

**March 3, 2003**

## **EPA's Draft Final Guidelines for Carcinogen Risk Assessment**

### **Questions and Answers**

The following questions and answers provide general information and a summary of key points in EPA's Draft Final "Guidelines for Carcinogen Risk Assessment" (cancer guidelines or draft final *Guidelines*). The draft final *Guidelines* are available for public review and comment.

## **SECTION I. GENERAL**

### **1. What are EPA's "Guidelines for Carcinogen Risk Assessment"?**

EPA's cancer guidelines set forth recommended principles and procedures to guide EPA scientists in assessing the cancer risks from chemicals or other agents in the environment. They also inform EPA decision makers and the public about these procedures. The cancer guidelines are used with other risk assessment guidelines that the Agency has developed, such as guidelines for exposure assessment, in developing an overall characterization of risk to human health. Collectively, all the risk assessment guidelines are intended to promote consistency and technical quality in EPA risk assessments while leaving EPA free to utilize yet-to-be-developed information and procedures.

### **2. What is the history of the cancer guidelines?**

EPA published final cancer guidelines in 1986. As with other risk assessment guidelines, EPA has been working to revise the cancer guidelines to reflect advances in scientific understanding as well as experience in using them. Milestones in the revisions to the guidelines include the following:

- In 1996, EPA issued proposed revisions to the cancer guidelines. The proposed guidelines have been subject to extensive public comment and scientific peer review, including three reviews by EPA's Science Advisory Board (SAB).
- In 1997, the SAB completed comments from its first review of the proposed guidelines.
- In January 1999, the SAB reviewed key sections of the proposed guidelines that had been revised to address prior SAB and public comments.
- In July 1999, the SAB began a third review that focused on revisions of the guidelines addressing risks to children. EPA received the report from this review in 2000.
- In November 2001, EPA published in the *Federal Register* a Notice of Intent to finalize the cancer guidelines, and provided an opportunity to provide additional information and comment. At the same time EPA identified the draft 1999 guidelines as interim EPA guidance pending issuance of final revised guidelines.

Since 2001, EPA has been revising the cancer guidelines in light of the SAB reviews, public comments, and recent scientific workshops EPA has hosted on children's cancer risks.

**3. What are the major principles and issues EPA has considered in its revisions to the *cancer guidelines*?**

EPA's guiding principle for revisions to the cancer guidelines is that EPA cancer risk assessments be both public health protective and scientifically sound. By public health protective, EPA means that risk assessments should consider a range of susceptibilities among the human population and, in the absence of complete knowledge, employ assumptions that will reflect the risks to susceptible subpopulations and lifestages. By scientifically sound, EPA means that risk assessments should reflect current and evolving scientific practice and describe risks in a clear, consistent, and reasonable manner. In particular, the revisions to the cancer guidelines are intended to promote greater use of the increasing scientific understanding of the mechanisms that underlie the carcinogenic process.

In applying these principles to the revision of the Guidelines, four interrelated issues have been the focus of EPA deliberation and are each discussed further below. These issues are: 1) use of default assumptions, 2) consideration of differences in susceptibilities to carcinogens among people, 3) use of mode-of-action information in the risk assessment process, and 4) weighing the evidence to characterize human carcinogen potential.

**4. What is the approach used in the draft final *Guidelines* for “default options”?**

Default options are approaches that EPA can apply in risk assessments when critical information about the effects of a substance on human health is unavailable, limited, or of insufficient quality. For example, if no information is available on the effects of a chemical on humans, a common default option is that adverse effects observed in animals due to chemical exposure have the potential to occur in humans as well. In the draft final *Guidelines*, EPA has more clearly articulated its policy on when it is appropriate to invoke various default assumptions, based on comments from the SAB and others. EPA's recommended approach is to begin with a critical analysis of available information, and then invoke default options if needed to address uncertainty or the absence of critical information. Use of default options is intended to be health protective while also being scientifically defensible. Specific examples of default options are discussed in additional questions below.

**5. How do the draft final *Guidelines* account for the variability in susceptibility to carcinogens among the human population?**

EPA's draft final *Guidelines* explicitly recognize that variability exists among people in their susceptibility to carcinogens. Individuals in some *subpopulations* may experience increased susceptibility to carcinogens throughout their lives, such as people who have an inherited predisposition to certain cancer types or reduced capacity to repair genetic damage. Also, during certain *lifestages* the entire population may experience heightened susceptibility to carcinogens. In particular, EPA notes that childhood may be a lifestage of greater susceptibility for a number of reasons, such as that related to the rapid growth and development that occurs prenatally and after birth. Some of the aspects of the draft final *Guidelines* that account for potentially susceptible subpopulations and lifestages include the following:

- The draft final *Guidelines* recommend estimating the internal dose of chemicals experienced by children to predict the toxic effects from such doses.

- The draft final *Guidelines* encourage and provide guidance for developing separate risk estimates for children when pertinent data are available.
- The draft final *Guidelines* encourage consideration of differences in diet and behavior patterns among subpopulations and lifestages that may increase exposure to potential carcinogens.
- In the absence of information on susceptibility, the default options that may be invoked result in a risk assessment that is expected to be public health protective for the general population. These include the default option that there is no threshold below which cancer risks are not present (i.e., linear extrapolation to low doses).

**6. How do the draft final *Guidelines* incorporate our knowledge of how a chemical causes cancer into the risk assessment process?**

Cancer refers to a group of diseases involving abnormal, malignant tissue growth. Research has revealed that the development of cancer involves a complex series of steps and that carcinogens may operate in a number of different ways. Ultimately, cancer results from a series of defects in genes controlling cell growth, division, and differentiation. Genetic defects leading to cancer may occur because a chemical (or other carcinogenic agent) damages DNA directly. Alternatively, an agent may have indirect effects that increase the likelihood, or accelerate the onset, of cancer without directly interacting with DNA. For example, an agent might interfere with DNA repair mechanisms, thereby increasing the likelihood that cell division will give rise to cells with damaged DNA. An agent might also increase rates of cell division, thus increasing the potential for genetic errors to be introduced as cells replicate their DNA in preparation for division.

The draft final *Guidelines* emphasize the value of understanding the biological changes that the chemical can cause and how these changes might lead to the development of cancer. They also discuss methods to evaluate and use such information, including information about a chemical's postulated *mode of action*, or the series of steps and processes that lead to cancer formation. Mode-of-action data, when available and of sufficient quality, may be useful in drawing conclusions about the potency of a chemical, its potential effects at low doses, whether findings in animals are relevant to humans, and which populations or lifestages may be particularly susceptible. In the absence of mode-of-action information, default options are available to address uncertainty.

**7. How does EPA characterize a chemical's potential for human carcinogenicity under the draft final *Guidelines*?**

The draft final *Guidelines* - recommend that an agent's human carcinogenic potential is described in a *weight-of-evidence narrative*. The narrative summarizes the full range of available evidence and describes any conditions associated with conclusions about an agent's hazard potential. For example, the narrative may explain that a chemical appears to be carcinogenic by some routes of exposure but not others (e.g., by inhalation but not ingestion). Similarly, a hazard may be attributed to exposures during sensitive lifestages of development but not at other times. The narrative also summarizes uncertainties and key default options that have been invoked.

To provide additional clarity and consistency in weight-of-evidence narratives, the draft final *Guidelines* suggest a set of standard *weight-of-evidence descriptors* to accompany the narratives. The draft final *Guidelines* emphasize that risk managers should consider the full range of information in the narratives and not focus exclusively on the descriptors. As in the case of the narratives, descriptors may apply only to certain routes of exposure, dose ranges, and durations of exposure. The five descriptors are:

- *Carcinogenic to Humans*
- *Likely to Be Carcinogenic to Humans*
- *Suggestive Evidence of Carcinogenic Potential*
- *Inadequate Information to Assess Carcinogenic Potential*
- *Not Likely to Be Carcinogenic to Humans*

This proposed approach differs from that used in EPA's 1986 cancer guidelines in its recommendation that carcinogenic potential be discussed in a narrative and in the particular descriptors employed.

#### **8. What is the status of the *Guidelines* revision process?**

On March 3, 2003, EPA issued a *Federal Register* notice announcing the public availability of the draft final *Guidelines* and the start of a 60-day public comment period. EPA issued final cancer risk assessment guidelines in 1986. This is the third time (1996, 1999, 2003) since 1986 that the Agency has disseminated revised cancer guidelines for public review and comment.

This current draft final *Guidelines* reflects the extensive public comment received on earlier drafts, as well as multiple rounds of expert scientific review by EPA's SAB. Therefore, EPA is requesting that public comments focus on issues that are substantively revised or newly addressed since the publication of the 1999 revised draft cancer guidelines. These issues include:

- the nature and use of default options;
- definition and application of hazard descriptors;
- identification of carcinogenic modes of action (in particular consideration of relevancy for children, for instance, the potential for differential lifestage susceptibility); and
- the default low-dose extrapolation approach for non-linear carcinogens.

Because the draft final *Guidelines* recommend consideration of possible sensitive subpopulations and lifestages (such as childhood), EPA is also releasing for public comment a draft supplemental guidance, entitled, "Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens," describing possible approaches that could be used to assess risks resulting from early life exposure to environmental contaminants (Supplemental Guidance is discussed in more detail in Section II). As with the draft final *Guidelines* themselves, the draft Supplemental Guidance is intended as a non-binding statement of policy. Risk assessments may employ different methods for a variety of reasons, including new information, methods, or scientific judgment.

After receipt of public comments and comments from other agency scientists, EPA will address those comments in its final revised *Guidelines for Carcinogen Risk Assessment*. After public comments

and comments from other agency scientists are received for the draft Supplemental Guidance, it will be reviewed by EPA's Science Advisory Board.

**9. What is new in the draft final *Guidelines* when compared to the July 1999 Draft Revised Guidelines?**

The draft final *Guidelines* reflect public comments received in response to the November 2001 *Federal Register* notice as well as EPA's experience in applying the July 1999 Draft Revised Guidelines. Specific changes include:

- Clarification that assessments should begin with a critical analysis of the available data and that default options are invoked on an as needed basis when there is too much uncertainty or critical data are missing.
- Refinement of the guidance addressing the weight of evidence narrative and use of the associated descriptors. The draft final *Guidelines* emphasize the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This is accomplished in a single step after assessing all of the individual lines of evidence. Examples of the kinds of results that can lead to the use of a particular descriptor are included in the draft final *Guidelines*.
- 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 lifestage. The framework for analysis of mode of action data has been revised to explicitly recommend consideration of any populations or lifestages that can be particularly sensitive in light of the hypothesized mode of action.
- In keeping with the goal of harmonizing cancer and noncancer risk assessment practices, the draft final *Guidelines* recommend the use of EPA's approach to setting noncancer reference values (oral reference doses [RfD] and inhalation reference concentrations [RfC]); See **SECTION III: IRIS** in situations where the carcinogenic mode of action is determined to be nonlinear.
- In the absence of agent-specific data, there is some general information to indicate that childhood can be a susceptible lifestage for exposure to some carcinogens; this warrants explicit consideration in each assessment. The potential for susceptibility from early-life exposure is expected to vary among specific agents and chemical classes. Draft *Supplemental Guidance* has been developed as a possible approach for addressing early lifestage susceptibility in situations of less than lifetime exposure.

**10. Why is EPA revising its 1986 final cancer guidelines?**

EPA began revising the 1986 cancer guidelines in light of significant advances in our understanding of the processes of carcinogenesis and the modes of actions of disease at the cellular level. Revising the cancer guidelines is in keeping with EPA's original intent when it issued the first set of final risk assessment guidelines in 1986. The risk assessment guidelines were meant to be dynamic, flexible documents that would evolve to reflect the current state of the science and risk assessment practices.

**11. What version of the EPA's cancer guidelines is currently being used in EPA human health risk assessment activities?**

On December 20, 2001, Linda J. Fisher, EPA Deputy Administrator, issued a memorandum regarding steps for finalizing the *Guidelines for Carcinogen Risk Assessment*. A key part of that memorandum designated the July 1999 Draft Revised Guidelines for Carcinogen Risk Assessment as interim guidance to EPA risk assessors in preparing cancer risk assessments, superseding all previous versions of the Guidelines. The Deputy Administrator's December 2001 memorandum identifying the July 1999 Draft Revised Guidelines for Carcinogenic Risk Assessment as EPA's operative guidance remains in effect until these draft guidelines are finalized.

## **SECTION II. DRAFT SUPPLEMENTAL GUIDANCE ON EARLY-LIFE EXPOSURE**

**12. What is the draft *Supplemental Guidance*? Why is it necessary?**

The draft *Supplemental Guidance* entitled, "Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens," describes possible approaches that EPA could use in assessing risks from early-life exposure to potential carcinogens. A final decision by EPA on the use of this or any alternative approach will reflect public comments and recommendations from the SAB's review of this document.

The draft *Supplemental Guidance* is part of EPA's response to the recommendation of the National Research Council (1994) that "EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults." For several potential carcinogens, there is some evidence of higher cancer risks following early-life exposure. Accordingly, the potential for higher risks from early-life exposure warrants explicit consideration in each assessment.

**13. What does the draft *Supplemental Guidance* contain? How will it be used?**

The draft *Supplemental Guidance* describes the possible approaches that EPA could use in assessing cancer risks following early-life exposures. The draft *Supplemental Guidance* also summarizes the results of the cancer studies that investigated early-life exposure, along with EPA's analysis of those studies.

When final, EPA's headquarters and regional offices will refer to the draft *Supplemental Guidance* when assessing exposure scenarios that include exposure during childhood. Several examples in the

draft *Supplemental Guidance* illustrate how early-life exposures can be assessed.

**14. Why has the draft *Supplemental Guidance* been issued separately rather than included in the draft final *Guidelines*?**

The draft *Supplemental Guidance* appears as a separate document because EPA intends to update this guidance as new research results increase understanding about the effects of early-life exposures. A separate guidance focused on early-life exposures will be more amenable to being updated in a timely manner. Frequent updates will likely be needed to help risk assessors reflect new scientific understanding in their risk assessments, particularly for chemical classes (for example, endocrine-disrupting chemicals) where new information is rapidly emerging. Also, the draft *Supplemental Guidance* will undergo review by EPA's Science Advisory Board (SAB) following the comment period, whereas the draft final *Guidelines* will not.

**15. Does the draft *Supplemental Guidance* address all potential carcinogens?**

The draft *Supplemental Guidance* recommends consideration of all studies on the effects of early-life exposures. For the common case where there are no early-life studies on a potential carcinogen, the draft final *Guidelines* suggest consideration of the carcinogen's mode of action. The draft *Supplemental Guidance* addresses carcinogens with a mutagenic mode of action in detail because currently most early-life studies are for carcinogens with a mutagenic mode of action. As new research leads to more conclusive evidence, EPA intends to update this guidance to address other modes of action. Furthermore, risk assessments should reflect emerging science even if the draft *Supplemental Guidance* has not been updated to reflect it.

**16. Do the draft final *Guidelines* or the draft *Supplemental Guidance* recommend development of specific data on children's risk?**

Both the draft final *Guidelines* and the draft *Supplemental Guidance* discuss general ways of proceeding when there are no early-life studies on a potential carcinogen. Nonetheless, there may be cases where these general approaches may not adequately reflect differential risks to children. As in all cases, specific data on the effects of early-life exposures is valuable in improving the assessment.

**17. How and when will the draft *Supplemental Guidance* be finalized?**

Soon after the close of the public comment period, the scientific data and rationale that support the *Supplemental Guidance* will be peer-reviewed by EPA's Science Advisory Board (SAB) in a public meeting. Details of the SAB's review will be available in the *Federal Register* and through the internet at [www.epa.gov/sab](http://www.epa.gov/sab). The SAB will provide written advice to EPA. After EPA considers that advice and makes appropriate changes, it will publish final *Supplemental Guidance*.

## SECTION III. IRIS AND THE CANCER GUIDELINES

### 18. What is IRIS ([www.epa.gov/IRIS](http://www.epa.gov/IRIS))?

IRIS, the Integrated Risk Information System, is an EPA data base containing EPA's consensus position on the potential adverse human health effects that may result from chronic (or lifetime) exposure to specified chemical substances found in the environment. IRIS currently provides health effects information on over 500 specific chemical substances. IRIS contains chemical-specific summaries of qualitative and quantitative health information in support of the first two steps of the risk assessment process, i.e., hazard identification and dose-response evaluation. IRIS information includes the reference dose for noncancer health effects resulting from oral exposure, the reference concentration for noncancer health effects resulting from inhalation exposure, and the cancer assessment for both oral and inhalation exposure. Combined with specific situational exposure assessment information, the summary health hazard information in IRIS may be used as a source in evaluating potential public health risks from chemical substances found in the environment.

### 19. How is the information in IRIS developed?

EPA's current process for developing IRIS information consists of: (1) an annual *Federal Register* announcement of EPA's IRIS agenda and call for scientific information from the public on the selected chemical substances, (2) a search of the current literature, (3) development of health assessments and draft IRIS summaries, (4) peer review within EPA, (5) peer review outside EPA, (6) EPA consensus review and management approval, (7) preparation of final IRIS summaries and supporting documents, and (8) entry of summaries and supporting documents into the IRIS data base.

### 20. What is the relationship between EPA's IRIS and the cancer guidelines?

Currently an IRIS file may include descriptive and quantitative human health risk information on both noncancer and cancer effects. EPA's cancer guidelines provide guidance to Agency risk assessors in developing the cancer risk assessment portion of the IRIS file. Since the mid-1980s, when IRIS was developed, the cancer summary files were based first on the 1984 proposed cancer guidelines and then on the 1986 final guidelines. While the 1986 guidelines have guided the development of the IRIS cancer risk information for many years, cancer risk assessments have been informed by other considerations such as evolving science, the facts of the particular case, and scientific judgment.

On November 29, 2001, EPA issued a *Federal Register* notice announcing: 1) an opportunity to provide additional information and comment on the July 1999 Draft Revised Guidelines for Carcinogen Risk Assessment, 2) the availability of the draft revised *Guidelines*, and 3) the adoption of the 1999 draft revised *Guidelines* as interim guidance. The *Federal Register* notice states that until final cancer guidelines are issued, the July 1999 Draft Revised Guidelines will serve as EPA's interim guidance to EPA risk assessors preparing new cancer risk assessments or revising old assessments. This notice is posted on the IRIS website. In order to provide consistency for IRIS users during the transition period from the use of the 1986 guidelines to the July 1999 Draft Revised Guidelines, new or revised cancer risk information on IRIS has been developed using both the 1986 final and July 1999 Draft Revised Guidelines. Recently a decision was made to discontinue the application of the 1986 guidelines and exclusively apply the July 1999 Draft Revised Guidelines. When the draft final *Guidelines* are finalized,



the IRIS program will begin using the final version in new or revised assessments.

## SECTION IV. ROLE OF CANCER GUIDELINES IN EPA DECISIONS

### 21. How will EPA use the final cancer guidelines?

EPA scientists will refer to the cancer guidelines as a framework for evaluating information on the carcinogenic potential of various chemicals. The resulting cancer risk assessments will then be considered in making regulatory decisions under various statutes.

### 22. How will EPA manage the transition to the new cancer guidelines? What are the implications of the new cancer guidelines for EPA's regulatory programs?

Since the publication of the 1986 guidelines, EPA's cancer assessment methodology has continued to evolve as new science and data have become available. EPA is currently using the July 1999 Draft Revised Guidelines as its operative guidance for conducting cancer risk assessments. Once the draft final *Guidelines* and draft *Supplemental Guidance* are finalized, cancer risk assessments will incorporate EPA's up-to-date guidance. Given the large number of substances for which cancer assessments have been conducted (for example those in the IRIS database), EPA will have to address a range of issues associated with making the transition to the new cancer guidelines. These include the circumstances under which EPA will prepare a reassessment under the new cancer guidelines. This and other implementation issues will be evaluated and addressed by EPA over the next several months, as well as when the draft final *Guidelines* are finalized.

## SECTION V. CANCER RESEARCH ACTIVITIES

### 23. What is EPA doing to reduce both its reliance on default options and the uncertainties that, to date, have been inherent in human health risk assessment?

EPA began revising the 1986 cancer guidelines in light of significant advances in our understanding of the processes of carcinogenesis and the modes of action of disease at the cellular level. Some of the work in these areas that led to these advances is the result of EPA research efforts over the past several years. Because our understanding of carcinogenicity, causation of disease, and effects on susceptible lifestages and populations are constantly and quickly evolving, EPA will continue research work in this area, as well as collaborate with other research organizations to produce research that ultimately serves to reduce both uncertainties in cancer risk assessments and reduce EPA's reliance on default options.

### 24. What is the cancer research area that EPA intends to focus on next?

To enhance EPA's understanding of age-related cancer susceptibility, EPA's Office of Research and Development (ORD) is expanding its research through an initiative that focuses on appropriate measures of dose, response characteristics, and exposure variables that may be affected by age. This research will be done via a combination of studies in EPA laboratories, ORD's Science to Achieve Results (STAR) grants program, and collaborations with other federal agencies.