

technical quality in risk assessments and to ensure that the risk assessment process was maintained as a scientific effort separate from risk management. EPA responded to this recommendation by publishing a set of risk assessment guidelines in 1986, including Guidelines for Carcinogen Risk Assessment (51 FR 33992, September 24, 1986). These Guidelines set forth principles and procedures to guide EPA scientists in assessing the cancer risks from chemicals or other agents in the environment and to inform the public about these procedures. EPA continues to revise its risk assessment guidelines and to develop new guidelines as experience and scientific understanding evolve. Revisions to the Guidelines for Carcinogen Risk Assessment are intended to make greater use of the increasing scientific understanding of the mechanisms that underlie the carcinogenic process. As part of that process, the Agency published Proposed Guidelines for Carcinogen Risk Assessment in 1996 (61 FR 17960, April 23, 1996).

The draft revisions to the Guidelines have been subject to extensive public comment and scientific peer review, including three reviews by EPA's Science Advisory Board (SAB). In 2001, EPA published a notice (66 FR 59593, November 29, 2001) providing an additional opportunity for public comment on a 1999 draft of the Guidelines. Comments were invited on experience gained in applying previous draft revised Guidelines and on issues raised in previous comments by the SAB and the public. EPA has also considered the recommendations of the NRC (Science and Judgment in Risk Assessment, 1994) in revising the Guidelines. EPA's approach to the recommendations is reflected in the Guidelines themselves. Draft EPA responses to the NRC recommendations were presented in the preamble to the 1996 draft of these revised Guidelines (61 FR 18003, April 23, 1996). EPA anticipates issuing final responses to the NRC recommendations when it issues final Guidelines.

#### **Role of Risk Assessment Guidelines at EPA**

The final Guidelines will be guidance only. They will not establish any substantive "rules" under the Administrative Procedure Act or any other law and will have no binding effect on EPA or any regulated entity, but instead will represent a non-binding statement of policy. EPA believes that the Draft Final Guidelines represent a sound and up-to-date approach to cancer risk assessment, and the final

Guidelines will enhance the application of the best available science in EPA's risk assessments. However, EPA cancer risk assessments may be conducted differently than envisioned in the final Guidelines for many reasons, including (but not limited to) new information, new scientific understanding, or new science policy judgment. The science of risk assessment continues to develop rapidly, and specific components of the final Guidelines may become outdated or may otherwise require modification in individual settings. Use of the final Guidelines in future risk assessments will be based on decisions by EPA that approaches from the final Guidelines 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.

Even though the final Guidelines will not be binding rules, EPA is issuing them in a manner consistent with the procedures in the Administrative Procedure Act that are generally applicable to rulemaking, including providing an opportunity for public comment. EPA will consider and respond to all significant public comments as it prepares the final Guidelines, and will send a copy of the final Guidelines to Congress. EPA certifies that the Draft Final Guidelines will not have a significant impact on a substantial number of small entities because the Guidelines are for the benefit of EPA and impose no requirements or costs on small entities.

#### **Issues Identified in 2001 Public Comments**

A range of views were expressed in the comments submitted to EPA in response to the 2001 notice (66 FR 59593, November 29, 2001) (see the Addresses section for information on viewing these comments). Comments on four issues of interest identified by EPA in the 2001 notice included the following:

(1) Default assumptions. Default assumptions are options that EPA can apply in risk assessments when 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 assumption is that adverse effects observed in animals due to chemical exposure have the potential to occur in humans as well.) Commenters differed on whether default assumptions should be (a) built into each risk assessment unless sufficient evidence is available to

depart from them, or (b) invoked only when determined to be necessary given the data available in a particular risk assessment. Commenters also differed on whether EPA's proposed default assumptions should be more protective of public health versus already being excessively conservative.

(2) Hazard descriptors. Under the 1999 draft Guidelines, one or more standard descriptors (e.g., "Likely to be Carcinogenic to Humans") were used to express conclusions about the weight of evidence for human carcinogenic potential. Many commenters generally agreed with EPA's approach for the descriptors, but most recommended that EPA refine the phrases and descriptions to enhance their clarity. Two commenters preferred that descriptors not be used at all. A number of commenters advised the Agency to use the "Carcinogenic to Humans" descriptor only when epidemiological evidence of carcinogenicity is conclusive.

(3) Mode of action. EPA's draft 1999 Guidelines emphasized the value of understanding a chemical's "mode of action," which refers to the series of steps and processes that lead to cancer formation. Many commenters disagreed with EPA's proposal that confirmatory data be available or a "cogent biological rationale" be developed before a mode of action identified in adults (or mature animals) could be considered applicable to children as well. On the other hand, several commenters stated that EPA should require much stronger evidence before concluding that a particular mode of action operates in both adults and children.

(4) Margin of exposure analysis. A margin of exposure analysis is an approach described in the 1999 draft Guidelines to inform decision-makers about cancer risks at relatively low levels of exposure. The 1999 draft Guidelines suggested its use in the case of certain carcinogens where mode of action data support a nonlinear approach for describing the relationship between dose and response for the chemical. Several commenters expressed concern that the margin of exposure analysis as described by EPA would not be sufficiently protective of public health. Other commenters stated that it inappropriately mixed risk assessment and risk management considerations and was problematic because it removed quantitative estimation of cancer risk from risk assessment.