which a study at 1 mg/g body weight by intraperitoneal injection shows a very high tumor response with only slight age dependency between 2 and 10 weeks, while a dose-response study show a clear difference at 0.25 mg/g with a high response at 3 weeks and a much lower response at 8 weeks. The increased sensitivity at very young ages is observable in multiple tissues, though not every tissue.

**A. COMMENT: The 10-fold adjustment factor is based on a rather limited and perhaps non-representative database.**

RESPONSE: The multiple-dosing-regimen studies on mutagenic chemicals, including those from different laboratories, were consistent in showing a higher lifetime cancer risk when exposure began early in life. These were supplement by many single-dose studies, which also showed that cancer risks are higher when exposure occurs early in life. In addition, several mechanistic considerations discussed in the Supplement Guidance provide biological plausibility for the conclusion about chemicals with a mutagenic mode of action. The Supplemental Guidance states: "The challenge for this analysis was how to use the existing, but limited, scientific database on early postnatal and juvenile exposures to carcinogens to inform a science policy decision on whether, and if so how, to assess the risk from childhood exposures to chemicals for which we have evidence of carcinogenicity only in adult humans or sexually mature laboratory animals. The database overall is of modest size (particularly compared with the number of chemicals that have been studied in adult occupational epidemiological studies or chronic bioassays). ... The comparative experimental studies used 18 chemicals, 12 of which had mutagenic modes of action .... Two other kinds of information can contribute toward developing a scientifically informed policy: theoretical analyses and analyses of stop studies."

**XII. GENERAL COMMENT: Lifetime studies (except DEN) were not analyzed.**

RESPONSE: In the original draft Supplemental Guidance, the analysis did not include lifetime study designs when there were also partial lifetime study designs (e.g., Chhabra et

al., 1992, 1993a, 1993b). The revised analysis includes lifetime study designs and partial lifetime study designs when they are available. Some discussion of the relative utility of these different study design has been added to Section 4, as discussed in the next response.

**A. COMMENT: The most relevant information would be obtained by comparison of full-life exposure studies with adult-only exposure studies, but this was done for only a few chemicals.**

RESPONSE: The scientific analysis presented in the Supplemental Guidance has been revised to include all chemicals for which both full-life exposure (that is, exposure from birth until the end of the experiment) and adult-only exposure studies are available. EPA also included chemicals for which both early-life-only exposure studies and adult-only exposure studies are available. Including both study designs increased the breadth of the database on which the conclusions were based. While the lifetime study design is a useful one, an analysis is now presented in section 4 indicating that the early-life-only and adult-only study design is often, though not always, more sensitive for evaluating age-dependent susceptibility to exposure to carcinogenesis than the lifetime study design. Thus, both study designs can be useful and have been included.

**B. COMMENT: The Supplemental Guidance should address later-life exposures.**

RESPONSE: EPA searched for, but could not find, data to develop recommendations for different procedures for assessing risk for later-life exposures.