

Key Features of the Draft Final Guidelines

EPA's guiding principle for revisions to the Guidelines is that Agency 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 Guidelines are intended to make greater use of the increasing scientific understanding of the mechanisms that underlie the carcinogenic process. EPA has also designed the Guidelines to be flexible enough to accommodate future scientific advances in science and risk assessment practices. EPA is particularly interested in public comments on the following areas that have been the focus of the Agency's attention in preparing today's Draft Final Guidelines:

(1) Use of default options. The Draft Final Guidelines clarify the role of default options (default assumptions) in the Agency's risk assessments. Rather than view default options as the starting point from which departures may be justified by new scientific information, the Guidelines emphasize that assessments begin with a critical analysis of the available data, and defaults would be invoked as needed when too much uncertainty exists or critical data are missing. In keeping with EPA's mission and the advice of numerous scientific advisory panels, the Agency's default options are constructed to be public health protective. The decision to invoke a default option would be determined on a case-by-case basis. Given the multitude of different types of risk assessments and potential default options, it is neither possible nor desirable to specify step-by-step criteria for decisions to invoke a default option. The Guidelines, however, identify general principles for invoking default options (as originally articulated by the National Research Council): Such decisions should be scientifically defensible, consistent with EPA's statutory mission, and responsive to the needs of decision-makers.

(2) Hazard descriptors. The Draft Final Guidelines continue to emphasize the importance of weighing all of the

evidence in reaching conclusions about the human carcinogenic potential of agents, with hazard descriptors used to facilitate clarity in describing carcinogenicity conclusions. Several of the hazard descriptors presented in the Draft Final Guidelines have been modified from previous drafts of the Guidelines, and the discussion of when they would apply has been strengthened. Descriptors may apply only to certain routes of exposure, dose ranges, and durations of exposure. The following five descriptors are discussed in the Guidelines: 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.

(3) Mode of action. The use of mode of action in the assessment of potential carcinogens is the main thrust of the Draft Final Guidelines. This area of emphasis arose because of scientific breakthroughs concerning the causes of cancer induction. As discussed in the Draft Final Guidelines, an important use of mode-of-action information is to identify susceptible populations and lifestages. Because it is rare to have epidemiologic studies or animal bioassays conducted in susceptible individuals, identifying the key events of the mode of action and the risk factors that can augment these key events can be critical in understanding risks to susceptible populations.

(4) Extrapolation to lower doses. An important issue to address in most EPA risk assessments is the estimation of risks at levels of environmental exposure (doses) that are lower than the levels at which adverse effects (responses) have been observed. Historically, EPA used an approach known as linear extrapolation for all potential carcinogens, which involves modeling risk in an approximately straight line extrapolation from a particular dose level (the point of departure) to the zero dose/zero response point. This approach differs from that used by EPA in assessing risks in the case of most noncancer effects, which typically involve nonlinear extrapolation. The Draft Final Guidelines generally reaffirm the use of a linear extrapolation approach for carcinogens when mode of action information is limited or indicates a linear dose-response relationship, such as in the case of mutagenic agents. The Draft Final Guidelines also discuss potential uses of nonlinear extrapolation when consistent with understanding of the mode of action, and recommend the development of a reference dose (or

reference concentration) as established by EPA for effects other than cancer. This default approach is in keeping with the Agency's goal of harmonizing the assessment of risks from agents, whether carcinogens or not, that operate by a nonlinear mode of action.

(5) Susceptible populations and lifestages. The Draft Final Guidelines explicitly recognize that variability exists among people in their susceptibility to carcinogens and emphasize that this variability should be considered in risk assessment. Some subpopulations may experience increased susceptibility to carcinogens throughout their lives, such as people who have inherited a 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, the Guidelines note that childhood may be a lifestage of greater susceptibility for a number of reasons, such as susceptibility related to the rapid growth and development that occurs prenatally and after birth.

Supplemental Guidance on Early-Life Exposure

The discussion of consideration of childhood risks in the Draft Final Guidelines has been augmented by the development of the separate draft document entitled "Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens." This document contains an analysis of studies and a possible approach for how quantitative scientific data could inform risk assessments when exposure to carcinogens occurring during childhood is considered. The draft document will be reviewed by EPA's Science Advisory Board following the public comment period. After SAB recommendations and public comments are incorporated into the document, the supplemental guidance will be issued separately from the final Cancer Guidelines so that it may be more easily updated in a timely manner given the expected rapid evolution of scientific understanding about the effects of early-life exposures.

Request for Comment

EPA requests comments on today's Draft Final Guidelines and will consider all comments in completing final Guidelines. Comments on earlier drafts of the revised Guidelines already submitted to EPA need not be resubmitted. Public comments are also invited on the draft supplemental guidance on early-life exposure to carcinogens. Following the public