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External Review Draft

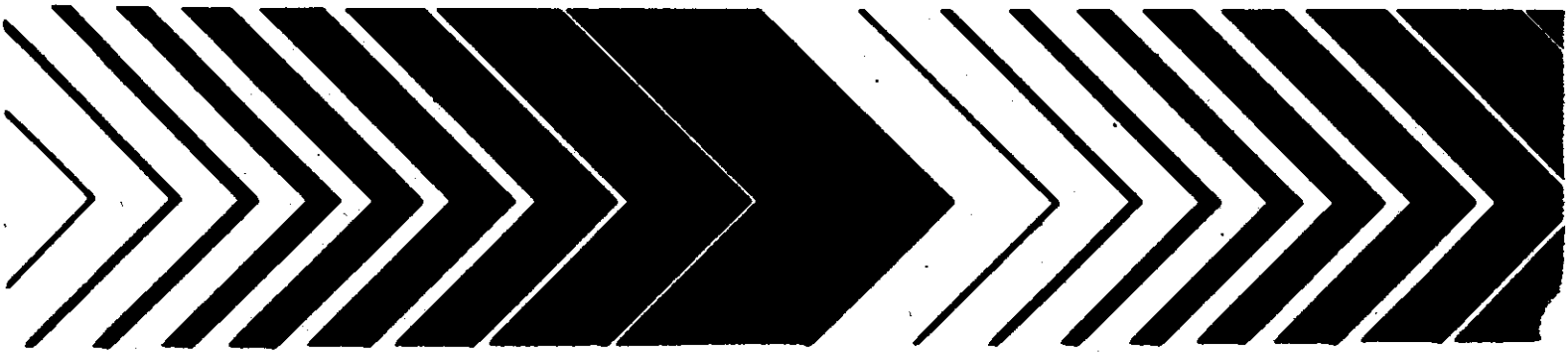
EPA

Draft Revisions to the Guidelines for Carcinogen Risk Assessment

Review Draft (Do Not Cite or Quote)

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.



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Office of Health and Environmental Assessment
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or pharmacokinetics studies. For certain agents there may be enough known about properties of their class to make confident conclusions regarding absorption by different routes. For others, more data on the specific agent may be necessary as conclusions may be less confident, or not possible, without such information. Discussion of these issues is part of the characterization.

Relationship of dose level, pattern, and duration of exposure to effects can theoretically take many forms. Hazard assessment examines all of the kinds of evidence to see what processes or events in carcinogenesis a specific agent appears to affect. This information is used to relate the mode of action in general terms to the approach to quantitative dose-response assessment. The mode of action may imply a linear or a non-linear dose-response relationship, or a threshold of dose below which effects will not occur in an individual. The implications of available information about human variability in sensitivity or with respect to threshold effects are important elements. These implications relate to both the qualitative characterization of hazard and the quantitative assessment of dose-response.

2.5.3. Descriptions of Weight of Evidence

The hazard narrative, described in the following subsection, presents the weight of evidence in terms of likelihood of human carcinogenicity using descriptors. The descriptors are not meant to replace an explanation of the nuances of the biological evidence, but rather to summarize it. Each descriptor spans a wide variety of data sets and weights of evidence. There will always be gray areas, gradations, and borderline cases. The narrative preserves and presents this complexity, which is an essential part of the hazard characterization. Applying a descriptor is a matter of judgment and cannot be reduced to a formula. Risk managers should consider the entire range of information included in the narrative rather than focus simply on the descriptor.

Note that one agent may fit more than one descriptor, if, for instance, the agent were likely to be carcinogenic by one route of exposure and not by another. Use of the descriptors is illustrated in Appendix A.

The descriptions below are intended only as guidance and provide some typical examples; the examples are not exhaustive or comprehensive.

"Likely" or "Known"

These descriptors are appropriate when the evidence provides a reasonable assurance of carcinogenic potential for human beings and supports proceeding with the risk assessment. "Likely" is the descriptive term generally used. "Known" is used when the weight of evidence gives especially high assurance because either an association between carcinogenicity and a specific route of exposure is drawn from human data, or conclusions from other kinds of data give confidence that is equal to having human data.

"Cannot be determined"

"Cannot be determined" is appropriate whenever support for a conclusion about carcinogenic potential for human beings is not sufficient to proceed with the assessment. Where appropriate, the narrative explains the situation. Examples may include the following, among others.

- The evidence raises a concern for carcinogenic effects, but falls short of supporting a conclusion about the likelihood of effects. The narrative provides a summary of the research or testing needed to explore the issue further. The added descriptor, "testing candidate" is appropriate in these cases to flag the agent for attention by testing programs.
- The data are inadequate to perform an assessment.
- The information is inconclusive or conflicting, e.g., some evidence is suggestive of carcinogenic effects, but other equally pertinent evidence does not confirm any concern.

"Not Likely"

"Not likely" is appropriate whenever evidence about an agent generally, or about a condition of exposure, is satisfactory for deciding that there is not a basis for concern. Again, the narrative explains the conclusion. Examples may include the following:

- The agent has been adequately characterized empirically, and the conclusion is negative, or the only positive data are not considered relevant to human beings. Adequate empirical characterization generally includes well conducted, long-term animal studies on an agent or its structural analogue with consistent findings from analysis of other key evidence.
- The evidence shows that under certain conditions of exposure, no expression of carcinogenic effects is anticipated. The agent's carcinogenic potential is categorized as "not likely" for those conditions, e.g., a route of exposure or a defined dose level.
- The agent has been adequately characterized empirically, and the only positive indication of effects was seen under experimental circumstances that are implausible for raising an environmental concern, e.g., injection of a polymer.

2.5.4. Hazard Narrative

A narrative summarizes the results of hazard characterization. The narrative, ·timally two pages or less in length, explains an agent's human carcinogenic potential and ·: conditions of its expression. If data do not allow a conclusion, the narrative explains this determination. Examples of narratives appear in Appendix A below as guidance for format and content. The items regularly included are these:

- name of agent and Chemical Abstracts Services number, if available
- a brief identification of the kinds of data available
- conclusions (by route of exposure) about human carcinogenicity, described as "known" or " likely," "not likely," or "cannot be determined"
- summary of tumor data, human or animal, on the agent and/or its structural analogues, their relevance, and biological plausibility