Charge to the SAB on the *Consolidated Human Toxicity Assessment Guideline*

Background

EPA has developed numerous guidelines and technical reports related to human toxicity assessment[1]. Some endpoint-specific toxicity documents were developed more than 2 to 3 decades ago (e.g., mutagenicity - 1986; developmental toxicity - 1991; reproductive toxicity - 1996; neurotoxicity – 1998). Since the development of these early toxicity guidelines, EPA has also developed additional guidelines that address common elements in Agency risk assessments, such as planning and scoping/problem formulation, and benchmark dose modeling. Many scientific advances have occurred since the development of the existing EPA guidelines; and there are also risk assessment elements and toxicity endpoints, such as immunotoxicity, for which EPA does not have guidelines. As a result, the Administrator tasked EPA's Risk Assessment Forum with revising existing or developing new assessment guidelines.

One of the early steps in this process was requesting advice from the EPA Science Advisory Board (SAB). This request was discussed with the SAB at a public meeting in June 2019, from which EPA received many valuable comments from SAB members. Having considered the comments from this SAB consultation[2], as well as internal Agency discussions, EPA is now initiating the development of a single Consolidated Human Toxicity Assessment Guideline ("Consolidated Guideline") that will focus on hazard characterization and dose-response assessment. Hazard characterization and dose-response assessment are two critical considerations which, when combined with exposure evaluation[3] in case- or location-specific circumstances, support risk assessment.[4]

EPA is proposing to revisit its overall approach to risk assessment guideline development. The Agency intends to utilize a modular approach in developing the Consolidated Guideline. This modular approach will result in the development of one consolidated guideline that consists of focused modules. This modular approach is similar to that taken by EPA in updating its Exposure Factors Handbook.[5] This contrasts with the past approach of developing discreet and independent toxicity-endpoint and common-element guidelines. Use of a modular approach in the Consolidated Guideline will allow EPA to accrue the benefits of consolidation, such as enabling EPA risk assessors to more easily access and use relevant parts of the Consolidated Guideline, while providing for an efficient and timely update of the Consolidated Guideline as modules are completed.

Given the number of commonalities in cancer and non-cancer assessments, the Consolidated Guideline will include assessment of both cancer and non-cancer endpoints. It will also include approaches that are common across endpoints and consideration of state-of-the-science

[1] https://www.epa.gov/risk/risk-assessment-guidelines#tab-1

[2] https://yosemite.epa.gov/sab/sabproduct.nsf/357DC7E5C59BA9AD85258438005BA457/$File/EPA-SAB-19-003+.pdf

[3] See *Guidelines for Human Exposure Assessment* https://www.epa.gov/risk/guidelines-human-exposure-assessment

[4] See *EPA's Framework for Human Health Risk Assessment to Inform Decisionmaking* (2014) https://www.epa.gov/risk/framework-human-health-risk-assessment-inform-decision-making

[5] https://www.epa.gov/expobox/about-exposure-factors-handbook

approaches for characterization of dose-response, in addition to the incorporation of new approach methodologies (NAMs). Emphasis will be placed on examining the state-of-the-science and incorporating updated best practices for estimating risk at environmental exposure levels of concern for Agency decision-making.

The Consolidated Guideline will include two types of modules:

- Modules addressing common elements of an assessment (*i.e.*, "common-element" modules) that pertain to all health endpoints (*e.g.*, project planning and scoping, generic aspects of dose-response modeling), and
- Modules addressing specific types of toxicity ("endpoint-specific" modules) that focus on aspects of the hazard characterization and dose-response issues and methods that are specific to that toxicity-endpoint.

EPA will develop the Consolidated Guideline in a stepwise modular fashion (see page 6, Figure 1 illustrating the implementation approach). Modules will be developed and completed or updated individually in response to advances in science and Agency practice, without having to update entire sets of Agency guidelines. Any significant new aspects of the Consolidated Guideline will undergo public comment and external scientific peer review. EPA intends to complete the design of the Consolidated Guideline and prioritize the modules to be developed in December 2020. EPA will initiate the development of the modules in January 2021.

SAB Consultation

EPA considered the many recommendations submitted through the June 2019 SAB consultation, which particularly emphasized the need to update or add to EPA's risk assessment guidelines to ensure the use of the best available science at all phases of risk assessment and to provide the guidelines in a centralized location. Many SAB member recommendations were specific to toxicity endpoints and dose-response issues, including the need for updated guidelines on developmental toxicity, new guidelines on immunotoxicity, and considerations of dose-response issues, such as guidance for the use of various dose-response modeling approaches (e.g., model averaging), further consideration of the use of low-dose extrapolation approaches, additional consideration of endogenous production of environmental contaminants, and methods that would harmonize the evaluation of dose-response for cancer and noncancer effects. EPA considered these comments as the Agency developed the consolidated guideline concept.

This new consultation on the approach EPA proposes to use to develop the Consolidated Guideline is the first of what the Agency suggests should be regular consultations with the SAB during the development of this work plan and the many modules to follow. Consultation at this early stage is important because establishing a robust framework is key to developing a Consolidated Guideline that will support EPA's use of the best available science in its risk assessments.

Discussion/Charge Questions

(1) EPA is planning on using a modular approach to develop its Consolidated Guideline. Please comment on this proposed approach, and if there are other approaches SAB members would recommend EPA consider? This can include comments on Figure 1, Process/Timeline.

(2) Please comment on the scientific adequacy, completeness, organization and other relevant considerations regarding EPA's list of proposed "common element modules" (See Table 1). Comments should include an assessment of each module's description. Any recommendations for new, expanded, consolidated or split modules should come with suggested descriptions.

(3) Please comment on the scientific adequacy, completeness, organization and other relevant considerations regarding EPA's list of proposed "endpoint-specific modules" (See Table 1). Any recommendations for new, expanded, consolidated or split modules should come with suggested descriptions and other relevant guidance.

(4) EPA will need to set priorities and start some modules before others. What modules would SAB members suggest EPA work on first and why? This may include commentary on the extent of update needed for each of the existing guidelines.

(5) EPA received many comments from SAB members on dose-response issues. Comments that came up multiple times include those shown below. Please comment on which of these or other issues SAB members would consider to be of higher priority:

- Use of various dose-response modeling approaches (e.g., model averaging);
- Further consideration of the use of low-dose extrapolation approaches;
- Additional consideration of endogenous production of environmental contaminants; and
- Methods that would harmonize the evaluation of dose-response for cancer and noncancer effects.

Table 1: Proposed Modules

Modules are in order of how the Consolidated Guideline could potentially be organized, but not necessarily the order in which they would be written.

Common Element Modules *These proposed modules would address common elements of an assessment that pertain to all health endpoints*	**Module 1. Planning and Scoping a Human Toxicity Assessment** This module will provide an overview of human health toxicity assessment including key concepts such as fit for purpose, problem formulation, consideration of potential routes of exposure and overarching considerations including lifestage susceptibility, vulnerable populations and cumulative risk.

	Module 2. Identifying and Evaluating Toxicity Studies This module will cover general principles associated with collecting potentially relevant studies including conducting a literature search (systematic review), critically appraising different types of data (animal, epidemiological, chamber, modeling, in silico, NAMs, etc.) with respect to study design, power and reliability, data quality evaluation, and identifying data gaps.
	Module 3. Hazard Identification This module will cover integrating/weighing evidence/synthesizing results across studies, evaluating possible mechanisms/modes of action/adverse outcome pathways including human relevance, and consideration of lifestage susceptibility.
	Module 4. Dose-Response Assessment This module will cover a comprehensive set of issues including but not necessarily limited to: • Consideration of a unified approach for dose-response assessment; • Absorption, distribution, metabolism, and excretion (ADME) considerations; • Toxicodynamic versus toxicokinetic considerations; • Data quality considerations; • Types of dose-response data: animal tests; human chamber tests; epidemiological studies; occupational studies; high throughput testing; virtual tissue modeling; • Benchmark dose modeling including choosing a response rate, identifying a point-of-departure (POD) and extrapolation of dose-response to exposures lower than POD; • Deriving a POD, reference value, or margin of exposure; • Probabilistic modeling; • Model averaging; • Characterization of lifestage and population variability and vulnerability;

	• Physiologically Based Pharmacokinetic (PBPK) and Biologically Based Dose-Response (BBDR) modeling; • Use of adjustment factors including data derived extrapolation factors (DDEFs) and age-dependent adjust factors (ADAFs) to account for uncertainty, variability, susceptibility and use of generic default adjustment factors (e.g., body weight to the ¾-power); and • Cumulative risk considerations.	
Endpoint Specific Modules *These proposed modules would focus on aspects of the hazard characterization and dose-response issues and methods that are specific to that endpoint*	**Module 5. Developmental Toxicity** **Module 6. Reproductive Toxicity** **Module 7. Immunotoxicity** *(no EPA guideline currently exists)* **Module 8. Carcinogenicity** **Module 9. Mutagenicity** *(mutagenicity as a mode-of-action would be addressed in both Module 3 – Hazard Identification & Module 4 – Dose-Response Assessment)* **Module 10. Neurotoxicity** **Module 11. Other Endpoints?** *(could add additional modules in the future for other issues or endpoints to potentially include, (e.g., Target Tissue Specific Considerations, Susceptible Lifestages and Population Groups)*	These proposed modules would cover definitions, critical concepts, test systems, data interpretation, and endpoint specific dose-response and exposure assessment considerations as needed.
Appendix	**Glossary** *(update after each module is developed)*	

Figure 1: Process/Timeline for Developing EPA's Consolidated Human Toxicity Assessment Guideline