United States Environmental Protection Agency

March 3, 2003
FACT SHEET: EPA's GUIDELINES FOR CARCINOGEN RISK ASSESSMENT – What are they?, What do they say?, and How are they used?

INTRODUCTION: On September 24, 1986, the U.S. Environmental Protection Agency (EPA or Agency) issued final risk assessment guidelines relating to five areas: carcinogenicity, mutagenicity, chemical mixtures, developmental toxicants, and estimating exposures (http://www.epa.gov/ncea/raf/). The guidelines were developed to promote high technical quality and Agency-wide consistency in the process of assessing the potential health effects impacts of human exposure to environmental contaminants. The guidelines were also meant to inform decision-makers and the public on the processes that EPA would use to assess these possible health effects, thereby providing the transparency needed to permit the public to actively engage in a dialogue with the EPA, as the Agency developed risk assessments using the risk assessment guidelines.

BACKGROUND: In 1983, the National Academy of Sciences (NAS)/National Research Council (NRC) published a report entitled *Risk Assessment in the Federal Government: Managing the Process* that included a discussion of the nature of risk assessment. It stated that risk assessment is the use of the factual basis - the underlying scientific information - to define the potential health effects that may result from exposure of individuals or populations to hazardous materials. The NRC supported the use of risk assessment in the regulatory decision making process, while at the same time acknowledging the inherent uncertainties in the risk assessment process. In that report, the NRC also recommended that Federal regulatory agencies establish "inference guidelines" to promote consistency and 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 the Guidelines for Carcinogen Risk Assessment.

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 and risk assessment practices.

RISK ASSESSMENT: Risk assessment is a process for organizing and analyzing information to determine if an environmental chemical or other agent might cause harm to exposed persons and ecosystems. The risk assessment process consists of four primary steps: hazard assessment, dose-response assessment, exposure assessment, and risk characterization. The steps are interrelated, but all include a consideration of all relevant information and a detailed discussion of the strengths and weaknesses of that information. The current cancer guidelines revision effort emphasizes full characterization of all information, the expanded role of mode-of-action information (key events and processes, starting with the interaction of an agent with a cell, through functional and anatomical changes, resulting in cancer or other health endpoints), the use of all information to design a dose-response approach, and a two-step process for dose-response assessment.

Hazard Assessment is the determination of whether a particular chemical is or is not causally linked to particular health effects. Current approaches to hazard characterization include consideration of

evaluation of mechanism(s) of action and biologically-based models. Mechanistic data can aid in the interpretation and extrapolation of exposure to dose.

In the draft final cancer guidelines, one of the key components of the hazard assessment is the analysis of the weight of the evidence. A weight-of-evidence evaluation is a collective evaluation of all pertinent information so that the full impact of biological plausibility and coherence is adequately considered. Identification and characterization of human carcinogenicity is based on human and experimental data, and the nature, advantages, and limitations of the information. To express conclusions about the weight of evidence for human carcinogenic potential, the draft final cancer guidelines call for a complete characterization in a weight of evidence narrative. To give some measure of consistency in an otherwise free-form narrative, standard descriptors are utilized as part of the hazard assessment narrative. The descriptors are not meant to replace an explanation of the nuances of the biological evidence, but rather to summarize it. The descriptor is always followed by a narrative that fully characterizes the weight of the evidence.

*Carcinogenic To Human*s: This descriptor is appropriate when there is convincing epidemiologic evidence demonstrating causality between human exposure and cancer, or exceptionally when there is strong epidemiological evidence, extensive animal evidence, knowledge of the mode of action, and information that the mode of action is anticipated to occur in humans and progress to tumors.

Likely To be Carcinogenic To Humans: This descriptor is appropriate when the available tumor effects and other key data are adequate to demonstrate carcinogenic potential to humans, but does not reach the weight-of-evidence for the descriptor "carcinogenic to humans."

Suggestive Evidence of Carcinogenic Potential: This descriptor is appropriate when the evidence from human or animal data is suggestive of carcinogenicity, which raises a concern for carcinogenic effects but is judged not sufficient for a stronger conclusion.

Inadequate Information to Assess Carcinogenic Potential: This descriptor is used when available data are judged inadequate to perform an assessment.

Not likely To Be Carcinogenic To Humans: This descriptor is used when the available data are considered robust for deciding that there is no basis for human hazard concern.

Dose-Response Assessment is the determination of the shape and form of the relationship between exposure and the health effects in question. As proposed in the draft final cancer risk guidelines, dose-response assessment is a two-step process. In step one, the risk assessor uses the animal or human effect data and other data to model in the range of empirical observation from early responses such as biochemical alterations to more complicated responses such as cancer and developmental defects. The preferred models are generally those that are biologically-based, followed in preference by the use of an appropriate curve-fitting model. The risk assessor also needs to explore the lower range of the observed data to identify a benchmark dose for comparison with noncancer effect assessment and to identify lowest reliable part of the dose response curve. This point is then determined to be the point of departure for extrapolation below the range of observation. The precision of these estimates will focus on the nature and quality of the available information within this range.

Step two of the dose response assessment is the extrapolation below the range of observation to determine the range of human exposure. This is accomplished by using a biologically-based model if there is sufficient and appropriate data, or by using default procedures -- linear, or non-linear. The choice of what approaches are used is indicated by what is known about the mechanism of action of the agent. Thus, extrapolation to the lowest dose will involve explicit decisions regarding the type of model to be used, if any, for calculating low dose upper bound estimates of risk. For some agents no probabilistic estimates of low-dose risk will be calculated, but a reference dose/reference concentration will be applied. The key is to fully characterize the results including the nature and quality of the data, the assumptions and uncertainties and the presentation of alternative approaches when appropriate.

Exposure Assessment is the determination of the extent of human exposure. Some of the desirable attributes of the exposure analysis component are that methods are clearly described, specific populations/subpopulations are identified, potential sources/pathways/routes of exposure are identified and characterized, description of uncertainty and relative importance of data/models/assumptions is included, level of confidence of data is expressed, and research to increase confidence is described.

Risk Characterization is the description of the nature and often the magnitude of human risk. The desirable characteristics of the risk characterization step are: summarize all data, strengths and weaknesses, integrate information from previous steps, discuss uncertainties and assumptions, develop estimates of risk for public health and ecological integrity, and provide tools for risk managers who make decisions.

DRAFT FINAL CANCER 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 individuals. 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. The draft final Guidelines include discussions of all of the four steps of the risk assessment process and provide guidance to risk assessors on these steps.

In applying these principles to the revision of the Guidelines, four interrelated issues have been the focus of EPA deliberation:

Use of default options. Default options are approaches that EPA can apply in risk assessments when scientific information about the effects of a substance on human health is unavailable, limited, or of insufficient quality. Under the Guidelines, EPA's approach is to begin with a critical analysis of available information, and then invoke defaults if needed to address uncertainty or the absence of critical information. Use of defaults is intended to be health protective as well as also being scientifically defensible.

Consideration of mode of action. 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.

In assessing the cancer risks of a chemical, 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 how 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, cancer risks can still be assessed under the Guidelines but it is likely that default options will need to be invoked to address uncertainty.

Fuller characterization of carcinogenic potential. Under the Draft Final Guidelines, 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 life-stages 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 Guidelines present a set of standard weight-of-evidence descriptors that accompany the narratives. The 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.

Consideration of differences in susceptibility. The Draft Final Guidelines explicitly recognize that variation exists among people in their susceptibility to carcinogens. Some subpopulations may experience increased susceptibility to carcinogens throughout their life, such as people who have 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, differences related to an immature metabolic system, and differences in diet and behavior patterns that may increase exposure.

These changes in direction will address some of the previous misconceptions regarding the precision of cancer risk estimates and will make the uncertainties inherent in the risk assessment process clearer and more transparent. They will also help to improve communication of the strengths and weaknesses of the available data.