July 5, 2019

Thomas Armitage, Ph.D.
Designated Federal Officer
EPA Science Advisory Board (1400R)
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Dear Dr. Armitage,

This letter, along with its enclosure, constitute a reiteration and extension of the oral and written comments I presented on the occasion of the June 5-6 meeting of EPA's chartered Science Advisory Board. At that meeting, Ed Ohanian and Dave Bussard facilitated a conversation with the Board on the subject of risk assessment guideline updating and development, with special attention given to the 2005 cancer guidelines and yet-to-be-written non-cancer guidelines.

To summarize my earlier written comments:

1. To propose and expect that, before the end of 2020, the agency can succeed in articulating a set of principles that will find acceptance in the broader scientific community is hopelessly unrealistic, and naïve, at best. In my view, an optimistic timeline if no significant hurdles arise, is 4-5 years. However, a more realistic timeline would be 5-6 years because unanticipated hurdles always arise.

2. Adequate agency resources, representing every Program and Region as well as ORD, and time need to be committed and sustained along with credible engagement of outside experts in both development and review roles.

3. Before updated or new guidelines can be written, EPA must address the unfinished business with regard to the agency's response to, and implementation (or not) of recommendations made by the National Research Council in its 2009 report *Science and Decisions: Advancing Risk Assessment*. These recommendations address several seemingly intractable challenges that transcend any endpoint-specific guideline: uncertainty and variability, dose response assessment, default factors and cumulative risk assessment. The first three issues must be resolved first and would best be presented as stand-alone policy papers. The fourth issue, cumulative risk assessment, can be addressed on a separate track and timeline.

4. EPA should conduct a rigorous program of engagement of the broader scientific community, beginning with robust intra-agency and external peer involvement in drafting the products, public discussions in many venues, peer review by a Science Advisory Board committee supplemented with representatives from the FIFRA SAP and the TSCA SACC, as well as additional outside experts to ensure both the necessary expertise and a balance of perspectives within the scientific community. It should include referral back to the NAS to engage it in the review of the *Science and Decisions*-related issue papers, the guidelines and the qualifications of the SAB review panel to confirm that the outputs reflect an objective view of the state of the science.

During the guidelines discussion with the SAB on June 5, the members were asked to provide their thoughts on a series of topics and questions, in particular, in the context of Scope and topics, Prioritization of effort and Process. Never hesitant to offer an opinion, I am submitting my unsolicited feedback on these questions and other related topics. I believe I bring a different, and, perhaps, more enlightened perspective than the SAB members can to the table, given that I "lived it" for so many years on the inside.

1. It is critical that there be an *exclusion* of any language in a final Transparency rule that describes requirements by regulation on how to conduct risk assessment. Such an approach can be construed from this example in the proposed rule [Page 18770 Federal Register / Vol. 83, No. 83 / Monday, April 30, 2018 / Proposed Rules] which states "In addition, this proposed regulation is designed to increase transparency of the assumptions underlying dose response models. As a case in point, there is growing empirical evidence of non-linearity in the concentration response function for specific pollutants and health effects. The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies that explore: A broad class of parametric concentration response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models"].

   Proscription by regulation has no place in risk assessment for several reasons: 1) The directive is out-of-date before the ink has dried on the regulation; 2) The Agency gets trapped into using outdated science for many years, given the time it takes to undo or re-write a regulation; 3) The Agency is already buffeted with criticism that it doesn't

incorporate new science or new ways of looking at the science in a timely manner and 4) This and other similar topics are better addressed in guidance to assure a more responsible and credible application of up-to-date science.

2. EPA should NOT write separate guidelines for cancer and non-cancer. This idea of "separate" is driven primarily by the dichotomous approach the agency has taken historically in conducting dose response assessments. There is a big push now from several quarters to develop a harmonized approach, although opinions differ on what direction that should take. A single guideline will make it easier to assess cancer and other chronic endpoints in an integrated manner. Treat the assessment of cancer as one of the many potential adverse outcomes that may occur in a long-term exposure setting. A single document coupled with the Mutagenicity guidelines should suffice. I would not propose to fold the developmental, reproductive or neurotoxicity guidelines into the same big package, however. These endpoints are sufficiently different to warrant stand-alone guidelines. In my view, based upon what we have learned about the etiology of different tumor types in different species, cancer is not inherently that different.

   I have taken a first crack at revising the Introduction to the 2005 cancer guidelines to illustrate how easy it should be to transform them into a single guidance document for both cancer and generic non-cancer endpoints of concern. The revision example is included as the enclosure and I have made some additional comments about it in the latter portion of this letter.

3. My answer to Question #1: "Yes." First among them are three of the topic areas addressed in *Science and Decisions* (Uncertainty and variability, dose response assessment and default factors). And, specifically, for cancer risk assessment, there needs to be an in-depth, systematic review of the literature related to the current assumption that agents which react directly with DNA in the initial stage of the carcinogenic process do so in a no-threshold manner. The last few years have seen an increasing number of papers challenging that premise. It is time, perhaps, past time, to do a serious, objective review of these publications.

4. My answer to Question #2: Again, "Yes." There should be a discussion of systematic review and at least a brief description of the steps EPA will employ in conducting such an exercise when implementing any risk assessment guideline. Also there should be a discussion about NAMs (New Assessment Methodologies)—the roles they can play in the near term (*e.g.,* in MOA analyses and establishment of Adverse Outcome Pathways (AOPs)) and the roles they could play in the long term as the use of animals in research and testing is phased out. Lastly, the concept of Adverse Outcome Pathways—what they

are, how they mesh with Mode of Action analyses and how to integrate them into the evaluation of specific endpoints of carcinogenicity and other effects of concern.

5. Uncertainty analysis: Some parties have advocated for inclusion of in-depth, multi-faceted uncertainty analyses in virtually every risk assessment EPA conducts. Others have challenged the value-added of such an approach and whether it contributes in a significant way to the decision-making process. I would suggest that, as the policy paper on Uncertainty Analysis (UA) is being crafted, the Agency should design a tiered approach which mirrors its existing tiered approach to risk assessment, but retaining the flexibility of case-by-case. For instance, no UA when doing screening or prioritization exercises, increasing the level of effort only as the complexity and potential impact of a risk assessment increases.

6. My thoughts on priorities-What to do and in what order.

   <u>High Priority</u>
   a. Issue the updated mutagenicity guidelines without further delay
   b. Complete and issue the updated exposure guidelines (although these may require another round of external peer review since the first external review panel recommended major changes)
   c. Draft, externally peer review, complete and issue the three policy papers on uncertainty/variability analysis, dose-response assessment and default factors
   d. Draft, externally peer review, complete and issue a SINGLE guidance document on general principles of toxicity assessment which contains a chapter on cancer.
   e. Revise, externally peer review, complete and issue a re-named "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens," which would now include an account of potential susceptibility to other chronic adverse health outcomes following early life stage exposure.

   <u>Next level priority</u>:
   a. Draft, externally peer review, complete and issue guidelines for the assessment of epidemiology studies.
   b. Draft, externally peer review, complete and issue guidelines for the assessment of immunotoxicity.
   c. Update, externally peer review, complete and issue guidelines for the assessment of neurotoxicity, developmental and reproductive toxicity, in that order.

   These five products should reflect inclusion of the general principles articulated in the three *Science and Decisions*-identified policy papers and the General Principles of

Toxicity Assessment guideline, tailored to fit the specific set of endpoints associated with each guideline

7. My thoughts on Process- What to do and in what order for the High Priority items
   a. Development of Action Plans in consultation with the SAB and other key players (June 5 did not count as this consultation)
   b. Discussions in public forums
   c. Drafting of the three issue papers, one integrated toxicity guideline, updating of the exposure guideline and Supplemental Guidance, with engaged external peer involvement

   Overlapping

   d. Internal review and sign-off
   e. Executive Branch (EB) reviews (guidelines only?)
   f. Revision in response to EB reviews
   g. Referral to NAS
   h. Revision in response to NAS review
   i. SAB peer review and public comment
   j. Revision and response-to-comments
   k. Internal review and sign-off
   l. Another round of Executive Branch (EB) review?
   m. Revision and response-to-comments?
   n. Internal review and sign-off?
   o. Publication of final issue papers, guidelines and Supplemental Guidance

8. The Enclosure-My vision of a single, integrated guideline-The Beginning of a revision to the 2005 cancer guidelines

As I mentioned above, I have drafted a revision of the Introduction to the 2005 cancer guidelines. I did this to illustrate that it would be relatively easy to modify existing text to accommodate an expansion to coverage of general systemic toxicity writ large. There remains much of value in the 2005 guidelines which should not be discarded. Nonetheless, it is timely to consider an update. I've already noted some new categories of information that warrant inclusion and others that warrant a revisit and updating.

How could these guidelines be modified to transform them into guidance for assessing both non-cancer and cancer endpoints in an integrated manner? First step—change the name of the guideline. That's a bit more of a challenge than I initially anticipated. On the cover page, I have included two possibilities: 1) Guidelines for the Assessment of Systemic Toxicity and 2) General Principles for the Assessment of Toxicity.

The first choice has appeal because it is inclusive; it covers all toxicities to all organs following uptake and distribution to those organs. What it doesn't appear to do is include toxicities that may arise at the point of entry, depending upon the exposure route. And, we want

to assess the potential for toxicity on/in the skin, in the respiratory tract and the GI tract as well as systemically. We know of examples in which an agent has caused some kind of toxicity, including carcinogenicity, in/on the skin, in the respiratory system or the GI tract following direct contact at those sites.

It would be tempting to replace "systemic" with "chronic," but that might be short-sighted. While it may be that IRIS assessments focus only on development of reference values for effects occurring after long-term exposures, many other program-specific assessments also do the same for acute and short-term exposure scenarios. The same general toxicity assessment principles should be applied no matter the exposure setting into which the hazard assessment will be integrated. Thus, the second possible title is "General Principles for the Assessment of Toxicity." It's broad enough to cover everything---non-cance+cancer, any duration of exposure.

Second step---Chapter placement and headings. Chapters 2-5 should retain their order and headings, but their cancer-specific content should be moved into a single new Chapter 6 devoted to carcinogenicity. While cancer should, for valid scientific and assessment reasons, now be thought of as just another chronic endpoint of concern/adverse outcome, there will remain, for the time being, some variations in the kinds of information collected and assessed that warrant special attention. Chapters 2-5 should be revised/expanded to address assessment principles applicable to toxicity in its broadest sense. The new Chapter 6 can be split up into Sections that match the old chapter headings of Hazard Assessment, Dose Response Assessment, Exposure Assessment, Risk Characterization to promote consistency. These sections should be shorter than they are now, because only the cancer-specific information will be placed here. The rest will remain in the original chapters 2-5 and be modified/expanded to reflect the principles shared by, and applicable to, all endpoints of toxicity covered by this guideline.

Appendix A-Major Default Factors. This Appendix should be modified/updated to reflect the findings/policy determinations made in the new *Science and Decisions*-prompted issue paper on Default Factors.

I hope that I have provided some useful points to consider as the agency proceeds with these tasks. There are some significant challenges here. If there is any I can do to help, do not hesitate to contact me. I have no conflicts of interest, financial or otherwise, and I do want the agency to do the right thing and succeed in these difficult times.

Sincerely,

Penelope A. Fenner-Crisp, PhD, DABT
North Garden, VA

Enclosure

~~EPA/630/P-03/001F~~
~~March 2005~~

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Guidelines for the Assessment of Systemic Toxicity

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or

General Principles for the Assessment of Toxicity

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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1. INTRODUCTION

1.1. PURPOSE AND SCOPE OF THE GUIDELINES

These systemic/general toxicity guidelines revise and replace the U.S. Environmental Protection Agency's (EPA's, or the Agency's) *Guidelines for Carcinogen Risk Assessment*, published in 70 FR 17765, April 7, 2005 (U.S. EPA, 2005a), *Guidelines for Carcinogen Risk Assessment,* published in 51 FR 33992, September 24, 1986 (U.S. EPA, 1986a), ~~-~~and the 1999 interim final guidelines (U.S. EPA, 1999a; see U.S. EPA 2001b) They provide EPA staff with guidance for developing and using risk assessments. They also provide basic information to the public about the Agency's risk assessment methods.

These ~~cancer~~ systemic/general toxicity guidelines are used, as appropriate, in conjunction with other risk assessment guidelines, such as the *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, ~~1986b~~) and the *Guidelines for Exposure Assessment* (U.S. EPA, ~~1992a~~). Consideration of other Agency guidance documents is also important ~~in~~ when assessing ~~cancer~~ systemic toxicity risks where procedures for evaluating specific target organ effects have been developed (e.g., assessment of thyroid follicular cell tumors, U.S. EPA, 1998a). All of EPA's guidelines should be consulted when conducting a risk assessment in order to ensure that information from studies on systemic toxicity, including carcinogenesis and other health effects of concern are considered together in the overall characterization of risk. This is particularly true in the case in which a precursor effect for ~~a tumor~~ one adverse outcome is also a precursor or endpoint of other health effects or when there is a concern for a particular susceptible life-stage for which the Agency has developed guidance, for example, *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a). The developmental guidelines discuss hazards to children that may result from exposures during preconception and prenatal or postnatal development to sexual maturity. Similar guidelines exist for reproductive toxicant risk assessments (U.S. EPA, 1996a) and for neurotoxicity risk assessment (U.S. EPA, 1998b). The overall characterization of risk is conducted within the context of broader policies and guidance such as Executive Order 13045, "Protection of Children From Environmental Health Risks and Safety Risks"(Executive Order 13045, 1997) which is the primary directive to federal agencies and departments to identify and assess environmental health risks and safety risks that may

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disproportionately affect children.

The systemic/general toxicity guidelines expand the scope of the kinds of adverse outcomes/endpoints of concern that may result from short-term, intermediate or long-term exposure to environmental agents of interest. They examine endpoints of concern in addition to carcinogenicity to determine the role(s) that systemic toxicity plays in their etiology, as one expects to find that they may share one or more common features. They encourage both consistency in the procedures that support scientific components of Agency decision making and flexibility to allow incorporation of innovations and contemporaneous scientific concepts. In balancing these goals, the Agency relies on established scientific peer review processes (U.S. EPA, 2000a; OMB 2004). ~~The cancer~~ These guidelines incorporate basic principles and science policies based on evaluation of ~~the~~ currently available information. The Agency intends to revise these ~~cancer~~ guidelines when substantial changes are necessary. As more information about systemic/general toxicity including carcinogenesis develops, the need may arise to make appropriate changes in risk assessment guidance. In the interim, the Agency intends to issue special reports, after appropriate peer review, to supplement and update guidance on single topics (e.g., U.S. EPA, 1991b). One such guidance document, *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* ("Supplemental Guidance"), was developed in conjunction with ~~these~~ the 2005 - cancer guidelines (U.S. EPA., 2005b). Because both the methodology and the data in the Supplemental Guidance (see Section 1.3.6) are expected to evolve more rapidly than the issues addressed in the~~se~~ 2005 cancer guidelines, the two were developed as separate documents. The Supplemental Guidance, however, as well as any other relevant (including subsequent) guidance documents, should be considered along with these ~~cancer~~ guidelines as risk assessments ~~for carcinogens~~ are generated. The use of supplemental guidance, such as the Supplemental Guidance for Assessing Cancer Susceptibility from Early-life Exposure to Carcinogens, has the advantage of allowing the Supplemental Guidance to be modified relatively quickly as more data become available. Thus, the consideration of new, peer-reviewed scientific understanding and data in an assessment can always be consistent with the purposes of these ~~cancer~~ guidelines. With the issuance of these new systemic/general toxicity guidelines, an update/expansion of the Supplemental Guidance is warranted.

These ~~cancer~~ systemic/general toxicity guidelines are intended as guidance only. They do not establish any substantive "rules" under the Administrative Procedure Act or any other law and have no binding effect on EPA or any regulated entity, but instead represent a non-binding statement of policy.

EPA believes that ~~the cancer~~ these guidelines represent a sound and up-to-date approach to ~~cancer~~ risk assessment, and the ~~cancer~~ guidelines enhance the application of the best available science in EPA's risk assessments. However, some EPA ~~cancer~~ risk assessments may be conducted differently than envisioned in ~~the cancer~~ these guidelines for many reasons, including (but not limited to) new information, new scientific understanding, or new science policy judgment becoming available after these guidelines were issued. The science of risk assessment continues to develop rapidly, and specific components of the guidelines may become outdated or may otherwise require modification in individual settings. Use of ~~the cancer~~ these guidelines in future risk assessments will be based on decisions by EPA that the approaches are suitable and appropriate in the context of those particular risk assessments. These judgments will be tested through peer review, and risk assessments will be modified to use different approaches, if appropriate.

1.2. ORGANIZATION AND APPLICATION OF THE ~~CANCER~~ SYSTEMIC/GENERAL TOXICITY GUIDELINES

1.2.1. Organization

Publications by the Office of Science and Technology (OSTP, 1985) and the National Research Council (NRC) (NRC, 1983, 1994) provide information and general principles about risk assessment. Risk assessment uses available scientific information on the properties of an agent[1] and its effects in biological systems to provide an evaluation of the potential for harm as a consequence of environmental exposure. The 1983 and 1994 NRC documents organize risk assessment information into four areas: hazard identification, dose-response assessment, exposure assessment, and risk characterization. This structure appears in these ~~cancer~~ guidelines, with additional emphasis placed on characterization of evidence and conclusions in each area of the assessment. In particular, ~~the cancer~~ these guidelines adopt the approach of the NRC's 1994 report in adding a dimension of characterization to the hazard identification step: an evaluation

of the conditions under which its expression is anticipated. Risk assessment questions addressed in these ~~cancer~~ guidelines are as follows.

- For hazard—Can the identified agent present a systemic toxicity ~~carcinogenic~~ hazard to humans (including carcinogenicity) and, if so, under what circumstances?

- For dose response—At what levels of exposure might systemic effects occur?

- For exposure—What are the conditions of human exposure?

- For risk—What is the character of the risk? How well do data support conclusions about the nature and extent of the risk from various exposures?

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[1] The term "agent" refers generally to any chemical substance, mixture, or physical or biological entity being assessed, unless otherwise noted (See Section 1.2.2 for a note on radiation.).

The risk characterization process first summarizes findings on hazard, dose response, and exposure characterizations and then develops an integrative analysis of the whole risk case. It ends in the writing of a technical risk characterization. Other documents, such as summaries for the risk managers and the public, reflecting the key points of the risk characterization are usually written. A summary for managers is a presentation for those who may or may not be familiar with the scientific details of ~~cancer~~ hazard and risk assessment. It also provides information for other interested readers. The initial steps in the risk characterization process are to make building blocks in the form of characterizations of the assessments of hazard, dose response, and exposure. The individual assessments and characterizations are then integrated to arrive at risk estimates for exposure scenarios of interest. As part of the characterization process, explicit evaluations are made of the hazard and risk potential for susceptible lifestages, including children (U.S. EPA, 1995, 2000b).

[The 1994 NRC document also explicitly called attention to the role of the risk assessment process in identifying scientific uncertainties that, if addressed, could serve to reduce their uncertainty in future iterations of the risk assessment. NRC recommended that when the Agency "reports estimates of risk to decisions-makers and the public, it should present not only point estimates of risk, but also the sources and magnitudes of uncertainty associated with these estimates" (p. 15). Thus, the identified uncertainties serve as a feedback loop to the research community and decision makers, specifying areas and types of information that would be particularly useful.]

Commented [X4]: This section should also describe the observations and recommendation made on uncertainty in the 2009 NRC report *Science and Decisions* and what, if anything, gets trapped in the final Transparency Rule.

There are several reasons for individually characterizing the hazard, dose response, and exposure assessments. One is that they are often done by different people than those who do the integrative analyses. The second is that there is very often a lapse of time between the conduct of hazard and dose-response analyses and the conduct of exposure assessment and integrative

analysis. Thus, it is important to capture characterizations of assessments as the assessments are done to avoid the need to go back and reconstruct them. Finally, frequently a single hazard assessment is used by several programs for several different exposure scenarios. There may be one or several documents involved. "Integrative analysis" is a generic term; and many documents that have other titles may contain integrative analyses. In the following sections, the elements of these characterizations are discussed.

1.2.2. Application

~~The cancer~~ These systemic/general toxicity guidelines apply within the framework of policies provided by applicable EPA statutes and do not alter such policies.

- ~~The cancer~~ These guidelines cover the assessment of relevant available data. They do not imply that one kind of data or another is prerequisite for regulatory action concerning any agent. It is important that, when evaluating and considering the use of any data, EPA analysts incorporate the basic standards of quality, as defined by the EPA Information Quality Guidelines (U.S. EPA, 2002a see Appendix B) and other Agency guidance on data quality such as the EPA Quality Manual for Environmental Programs (U.S. EPA, 2000e), as well as *OMB Guidelines for Ensuring and Maximizing the Quality, Utility, and Integrity of Information Disseminated by Federal Agencies* (OMB, 2002). It is very important that all analyses consider the basic standards of quality, including objectivity, utility, and integrity. A summary of the factors and considerations generally used by the Agency when evaluating and considering the use of scientific and technical information is contained in EPA's *A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information* (U.S. EPA, 2003).

Commented [X5]: Here is where you would add reference to any additional general OMB or Agency guidance that has been issued since 2005.

- Risk management applies directives in statutes, which may require consideration of potential risk or solely hazard or exposure potential, along with social, economic, technical, and other factors in decision making. Risk assessments may be used to support

decisions, but in order to maintain their integrity as decision-making tools, they ~~are~~ should not be influenced by consideration of the social or economic consequences of regulatory action.

[The assessment of risk from radiation sources is informed by the continuing examination of human data by the National Academy of Sciences/NRC in its series of numbered reports: "Biological Effects of Ionizing Radiation." Although some of the general principles of these ~~cancer~~ guidelines may also apply to radiation risk assessments, some of the details of their risk assessment procedures may not, as they are most focused on other kinds of agents. Therefore, these ~~cancer~~ guidelines are not intended to provide the primary source of, or guidance for, the Agency's evaluation of the carcinogenic risks of radiation.\

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Not every EPA assessment has the same scope or depth, a factor recognized by the National Academy of Sciences (NRC, 1996). For example, EPA's Information Quality Guidelines (U.S. EPA, 2002a, see Appendix B) discuss influential information that "will have or does have a clear and substantial impact ... on important public policies or private sector decisions ... that should adhere to a rigorous standard of quality." It is often difficult to know *a priori* how the results of a risk assessment are likely to be used by the Agency. Some risk assessments may be used by Agency economists and policy analysts, and the necessary information for such analyses, as discussed in detail later in this document, should be included when practicable (U.S. EPA, 2002a). On the other hand, Agency staff often conduct screening-level assessments for priority setting or separate assessments of hazard or exposure for ranking purposes or to decide whether to invest resources in collecting data for a full assessment. Moreover, a given assessment of hazard and dose response may be used with more than one exposure assessment that may be conducted separately and at different times as the need arises in studying environmental problems related to various exposure media. ~~The cancer~~These guidelines apply to these various situations in appropriate detail, given the scope and depth of the particular assessment. For example, a screening assessment may be based almost entirely on structure- activity relationships (SARs), other *in silico* , *in chemico* tools or short-term assay results and default options, when other data are not readily available.

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When more data and resources are readily available, assessments can use a critical analysis of all

of the available data as the starting point of the risk assessment. Under these conditions, default options would only be used to address uncertainties or the absence of critical data. Default options are inferences based on general scientific knowledge of the phenomena in question and are also matters of policy concerning the appropriate way to bridge uncertainties that concern potential risk to human health.

These ~~cancer~~ guidelines do not suggest that all of the kinds of data covered here will need to be available or used for either assessment or decision making. The level of detail of an assessment is a matter of Agency management discretion regarding applicable decision-making needs. The Agency generally presumes that key ~~cancer~~ toxicity information (e.g., assessments contained in the Agency's Integrated risk Information System) is "influential information" as defined by the EPA Information Quality Guidelines and "highly influential" as defined by OMB's Information Quality Bulletin for Peer Review (OMB 2004).

1.3. KEY FEATURES OF THE ~~CANCER~~ SYETEMIC TOXICITY GUIDELINES

1.3.1. Definitions

1.3.1.1. Systemic toxicity

One definition: "toxic effects caused as a result of absorption (by the oral, inhalation or dermal route) and distribution of a substance that affects multiple organs or the whole body rather than a specific (local) area, at a site distant from the point of entry. Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs, but usually cause significant toxicity to one or two organs. These are referred to as the target organs of toxicity for that agent."

1.3.1.2 Acute, subchronic and chronic toxicity

1.3.1.3 Adverse

1.3.1.4 Severity

1.3.1.5 Endpoint of Concern, Adverse Outcome, Critical Effect

1.3.1.6 Examples of major organ toxicities

Liver: cirrhosis and nonalcoholic fatty liver disease including NASH, cancer

Kidney: failure, cysts, stones, cancer

Pulmonary: asthma, COPD (emphysema and chronic bronchitis), fibrosis, cancer

Cardiovascular: hypertension, angina, arrhythmias, coronary artery

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disease (CAD), cardiomyopathy, heart failure

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1.3.2. Implementation of Systematic Review Procedures for Inforamtion Selection and Application

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[This new section should summarize the generic approach that will be implemented for information identification, gathering, selection, determination of quality, interpretation and integration]

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1.3.3. The Roles of Credible -Available Information and Default Options in the Assessment Process ~~as the Starting Point for Evaluation~~

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[This section requires revision/updating to reflect the Agency's responses to and changes in practice (or not) based upon the observations and recommendations made in the 2009 NRC report *Science and Decisions*… with regard to the analysis of uncertainty and the application of default options. Signficant editing is warranted. Some external voices have advocated for multiple, extensive uncertainety analyses to be conducted in all or most cases. The Agency must determine and articlaute its position on the value of expending resources on such an endeavor.]

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As ~~an~~ ~~increasing~~ the understanding of ~~carcinogenesis~~ systemic/general toxicity ~~is becoming available~~ continues to increase, these ~~cancer~~ guidelines adopt a view of default options that is consistent with EPA's mission to protect human health while adhering to the tenets of sound science. Rather than viewing default options as the starting point from which departures may be justified by new scientific information, these ~~cancer~~ guidelines view a critical analysis of all of the valid available information that is relevant to assessing ~~the carcinogenic~~ systemic/general toxicity risk as the starting point from which a default option may be invoked if needed to address uncertainty or in the absence of critical information. Preference is given to using information that has been peer reviewed, e.g., reported in peer-reviewed scientific journals or judged by individuals or panels with relevant technical expertise in a formal peer review setting, consistent with guidance presented in EPA's Peer Review Handbook (U.S. EPA, 2015). . The primary goal of EPA actions is protection of human health; accordingly, as an Agency policy, risk assessment procedures, including default options that are used in the absence of scientific data to the contrary, should be health protective (U.S. EPA, 1999b).

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[No substantive editing of this section follows (just some minor nitpicking such as replacing "cancer" with "systemic/general toxicity" or "these" and a few other minotr exceptions) because of need for major revisions, consistent with current Agency policy, some of which is yet to be formulated and affirmed.]

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Use of health protective risk assessment procedures as described in these ~~cancer~~ guidelines means that estimates, while uncertain, are more likely to overstate than understate hazard and/or risk. NRC (1994) reaffirmed the use of default options as "a reasonable way to cope with uncertainty about the choice of appropriate models or theory" (p. 104). NRC saw the need to treat uncertainty in a predictable way that is "scientifically defensible, consistent with the agency's statutory mission, and responsive to the needs of decision-makers" (p. 86). The extent of health protection provided to the public ultimately depends upon what risk managers decide is the appropriate course of regulatory action. When risk assessments are performed using only one set of procedures, it may be difficult for risk managers to determine how much health protectiveness is built into a particular hazard determination or risk characterization. When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision.

Encouraging risk assessors to be receptive to new scientific information, NRC discussed the need for departures from default options when a "sufficient showing" is made. It called on EPA to articulate clearly its criteria for a departure so that decisions to depart from default options would be "scientifically credible and receive public acceptance" (p. 91). It was concerned that *ad hoc* departures would undercut the scientific credibility of a risk assessment. NRC envisioned that principles for choosing and departing from default options would balance several objectives, including "protecting the public health, ensuring scientific validity, minimizing serious errors in estimating risks, maximizing incentives for research, creating an orderly and predictable process, and fostering openness and trustworthiness" (p. 81).

Appendices N-1 and N-2 of NRC (1994) discussed two competing standards for choosing default options articulated by members of the committee. One suggested approach would evaluate a departure in terms of whether "it is scientifically plausible" and whether it "tends to

protect public health in the face of scientific uncertainty" (p. 601). An alternative approach "emphasizes scientific plausibility with regard to the use of alternative models" (p. 631). Reaching no consensus on a single approach, NRC recognized that developing criteria for departures is an EPA policy matter.

The basis for invoking a default option depends on the circumstances. Generally, if a gap in basic understanding exists or if agent-specific information is missing, a default option may be used. If agent-specific information is present but critical analysis reveals inadequacies, a default option may also be used. If critical analysis of agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager. In this case, the default model not only fits the data, but also serves as a benchmark for comparison with other analyses. This case also highlights the importance of extensive experimentation to support a conclusion about mode of action, including addressing the issue of whether alternative modes of action are also plausible. Section 2.4 provides a framework for critical analysis of mode of action information to address the extent to which the available information supports the hypothesized mode of action, whether alternative modes of action are also plausible, and whether there is confidence that the same inferences can be extended to populations and lifestages that are not represented among the experimental data.

Generally, ~~cancer~~ risk decisions strive to be "scientifically defensible, consistent with the agency's statutory mission, and responsive to the needs of decision-makers" (NRC, 1994). Scientific defensibility would be evaluated through use of EPA's Science Advisory Board, EPA's Office of Pesticide Programs' FIFRA Scientific Advisory Panel, EPA's Office of Pollution Prevention and Toxics' Science Advisory Committee on Chemicals or other independent expert peer review panels to determine whether a consensus among scientific experts exists. Consistency with the Agency's statutory mission would consider whether the risk assessment overall supports EPA's mission to protect human health and safeguard the natural environment. Responsiveness to the needs of decision makers would take into account pragmatic considerations such as the nature of the decision; the required depth of analysis; the utility, time, and cost of generating new scientific data; and the time, personnel, and resources allotted to the risk assessment.

With a multitude of types of data, analyses, and risk assessments, as well as the diversity of needs of decision makers, it is neither possible nor desirable to specify step-by-step criteria for decisions to invoke a default option in every instance.. A discussion of major default options appears in the Appendix. Screening-level assessments may more readily use default parameters, even worst-case assumptions, that would not be appropriate in a full-scale assessment. On the other hand, significant risk management decisions will often benefit from a more comprehensive assessment, including alternative risk models having significant biological support. To the extent practicable, such probabilistic? assessments should provide central estimates of potential risks in conjunction with lower and upper bounds (e.g., confidence limits) and a clear statement of the uncertainty associated with these estimates.

[This may be the point at which the *Science and Decisions* recommendations regarding harmonization of dose response assessment could be introduced. Alternatively, it could be inserted later in the Dose-Response Assessment section.]

In the absence of sufficient data or understanding to develop of a robust, biologically based model, an appropriate policy choice is to have a single preferred curve-fitting model for each type of data set. Many different curve-fitting models have been developed, and those that fit the observed data reasonably well may lead to several-fold differences in estimated risk at the lower end of the observed range. In addition, goodness-of-fit to the experimental observations is not by itself an effective means of discriminating among models that adequately fit the data (OSTP, 1985). To provide some measure of consistency across different carcinogen systemic/general toxicity assessments, EPA uses a standard curve-fitting procedure for tumor incidence data. Assessments that include a different approach should provide an adequate justification and compare their results with those from the standard procedure. Application of models to data should be conducted in an open and transparent manner.

1.3.4. Mode of Action and Adverse Outcome Pathways

[This section takes on greater importance than it had in the 2005 guidelines, since so much more is known about MOA and how to conduct a good MOA analysis. Also, this section should introduce the concept of Adverse Outcome Pathways, and describe how MOA and AOPs

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interface with one another. Significant revision is warranted.

The use of mode of action[2] in the assessment of ~~potential carcinogens~~ syustemic/general toxicity is a main focus of these ~~cancer~~ guidelines. This area of emphasis arose because of the significant scientific advances that have developed concerning the causes of ~~cancer~~ the induction of an adverse effect. Elucidation of a mode of action for a particular ~~cancer~~ response in animals or humans is a data-rich determination.

Significant information should be developed to ensure that a scientifically justifiable mode of action underlies the process leading to ~~cancer~~ an endpoint of concern/adverse outcome at a given site. In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health- protective, default positions regarding the interpretation of toxicologic and epidemiologic data.

[2] The term *"mode of action"* is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A *"key event"* is an empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element. Mode of action is contrasted with "*mechanism of action*," which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action. The toxicokinetic processes that lead to formation or distribution of the active agent to the target tissue are considered in estimating dose but are not part of the mode of action as the term is used here. The active agent(s) should be determined before beginning the mode of action analysis. [There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.]

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animal ~~tumor~~ findings are judged to be relevant to humans,[and cancer risks are assumed to conform with low dose linearity.]

Understanding of mode of action can be a key to identifying processes that may cause chemical exposures to differentially affect a particular population segment or life stage. Some modes of action are anticipated to be mutagenic and are assessed with a linear approach. This is the mode of action of radiation and several other agents that are known carcinogens. Other modes of action may be modeled with either linear or nonlinear[3] approaches after a rigorous analysis of available data under the guidance provided in the framework for mode of action analysis (see Section 2.4.3).

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Commented [X9]: These two statements need to be revisited, given recent challenges to their validity. EPA needs to review recent literature asserting non0linearity for some effects with mutagenic components. This includes dose responsews for radation as well.

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~~1.3.1.~~1.3.5. Weight of Evidence Narrative

The ~~cancer~~ systemic/general toxicity guidelines emphasize the importance of weighing all of the evidence in reaching conclusions about the human ~~carcinogenic~~ hazard potential of agents. This is accomplished in a single integrative step after assessing all of the individual lines of evidence, ~~which is in contrast to the step-wise approach in the 1986 cancer guidelines~~in a manner consistent with the systematic review principles.. Evidence considered includes ~~tumor~~ the toxicity findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other ~~carcinogenic~~ agents; and studies addressing potential ~~carcinogenic~~ toxicity processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiologic studies are generally preferred for characterizing human ~~cancer~~ hazard and risk. However, all of the information discussed above could provide valuable insights into the possible mode(s) of action and likelihood of human ~~cancer~~ hazard and risk. ~~The cancer~~ These guidelines recognize the growing sophistication of research methods, particularly in their ability to reveal the modes of action of ~~carcinogenic~~ agents at cellular and subcellular levels as well as toxicokinetic processes.

[3]The term "*nonlinear*" is used here in a narrower sense than its usual meaning in the field of mathematical modeling. In these cancer guidelines, the term "*nonlinear*" refers to threshold models (which show no response over a range of low doses that include zero) and some nonthreshold models (e.g., a quadractic model, which shows some response at all doses above zero). In these ~~cancer~~ guidelines, a nonlinear model is one whose slope is zero at (and perhaps above) a dose of zero. A *low-dose-linear* model is one whose slope is greater than zero at a dose of zero. A

low-dose-linear model approximates a straight line only at very low doses; at higher doses near the observed data, a low-dose-linear model can display curvature. The term "*low-dose-linear*" is often abbreviated "linear," although a low-dose-linear model is not linear at all doses. Use of nonlinear approaches does not imply a biological threshold dose below which the response is zero. Estimating thresholds can be problematic; for example, a response that is not statistically significant can be consistent with a small risk that falls below an experiment's power of detection.

Weighing of the evidence includes addressing not only the likelihood of human ~~carcinogenic~~ effects of the agent but also the conditions under which such effects may be expressed, to the extent that these are revealed in the toxicological and other biologically important features of the agent.

The weight of evidence narrative to characterize hazard summarizes the results of the hazard assessment and provides a conclusion with regard to human ~~carcinogenic~~ hazard potential. The narrative explains the kinds of evidence available and how they fit together in drawing conclusions, and it points out significant issues/strengths/limitations of the data and conclusions. Because the narrative also summarizes the mode of action information, it sets the stage for the discussion of the rationale underlying a recommended approach to dose-response assessment.

{In order to provide some measure of clarity and consistency in an otherwise free-form, narrative characterization, standard descriptors are used as part of the hazard narrative to express the conclusion regarding the weight of evidence for carcinogenic hazard potential. There are five recommended standard hazard descriptors: "*Carcinogenic to Humans*," "*Likely to Be Carcinogenic to Humans*," "*Suggestive Evidence of Carcinogenic Potential*," "*Inadequate Information to Assess Carcinogenic Potential*," and "*Not Likely to Be Carcinogenic to Humans*." Each standard descriptor may be applicable to a wide variety of data sets and weights of evidence and is presented only in the context of a weight of evidence narrative. Furthermore, as described in Section 2.5 of these cancer guidelines, more than one conclusion may be reached for an agent.]

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~~1.3.2.~~1.3.6. Dose-response Assessment

[Perhaps, this is the place where the information on the development and application of modelling tools for the probabilistic determination of risk for non-linear effects (non-cancer and cancer alike) should be introduced and discussed]'

Dose-response assessment evaluates potential risks to humans at particular exposure levels. The approach to dose-response assessment for a particular agent is based on the conclusion reached as to its potential mode(s) of action for each ~~tumor~~ type of toxicity observed. Because an agent may induce multiple ~~tumor types~~ toxicities in multiple tissues, the dose-response assessment includes an analysis of all ~~tumor~~ types in all affected tissues, followed by

an overall synthesis that includes a characterization of the risk estimates across ~~tumor~~ types and target tissues, the strength of the mode of action information of each ~~tumor~~ type, and the anticipated relevance of each ~~tumor~~ type to humans, including susceptible populations and life stages (e.g., childhood).

Dose-response assessment for each ~~tumor~~ type of toxicity is performed in two steps: assessment of observed data to derive a point of departure (POD),[4] followed by extrapolation to lower exposures to the extent that is necessary. Data from epidemiologic studies, of sufficient quality, are generally preferred for estimating risks. When animal studies are the basis of the analysis, the estimation of a human-equivalent dose should utilize toxicokinetic data to inform cross- species dose scaling if appropriate and if adequate data are available. Otherwise, default procedures should be applied. For oral doses, based on current science, an appropriate default option is to scale daily applied doses experienced for a lifetime in proportion to body weight raised to the 3/4 power (U.S. EPA, 1992b). For inhalation doses, based on current science, an appropriate default methodology estimates respiratory deposition of particles and gases and estimates internal doses of gases with different absorption characteristics. When toxicokinetic modeling (see Section 3.1.2) is used without toxicodynamic modeling (see Section 3.2.2), the dose-response assessment develops and supports an approach for addressing toxicodynamic equivalence, perhaps by retaining some of the cross-species scaling factor (see Section 3.1.3). Guidance is also provided for adjustment of dose from adults to children (see Section 4.3.1).

Response data on precursor effects of the agent ~~on carcinogenic processes~~ on the endpoint of concern are analyzed ~~(nontumor data)~~ in addition to data on ~~tumor incidence~~ the identified adverse outcome. If appropriate, the analyses of data on ~~tumor~~ endpoint incidence and on precursor effects may be used in combination. To the extent the relationship between precursor effects and ~~tumor~~ endpoint incidence are known, precursor data may be used to estimate a dose-response function below the observable ~~tumor~~ endpoint data. Study of the dose-response function for effects believed to be part of the ~~carcinogenic~~ toxicity process influenced by the agent may also assist in evaluating the relationship of exposure and response in the range of observation and at exposure levels below the range of observation.

[4] A "*point of departure*" (POD) marks the beginning of extrapolation to lower doses. The POD is an estimated dose (usually expressed in human-equivalent terms) near the lower end of the observed range, without significant extrapolation to lower doses.

The first step of dose-response assessment is evaluation within the range of observation. Approaches to analysis of the range of observation of epidemiologic studies are determined by the type of study and how dose and response are measured in the study. In the absence of adequate human data for dose-response analysis, animal data are generally used. If there are sufficient quantitative data and adequate understanding of the ~~carcinogenic~~ toxicity process, a biologically based model may be developed to relate dose and response data on an agent-specific basis. Otherwise, as a default procedure, a standard model can be used to curve-fit the data.

The POD for extrapolating the relationship to environmental exposure levels of interest, when the latter are outside the range of observed data, is generally the lower 95% confidence limit on the lowest dose level that can be supported for modeling by the data. SAB (1997) suggested that, "it may be appropriate to emphasize lower statistical bounds in screening analyses and in activities designed to develop an appropriate human exposure value, since such activities require accounting for various types of uncertainties and a lower bound on the central estimate is a scientifically-based approach accounting for the uncertainty in the true value of the ED_{10} [or central estimate]." However, the consensus of the SAB (1997) was that, "both point estimates and statistical bounds can be useful in different circumstances, and recommended that the Agency routinely calculate and present the point estimate of the ED_{10} [or central estimate] and the corresponding upper and lower 95% statistical bounds." For example, it may be appropriate to emphasize the central estimate in activities that involve formal uncertainty analysis that are required by OMB Circular A-4 (OMB, 2003) as well as ranking agents as to their ~~carcinogenic~~ hazard. Thus, risk assessors should calculate, to the extent practicable, and present the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) to inform decision makers.

The second step of dose-response assessment is extrapolation to lower dose levels, if needed. This extrapolation is based on extension of a biologically based model if supported by substantial data (see Section 3.3.2). Otherwise, default approaches can be applied that are consistent with current understanding of mode(s) of action of the agent, including approaches that assume linearity or nonlinearity of the dose-response relationship, or both. A default approach for linearity extends a straight line from the POD to zero dose/zero response (see

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Section 3.3.3). The linear approach is used when: (1) there is an absence of sufficient information on modes of action or (2) the mode of action information indicates that the dose-response curve at low dose is or is expected to be linear. Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration (see Section 3.3.4).

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~~1.3.3.~~1.3.7. Susceptible Populations and Lifestages

An important use of mode of action information is to identify susceptible populations and life stages. It is rare to have epidemiologic studies or animal bioassays conducted in susceptible individuals. This information need can be filled by identifying the key events of the mode of action and then identifying risk factors, such as differences due to genetic polymorphisms, disease, altered organ function, lifestyle, and life stage, that can augment these key events. To do this, the information about the key precursor events is reviewed to identify particular populations or life stages that can be particularly susceptible to their occurrence (see Section 2.4.3.4). Any information suggesting quantitative differences between populations or life stages is flagged for consideration in the dose-response assessment (see Section 3.5 and U.S. EPA 2002b).

~~1.3.4.~~1.3.8. Evaluating Risks from Childhood Exposures

NRC (1994) recommended that "EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults." Executive Order 13045 (1997) requires that "each Federal Agency shall make it a high priority to identify and assess environmental health and safety risks that may disproportionately affect children, and shall ensure that their policies, programs, and standards address disproportionate risks that result from environmental health risks or safety risks." In assessing risks to children, EPA considers both effects manifest during childhood and early-life exposures that can contribute to effects at any time later in life.

These ~~cancer~~ guidelines view childhood as a sequence of life stages rather than viewing children as a subpopulation, the distinction being that a subpopulation refers to a portion of the population, whereas a life stage is inclusive of the entire population. Exposures

that are of concern extend from conception through adolescence and also include pre-conception exposures of both parents. These guidelines use the term "childhood" in this more inclusive sense.

Rarely are there studies that directly evaluate risks following early-life exposure. Epidemiologic studies of early-life exposure to environmental agents are seldom available. Standard animal bioassays generally begin dosing after the animals are several weeks old, when many organ systems are mature. This could lead to an understatement of risk, because an accepted concept in the science of carcinogenesis is that young animals are usually more susceptible to the carcinogenic activity of a chemical than are mature animals (McConnell, 1992).

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At this time, there is some evidence of higher cancer risks following early-life exposure. For radiation carcinogenesis, data indicate that risks for several forms of cancer are highest following childhood exposure (NRC, 1990; Miller, 1995; U.S. EPA, 1999c). These human results are supported by the few animal bioassays that include perinatal (prenatal or early postnatal) exposure. Perinatal exposure to some agents can induce higher incidences of the tumors seen in standard bioassays; some examples include vinyl chloride (Maltoni et al., 1981), diethylnitrosamine (Peto et al., 1984), benzidine, DDT, dieldrin, and safrole (Vesselinovitch et al., 1979). Moreover, perinatal exposure to some agents, including vinyl chloride (Maltoni et al., 1981) and saccharin (Cohen, 1995; Whysner and Williams, 1996), can induce different tumors that are not seen in standard bioassays. Surveys comparing perinatal carcinogenesis bioassays with standard bioassays for a limited number of chemicals (McConnell, 1992; U.S. EPA, 1996b) have concluded that

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- the same tumor sites are usually observed following either perinatal or adult exposure, and

- perinatal exposure in conjunction with adult exposure usually increases the incidence of tumors or reduces the latent period before tumors are observed.

The risk attributable to early-life exposure often appears modest compared with the risk from lifetime exposure, but it can be about 10-fold higher than the risk from an exposure of similar duration occurring later in life (Ginsberg, 2003). Further research is warranted to investigate the extent to which these findings apply to specific agents, chemical classes, and modes of action or in general.

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These empirical results are consistent with current understanding of the biological processes involved in carcinogenesis, which leads to a reasonable expectation that children can be more susceptible to many carcinogenic agents (Anderson et al., 2000; Birnbaum and Fenton, 2003; Ginsberg, 2003; Miller et al., 2002; Scheuplein et al., 2002). Some aspects potentially leading to childhood susceptibility are listed below.

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- Differences in the capacity to metabolize and clear chemicals can result in larger or smaller internal doses of the active agent(s).
- More frequent cell division during development can result in enhanced expression of mutations due to the reduced time available for repair of DNA lesions (Slikker et al., 2004).
- Some embryonic cells, such as brain cells, lack key DNA repair enzymes.
- More frequent cell division during development can result in clonal expansion of cells with mutations from prior unrepaired DNA damage (Slikker et al., 2004).
- Some components of the immune system are not fully functional during development (Holladay and Smialowicz, 2000; Holsapple et al., 2003).
- Hormonal systems operate at different levels during different lifestages.

- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life (Anderson et al., 2000; Birnbaum and Fenton, 2003; Fenton and Davis, 2002).

To evaluate risks from early-life exposure, these guidelines emphasize the role of toxicokinetic information to estimate levels of the active agent in children and toxicodynamic information to identify whether any key events of the mode of action are of increased concern early in life. Developmental toxicity studies can provide information on critical periods of exposure for particular targets of toxicity.

An approach to assessing risks from early-life exposure is presented in Figure 1-1. In the hazard assessment, when there are mode of action data, the assessment considers whether these data have special relevance during childhood, considering the various aspects of development listed above. Examples of such data include toxicokinetics that predict a sufficiently large internal dose in children or a mode of action where a key precursor event is more likely to occur during childhood. There is no recommended default to settle the question of whether ~~tumors~~ toxicity arising through a mode of action ~~are~~ is relevant during childhood; and adequate understanding the mode of action implies that there are sufficient data (on either the specific agent or the general mode of action) to form a confident conclusion about relevance during childhood (see Section 2.4.3.4).

In the dose-response assessment, the potential for susceptibility during childhood warrants explicit consideration in each assessment. These ~~cancer~~ guidelines encourage developing separate risk estimates for children according to a tiered approach that considers what pertinent data are available (see Section 3.5). Childhood may be a susceptible period; moreover, exposures during childhood generally are not equivalent to exposures at other times and may be treated differently from exposures occurring later in life (see Section 3.5). In addition, adjustment of unit risk estimates may be warranted when used to estimate risks from childhood exposure (see Section 4.4).

At this time, several limitations preclude a full assessment of children's risk. There are no generally used testing protocols to identify potential environmental causes of cancers that are

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unique to children, including several forms of childhood cancer and cancers that develop from parental exposures, and cases where developmental exposure may alter susceptibility to carcinogen exposure in the adult (Birnbaum and Fenton, 2003). Dose-response assessment is limited by an inability to observe how developmental exposure can modify incidence and latency and an inability to estimate the ultimate tumor response resulting from induced susceptibility to later carcinogen exposures.

To partially address the limitations identified above, EPA developed in conjunction with these cancer guidelines, *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* ("Supplemental Guidance"). The Supplemental Guidance addresses a number of issues pertaining to cancer risks associated with early-life exposures generally, but provides specific guidance on procedures for adjusting cancer potency estimates only for carcinogens acting through a mutagenic mode of action. This Supplemental Guidance recommends, for such chemicals when no chemical-specific data exist, a default approach using estimates from chronic studies (i.e., cancer slope factors) with appropriate modifications to address the potential for differential risk of early-lifestage exposure.

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The Agency considered both the advantages and disadvantages to extending the recommended, age dependent adjustment factors for carcinogenic potency to carcinogenic agents for which the mode of action remains unknown. EPA decided to recommend these factors only for carcinogens acting through a mutagenic mode of action based on a combination of analysis of available data and long-standing science policy positions which govern the Agency's overall approach to carcinogen risk assessment. In general, the Agency prefers to rely on analyses of data, rather than general defaults. When data are available for a sensitive lifestage, they would be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. In the case of nonmutagenic carcinogens, when the mode of action is unknown, the data were judged by EPA 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, a linear low-dose extrapolation methodology (without further adjustment) is recommended. It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach

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provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life sensitivity or when the mode of action is not mutagenic.

The Agency expects to produce additional supplemental guidance for other modes of action and other toxicities, as data from new research and toxicity testing indicate it is warranted. EPA intends to focus its research, and work collaboratively with its federal partners, to improve understanding of the implications of early life exposure to ~~carcinogens~~ toxic agents. Development of guidance for estrogenic agents and chemicals acting through other processes resulting in endocrine disruption ~~and subsequent carcinogenesis~~, for example, might be a reasonable priority in light of the human experience with diethylstilbesterol and the existing early life animal studies. It is worth noting that each mode of action for endocrine disruption will probably require separate analysis.

As the Agency examines additional ~~carcinogenic~~ agents and toxicities, the age groupings may differ from those recommended for assessing cancer risks from early-life exposure to chemicals with a mutagenic mode of action. Puberty and its associated biological changes, for example, involve many biological processes that could lead to changes in sensitivity to the effects of some carcinogens, depending on their mode of action. The Agency is interested in identifying life stages that may be particularly sensitive or refractory for all endpoints of concern, including carcinogenesis, and believes that the mode of action framework described in these ~~cancer~~ guidelines is an appropriate mechanism for elucidating these lifestages. For each additional mode of action evaluated, the various age groupings determined to be at differential risk may differ from those proposed in the Supplemental Guidance. For example, 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. If more data become available regarding carcinogens with a mutagenic mode of action and for other toxicities, consideration may be given to further refinement of these age groups.

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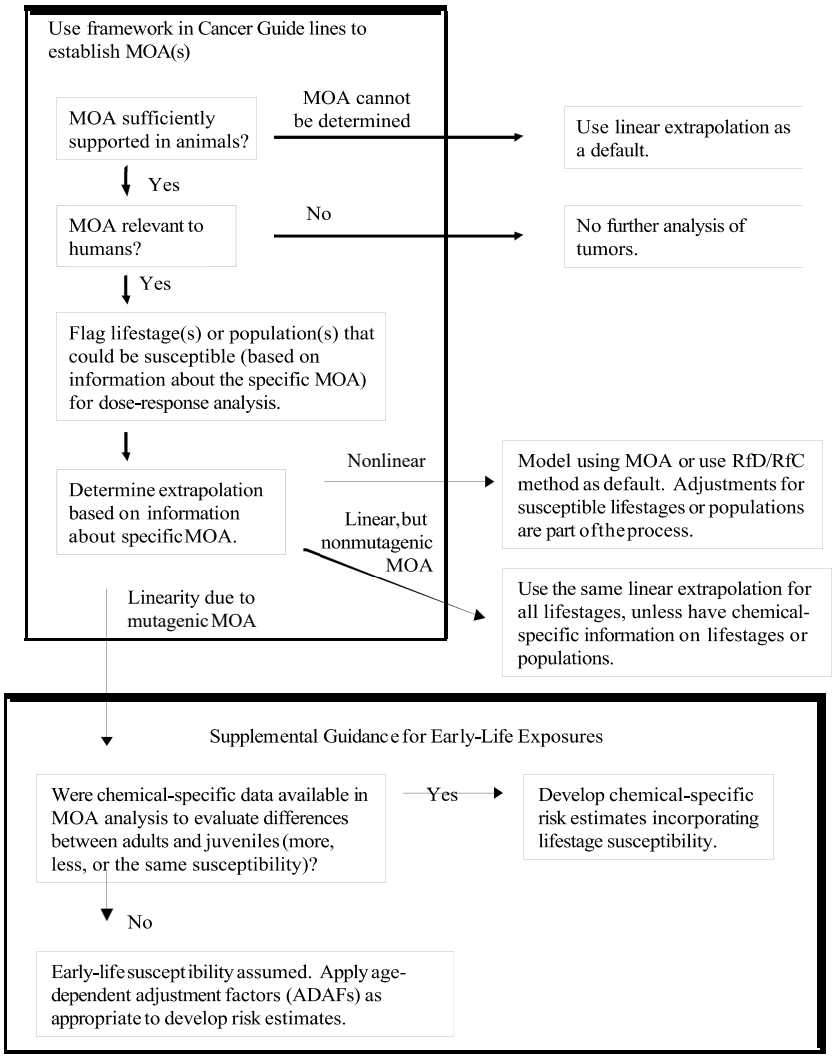
~~1.3.5.~~1.3.9. Emphasis on Characterization

~~The cancer~~These guidelines emphasize the importance of a clear and useful characterization narrative that summarizes the analyses of hazard, dose-response, and exposure assessment.

These characterizations summarize the assessments to explain the extent and weight of evidence, major points of interpretation and rationale for their selection, strengths and weaknesses of the evidence and the analysis, and discuss alternative conclusions and uncertainties that deserve serious consideration (U.S. EPA, 2000b). They serve as starting materials for the overall risk characterization process that completes the risk assessment.

Figure 1-1. Flow chart for early-life risk assessment using mode of action framework. [Needs revision to accommodate all toxicities



NEW and MODIFIED REFERENCES

U.S. EPA. (U.S. Environmental Protection Agency) (2005a) Guidelines for Cancer Risk Assessment. Risk Assessment Forum, Washington, DC. Available from: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

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