

SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

The U.S. EPA is interested in seeking consultation from the members of the SAB regarding upcoming activities related to an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and guidelines for noncancer risk assessment. In considering areas for future emphasis, as well as with the work currently underway, EPA's Risk Assessment Forum¹ (RAF) is considering various topic areas including use of defaults, inhalation dosimetry and susceptible populations and lifestages.

The U.S. EPA, primarily through the RAF, maintains a series of guidelines, guidance documents and methodologies that describe the way the Agency conducts its human health and ecological risk assessments.² Some key examples include:

- Guidelines concerning: exposure assessment, carcinogen risk assessment, mixtures risk assessment, reproductive toxicity risk assessment, developmental toxicity risk assessment, neurotoxicity risk assessment, and ecological risk assessment;
- Supplemental guidance for mixtures risk assessment, and assessing susceptibility from early-life exposure to carcinogens;
- Guidance for benchmark dose modeling, and applying quantitative data to develop data-derived extrapolation factors;
- Frameworks for cumulative risk assessment and for ecological risk assessment; and
- Methods for and reviews of RfD/RfC processes.

A more detailed listing of some of the Agency guidelines, guidance documents, and technical panel reports that address human health risk assessment is attached.

The RAF is currently engaged in various activities,³ ranging from drafting updates to longstanding guidelines documents to initial investigative steps on complex topic areas. Some current examples include an update to the Guidelines for Exposure Assessment,⁴ activities related to the development of cumulative risk assessment guidance,⁵ and consideration of new approaches to dose-response assessment that may be used in risk assessments to augment their usefulness for Agency decision making. Activities are also underway to address specific issues, such as additivity in mixtures risk assessment and consideration of several of the default uncertainty factors used in reference value methods.

The EPA is interested in consultation with the SAB with these general perspectives in mind.

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

¹ <https://www.epa.gov/osa/basic-information-about-risk-assessment-guidelines-development>

² A list of many of the human health assessment documents can be found at the following URL: <https://www.epa.gov/risk/risk-assessment-guidelines#tab-1>, and documents on ecological assessment can also be accessed from that webpage.

³ <https://www.epa.gov/osa/risk-assessment-current-projects>

⁴ <https://www.epa.gov/risk/guidelines-human-exposure-assessment>

⁵ <https://www.epa.gov/risk/framework-cumulative-risk-assessment>

2. Are there important topic areas that are not fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

As evident from the general questions above, EPA is seeking open-ended input and recommendations from SAB members and will consider all the input received to determine next steps for updating EPA guideline documents in a phased approach.

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis—including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?
4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 “Weight of Evidence Narrative” or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 “Dose Response Characterization”). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.
 - i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?
 - ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?
 - iii. What role should statistical analysis play in this characterization?
 - iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?
5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).
 - i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?
 - ii. Are there areas of overlap or disagreement between these guidelines?
 - iii. What issues or guideline documents would SAB members prioritize for update?

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?
7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.
 - i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?
 - ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

With these questions guiding, but not limiting, your review, please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment.

Attachment

Select Agency Guidelines, Guidance Documents, and Technical Panel Reports that Address Human Health Risk Assessment

- [U.S. EPA. 2012. Guideline for Microbial Risk Assessment: Pathogenic Microorganisms with Focus on Food and Water.](#) EPA/100/J-12/001, Jul 2012.
- [U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment](#) EPA/630/P-03/001F, Mar 2005.
- [U.S. EPA. 1998. Guidelines for Neurotoxicity Risk Assessment](#) EPA/630/R-95/001F, Apr 1998.
- [U.S. EPA, 1996. Guidelines for Reproductive Toxicity Risk Assessment](#) EPA/630/R-96/009, Oct 1996.
- [U.S. EPA. 1991. Guidelines for Developmental Toxicity Risk Assessment](#) EPA/600/FR-91/001, Dec 1991.
- [U.S. EPA. 1986. Guidelines for Mutagenicity Risk Assessment](#) EPA/630/R-98/003, Sep 1986.
- [U.S. EPA. 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures](#) EPA/630/R-98/002, Sep 1986.
- [U.S. EPA. 2014. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation.](#) EPA/100/R-14/022F, Sep 2014.
- [U.S. EPA. 2014. Framework for Human Health Risk Assessment to Inform Decision Making.](#) EPA/100/R-14/001, Apr 2014.
- [U.S. EPA. 2012. Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration \(RfC\) and Use in Risk Assessment.](#) EPA/600/R-12/044, Sep 2012.
- [U.S. EPA. 2012. Benchmark Dose Technical Guidance.](#) EPA/100/R-12/001, Jun 2012.
- [U.S. EPA. 2011. Recommended Use of Body Weight 3/4 as the Default Method in Derivation of the Oral Reference Dose.](#) EPA/100/R11/0001, Feb 2011.
- [U.S. EPA. 2006. A Framework for Assessing Health Risks of Environmental Exposure to Children.](#) EPA/600/R-05/093F, Sep 2006.
- [U.S. EPA. 2006. Approaches for the Application of Physiologically Based Pharmacokinetic \(PBPK\) Models and Supporting Data in Risk Assessment.](#) EPA/600/R-05/043F, Sep 2006.
- [U.S. EPA. 2005. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens](#) EPA/630/R-03/003F, Mar 2005.
- [U.S. EPA. 2002. A Review of the Reference Dose and Reference Concentration Processes.](#) EPA/630/P-02/002F, Dec 2002.
- [U.S. EPA. 2000. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures.](#) EPA/630/R-00/002, Aug 2000.
- [U.S. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry.](#) EPA/600/8-90/066F, Oct 1994.
- [U.S. EPA. 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment.](#) EPA 600/6-87/008, Feb 1988.