

EPA SAB AND CAAC

Update & Consolidation of EPA Human Toxicity Assessment Guidelines

June 23, 2020

Input on Updating and Developing Guidelines



March 2019: Administrator request to update Cancer Guidelines and develop Noncancer Guidelines

June 2019 -- SAB and CAAC consult

- Valuable input.
- \geq 160 pages of written input
- over 240 unique comments

Many specific SAB recommendations covering a wide range of specific topics:

- suggested many particular topics on which guidance would be useful;
- discussed characterizing uncertainty, variability and dose-response;
- suggested updating some older guidelines;
- recommended incorporating NAMs, AOPs and MOAs
- some suggested a more unified approach across cancer and noncancer.

Input on Updating and Developing Guidelines (cont)



EPA also considered

- prior NAS reviews
- prior EPA deliberations

After consideration, EPA is planning to

- update and consolidate its guidelines on assessing the toxicity and dose-response for human health effects of chemicals. (This effort is chaired by Michael Firestone /Office of Children's Health Protection/Office of the Administrator)
- start review of key dose-response issues for the updated and consolidated guidelines. (This effort is chaired by Lynn Flowers/ORD)

Today's meeting is focusing on design of "Consolidated Guideline".

Consolidated Guidelines Approach



- ❑ Modular approach – allows EPA to more easily and efficiently update aspects of human toxicity assessment without constantly having to update an entire document.

- ❑ Considering two types of modules:
 - **Common Element** – these modules apply across all endpoints

 - **Endpoint-Specific** – these modules would update and expand existing guidelines (or develop a new endpoint) that address specific types of effects

Preliminary Set of Modules



Preliminary Modules Topics Scoping Document consists of two types of modules, addressing both endpoint-specific topics reflecting existing RAF guidelines, as well as topics that apply across endpoints:

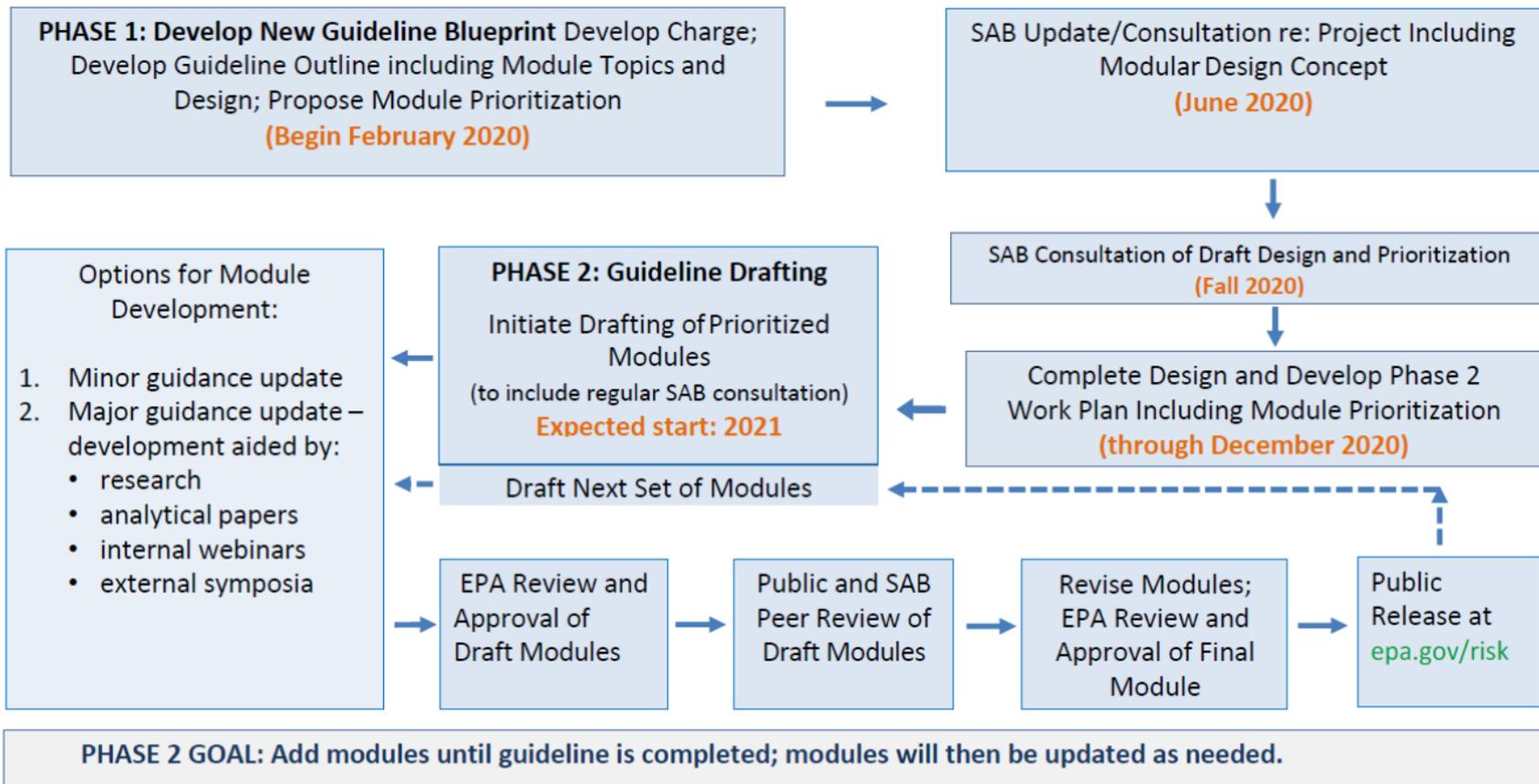
- Common Element Modules:
 - Module 1. Planning and Scoping a Human Toxicity Assessment
 - Module 2. Identifying and Evaluating Toxicity Studies
 - Module 3. Hazard Identification
 - Module 4. Dose-Response Assessment

- Endpoint Specific Modules
 - Module 5. Developmental Toxicity
 - Module 6. Reproductive Toxicity
 - Module 7. Immunotoxicity (new)
 - Module 8. Carcinogenicity
 - Module 9. Mutagenicity
 - Module 10. Neurotoxicity

Flowchart for Modular Approach



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



Charge Question (#1) - on Modular Approach



Charge question 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.

“Common Elements”



Some topics can mostly be handled in a unified way regardless of the type of toxicity effect.

Although implementation of assessment work on these topics might vary some depending on the health endpoint, there are common principles and it is most efficient to present it once rather than repeat it for each kind of health endpoint.

Examples in Table 1 of the charge:

- ❑ Planning and Scoping a Human Toxicity Assessment
- ❑ Identifying and Evaluating Toxicity Studies
- ❑ Hazard Identification
- ❑ Dose-Response Assessment

Charge Question (#2) on “Common Elements”



Charge question 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 [*in the charge*]).

Comments should include an assessment of each module’s description.

Any recommendations for new, expanded, consolidated or split modules should come with suggested descriptions.

“Endpoint-Specific Elements”



There are also topics that EPA is thinking are best presented and covered in the context of an “**endpoint-specific elements**”.

Types of endpoints for which EPA might develop chapters are listed as Modules 5 thru 11 in Table 1 of the charge:

- ❑ Developmental Toxicity
- ❑ Reproductive Toxicity
- ❑ Immunotoxicity (no EPA guideline currently exists)
- ❑ Carcinogenicity
- ❑ Mutagenicity
- ❑ Neurotoxicity
- ❑ Other Endpoints

Each of these modules would cover topics that are largely specific to that type of endpoint, such as:

- Key concepts for specific types of endpoint
- Data interpretation issues
- Dose-response issues arising from type of studies
- Exposure assessment considerations

Charge Question (#3) on Endpoint-Specific Elements



Charge question 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 [*of the charge*]).

Any recommendations for new, expanded, consolidated or split modules should come with suggested descriptions and other relevant guidance.

Priorities



EPA will need to set priorities:

- Which modules to tackle first; and
- Within those, which issues.

Charge Question (#4) - Module Priorities



Charge question 4

(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.

Dose-Response Issues



Some of the specific issues that SAB members raised in our 2019 consultation involved dose-response and other quantitative issues.

EPA assessors felt these were important issues to examine.

Some categories of dose-response issues that could be given priority are listed in the charge question (next slide).

Charge Question (#5) Dose-Response Issues



Charge question 5

EPA received many comments on dose-response issues from SAB members .

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.

Discussion



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.



Discussion/Charge Questions (cont)

(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.