

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

**Compilation of Preliminary Individual Comments from Members of the Chartered SAB and SAB Chemical Assessment Advisory Committee on Activities to Re-examine and Consolidate EPA’s Human Toxicity Assessment Guidelines**

**(As of June 24, 2020)**

<b>COMMENTS FROM CHARTERED SAB MEMBERS.....</b>	<b>3</b>
<i>Dr. Hugh Barton .....</i>	<b>3</b>
<i>Dr. Janice Chambers .....</i>	<b>6</b>
<i>Dr. Samuel Cohen .....</i>	<b>7</b>
<i>Dr. Tony Cox .....</i>	<b>10</b>
<i>Dr. Thomas Parkerton .....</i>	<b>11</b>
<i>Dr. Tara Sabo-Attwood.....</i>	<b>13</b>
<i>Dr. Mara Seeley .....</i>	<b>15</b>
<i>Dr. Kimberly White.....</i>	<b>16</b>
<i>Dr. Richard Williams.....</i>	<b>19</b>
<b>COMMENTS FROM SAB CHEMICAL ASSESSMENT ADVISORY COMMITTEE MEMBERS.....</b>	<b>20</b>
<i>Dr. Richard Belzer .....</i>	<b>20</b>
<i>Dr. Tiffany Bredfeldt .....</i>	<b>30</b>
<i>Dr. Karen Chou.....</i>	<b>36</b>
<i>Dr. Harvey Clewell .....</i>	<b>41</b>
<i>Dr. Michael Jayjock.....</i>	<b>45</b>
<i>Dr. Wayne Landis.....</i>	<b>46</b>
<i>Dr. Ted Simon .....</i>	<b>52</b>

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

*Dr. Eric Smith* ..... 53

## **Comments from Chartered SAB Members**

### ***Dr. Hugh Barton***

Discussion/Charge Questions for the Consolidated Human Toxicity Assessment Guideline

Hugh A. Barton

June 19, 2020

(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.

- The modular approach is appropriate as there are so many different aspects. From the outset, it needs to be defined what these guidelines are attempting to address. Historically, EPA human toxicity assessment guidelines focused on chronic or lifetime exposures rather than acute exposures, for example. With this modular approach, one could establish a framework that would be broader (e.g., including acute exposures such as accidental releases) that would be filled in over time, but in the meantime reference any current Agency guidance. Similarly, there have been differences in how toxicity assessments were done throughout the Agency under different laws, in different Offices of the Agency, and due to differences in available data. It is important to make clear what these guidelines are intended to address.

(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.

- The common element modules make sense as described as they represent the basic elements of toxicity assessment. In writing or updating these modules, they need to be open to new developments (e.g., new approach methods (NAMs)) and not lock in requirements for the whole animal studies that have been historically used. NAMs and in silico are mentioned in the described of Module 2 toxicity studies but need to be considered in each of these modules even though the methods for using them are still in development.
- Module 2 description: "chamber" is unclear, though in Module 4 it is more fully described as "human chamber tests".

(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.

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

- The addition of immunotoxicology guidance would be valuable and should be a high priority as this can underlie a host of human diseases.
- There is no guidance listed for most target organ toxicities (e.g., liver, kidney, spleen). At a minimum, this needs to be one module to address these or direct people to any existing Agency guidance.
- The proposed approach from OPP for considering waivers for chronic/carcinogenicity studies includes assessment of genotoxicity, endocrine effects, and immunological effects as predictors for potential chronic or carcinogenic effects. Guidance for addressing endocrine effects is needed here.
- A challenge for these endpoint-specific modules is that NAMs and other approaches, such as toxicogenomic signatures evaluated in short-term animal studies, seem likely to be useful to evaluate the toxicity of a chemical but not necessarily be able to predict the endpoints or target organs that would be observed either in animals or humans. It may be too early to develop guidance for such approaches as this is an area of active research, but it could be identified as a module to be created in the future.
- Another challenge is that many human health effects important to public health are not predicted by in vivo animal toxicity studies. A road map for research and development efforts to address this is needed and some guesstimate of a timeline for considering such effects in toxicity assessments developed. This might be a very short module but could be very informative.

(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.

- The four common element modules are a reasonable first priority.
- A public commenter, Dr Fenner-Crisp, indicated that a mutagenicity MOA guidance was nearly complete, in which case that makes sense as a high priority to complete.

(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.

Harmonization of evaluation of dose-response for cancer and noncancer effects should be the highest priority. Further consideration of low-dose extrapolation approaches seems likely to be part of this. This task alone has multiple components.

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

- Outside chemicals that are DNA-adducting mutagens or potent estrogenic, it appears that tumors in animals are typically another chronic toxicity caused by toxicity processes that lead to a variety of chronic effects (e.g., histologically observable tissue damage). The historic differences in dose-response approaches has led to a focus on cancer endpoints to the detriment of endpoints, such as cardiovascular disease, that are also very important to human health.
- Quantification of risk for cancer while continuing to estimate acceptable concentrations for noncancer endpoints has contributed to the under valuing of noncancer endpoints in risk assessments. Development of methods to estimate risks regardless of endpoint needs to be a high priority.

DO NOT CITE OR QUOTE.

***Dr. Janice Chambers***

Charge Questions for Human Toxicity Assessment—from Jan Chambers

- (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.** The modular approach makes sense in that it will be easier to concentrate on revision of each section in a focused manner and it will be easier to revise individual modules when needed and replace modules than the entire guidance document. The timeframe presented in Figure 1 is probably optimistic, especially if substantial rewrites or revisions are needed for some of the modules.
- (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.** One category missing from the Endpoint Specific Modules group is organ system specific toxicities, such as liver, kidney, and lung.
- (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.** Module 1 is probably quite straightforward and could be updated rather quickly, so would be a good place to start. Module 2 could probably also be updated quite easily. The others will require more thought and discussion.
- (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.**

The third option above is the lowest priority because it is specific to only a relatively few toxicants.

*Dr. Samuel Cohen*

**Summary of Recommendations from June 20, 2019, Consultation with Members of the EPA Chartered Scientific Charter SAB and CAAC**

I strongly endorse the efforts by the EPA to update their guidance for overall risk assessment approaches, especially their attempts to unify the cancer and non-cancer risk assessment. This is particularly true for nongenotoxic chemicals. Some specific comments regarding the points listed in the document sent to us follow.

Under problem formulation and scoping, I believe that the last bullet point, “reality check,” is particularly important. This has become quite evident in recent assessments, such as ethylene oxide, and others.

Under harmonization, I strongly support the effort to harmonize guidelines for cancer and non-cancer effects, including the dose response. This should be especially true for nongenotoxic chemicals (see below regarding genotoxicity assessment). Since for nongenotoxic chemicals, the mode of action always includes a precursor key event that is a non-cancer toxicity, protecting against this non-cancer toxicity will also protect against the risk of cancer. In particular, the default assumption for nongenotoxic carcinogens should be a threshold, nonlinear extrapolation to low dose, similar to what is performed for other types of toxic endpoints. Since the precursor lesions will be other types of toxicity beside cancer, the approach for non-cancer and cancer can be entirely the same. This requires that there be some understanding of mode of action, but again, it is essential that for nongenotoxic chemicals the default assumption be that there is a threshold. The continued use of a linear, non-threshold extrapolation to low dose is biologically inappropriate. Also, I would strongly encourage the EPA to utilize descriptors rather than just a scoring or labeling approach. The descriptors are much more useful in a risk management setting. For example, if the toxicity occurs only at a dose above a threshold that leads to a specific toxicity, there is no toxic risk, including cancer risk, below that level. Thus, if there is no evidence of the toxic endpoint precursor, there is no risk of cancer.

Under the general cancer issues, there are several issues that need to be addressed. Although there need to be updates of the cancer guidelines regarding statistical methods, it is important to emphasize that the biology is the predominant determinant of the risk assessment, not the statistical approach. For example, the standard joke regarding causation versus association illustrates this point strongly. One night a drunk goes out and drinks several scotch and sodas and gets a terrible hangover, becomes very sick. So, the next night, he goes out and has bourbon and soda, and the same thing happens. The third night, he goes out and has rye whiskey and soda, and the same thing happens. When he wakes up the third morning, he is terribly sick and he says, I have to just stop drinking that soda, it’s making me sick. It is a 100% correlation, but biologically ludicrous. Although, we laugh at this, there are numerous examples in the literature from epidemiology studies that make this mistake. There appears to be an increasing emphasis for Bayesian analysis. This might be helpful in some instances, but does not serve as a panacea for solving statistical issues. You still have to have basic biological information to make the judgements, both with regard to relevance and with regard to dose. Again, I would emphasize that the linear-no-threshold (LNT) approach as a default for low-dose extrapolation is totally inappropriate, certainly for nongenotoxic chemicals. As indicated above, the default assumption for nongenotoxic chemicals should be a nonlinear, threshold approach. With regard to animal models, it

DO NOT CITE OR QUOTE.

is important to keep in mind the relevance of the model being used, and especially the relevance of the mode of action for human risk. Likewise, the relevance of the dose at which the toxic endpoints are identified needs to be addressed. Careful consideration for MTD and KMD is especially important for extrapolating to lower doses. If toxicity is only seen at doses above the MTD or above the KMD, these are not appropriate for consideration for risk assessment. This should be explicitly stated in the guidelines. The suggestion to convene panels for human relevance of certain animal tumors is critical at this time. There remain several animal rodent tumors and modes of action that continue to be considered relevant to humans which are not actually relevant either qualitatively or quantitatively. These panels should include experts from veterinary and human medicine in addition to toxicology, pathology, statistics, and molecular biology. With regard to NAMs, I encourage the agency to continue development in this area, but I also caution that reasonable biological principles continue to be incorporated into these attempts. For example, doses used in these studies should not be above the MTD or above the KMD. Findings above those doses are meaningless with regard to actual human risk. In addition, the relevance of specific toxic endpoints in animal models needs to be addressed. This has become increasingly obvious in the pharmaceutical industry, where approximately one half of the pharmaceuticals that have been tested in two-year bioassays have positive results, and yet are still used in medicine. Examples include the statins (rodent liver tumors), proton pump inhibitors (gastric neuroendocrine tumors), and fibrates (PPAR $\alpha$  activators). These models are completely irrelevant to humans, based not only on biological evaluations, but extensive epidemiology studies involving hundreds of thousands of individuals. There are actually very few rodent tumor models that are relevant to humans. Likewise, there are several toxic endpoints that occur in animal models that do not extrapolate to the human situation.

With regard to specific cancer issues, there are several that I just listed. In addition, some of the specific points that are listed here need to be addressed. One that is critical is the bar for mutagenic MOA. There needs to be some clear guidance provided with regard to interpretation and consideration of the numerous genotoxicity assays that are performed. Utilization of OECD guidelines in this analysis, as well as the quality of specific studies needs to be carefully addressed. There are way too many examples of positive results in the literature that are not reproducible or that only occur under circumstances that do not extrapolate to the whole organism. A specific statement should be made that a negative finding in an *in vivo* assay overrides the findings of a positive result in an *in vitro* assay. With regard to cell-proliferation requirements, there should be some mention that a labeling index (such as BRDU, Ki-67, or PCNA) needs to be included for *in vivo* studies, particularly in short term studies, since reliance on histopathology will not be adequately sensitive. The suggestion to reevaluate practices for determining statistical significance for common tumors is essential. This was described originally by Joe Haseman at the NTP, and has been adopted by OECD and by FDA. There is strong biologic as well as statistical support for this approach. Without defining this, and even requiring it, leads to way too many false positive results from the bioassay. The suggestion to develop guidance for use of initiation-promotion studies for cancer I believe is misguided. The initiation-promotion model is outdated, and generally can be translated to initiation being synonymous for genotoxicity and promotion being for increased cell proliferation. The reality is that chemicals that act as initiators or promoters are actually carcinogens when investigated in the full two-year bioassay. The only advantage of using this model is that it can identify a nongenotoxic carcinogen in a shorter time, but the same information can be garnered by even shorter term cell-proliferation studies. In addition, this model does not help in addressing the issue of relevance to human cancer risk of the tumors that are induced. I would strongly encourage the EPA to abandon any consideration of the initiation/promotion studies.

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.  
DO NOT CITE OR QUOTE.

Samuel M. Cohen, MD, PhD  
Professor, Department of Pathology and Microbiology  
University of Nebraska Medical Center

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

*Dr. Tony Cox*

**Preliminary comments in response to the charge questions for the SAB consultation on EPA's Human Toxicity Assessment Guideline.**

- Validation of dose-response models and characterization of model uncertainty should be addressed in detail in Module 4 (Dose-Response Assessment).
- Chronic inflammation and inflammation-related MOAs should be added, either as a separate module, or as a distinct part of Module 7 (Immunotoxicity). Elucidation of the role of inflammasomes (especially the NLRP3 inflammasome) in many exposure-related diseases has revolutionized biological understanding in recent years, and this should be reflected in biologically based and biologically motivated toxicity assessment and risk assessment.
- Bayesian networks, causal biological network models, and systems biology methods and models should be added to Module 4.
- Ensemble methods other than model averaging (e.g., individual conditional expectation plots) should be added to Module 4.

DO NOT CITE OR QUOTE.

***Dr. Thomas Parkerton***

**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.

RESPONSE: EPA's proposed modular approach is a sensible way to tackle the issue of human health risk assessment. The modular approach will allow each module to be reviewed and updated as needed in a more rapid fashion. However, it is unclear how the proposed initiative effectively contributes to the Administrator's goal of reducing and eliminating animal testing. It is recommended that EPA consider how the consolidated guidelines can be developed and the modular elements of the guide structured and prioritized to address this key priority.

In EPA's Charge to the SAB on the Consolidated Guideline, it is stated that as this initiative proceeds, regular consultations with the SAB is envisioned to ensure a robust framework is developed to support EPA's use of the best available science in its risk assessments. However, given the extent of effort that is planned, I question if SAB advice to EPA for the Consolidated Guideline may be better served through the establishment of a dedicated SAB subpanel rather than the Chartered SAB. A key advantage of this alternate approach for SAB engagement is that a broader array of subject matter experts covering the technical aspects of both common and endpoint specific modules could be assembled from different sectors to offer timely expert input to EPA on this ambitious endeavor. Relevant experts from the Chartered SAB could be included on this subpanel to facilitate dialogue with the broader Chartered SAB members as needed.

(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.

RESPONSE: It is suggested that module 1 include non-testing approaches, like Threshold of Toxicological Concern (TTC), for use as first step to determine the need for more in depth hazard evaluation. Additionally, for this module, how can hypothesis-based prioritization be employed to logically focus the need for more detailed assessment? EPA should also consider describing best practices to help improve the replicability and transparency of hazard related research based on the recent National Academies report<sup>1</sup> and the Center for Open Science platform to publish experimental protocols a priori; share data, materials, or code; and increase collaboration between investigators<sup>2</sup>

For modules 2 and 3, it is recommended that EPA incorporate state of science approaches for data collection, quality scoring, systematic review, weight of the evidence analysis and mode of action assessment. A framework for deciding when New Approach Methods (NAMs) are deemed reliable to

---

<sup>1</sup> Committee on Science, Engineering, Medicine, and Public Policy; Policy and Global Affairs; National Academies of Sciences, Engineering, and Medicine National Academies of Sciences, Engineering, and Medicine 2019. Reproducibility and Replicability in Science. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25303>

<sup>2</sup> Center for Open Science. <https://www.cos.io/>

DO NOT CITE OR QUOTE.

include in WoE evaluation would be valuable to incorporate or provide as a separate module. Module 2 should also cover reporting and analysis of uncertainties in toxicity test data as well as uncertainty and confounding factors in epidemiology studies. EPA may also want to consider additional common modules on the identification and analysis of subpopulations (as assumptions about population susceptibility are often applied) as well as hazard communication.

It is suggested that Module 4 be divided into threshold and non-threshold dose-response models. Presumably, threshold models would cover the majority of endpoints. Focus should be on the process and the methodological considerations that guide dose response assessment and how additional, targeted, fit-for-purpose dose-response data can reduce uncertainty in risk assessment.

(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.

RESPONSE: It is important to clarify the purpose for these modules, i.e. how to interpret data generated from studies focusing on these endpoints or identify how risk assessment is done for these endpoints. If the later, it seems redundant with the dose response module. In the former, a key issue will be how are NAMs to be incorporated? Further, as NAMs are rapidly evolving, how will the guidance be practically updated.

For the endpoint specific modules it is suggested to consider the use of a decision tree or flow chart similar to the one found in OECD TG 150. The OECD TG 150 discusses the use of in vitro assays to detect potential endocrine disruption. In this guidance, there are decision trees describing the potential interpretations of the in-vitro tests and then what next test the researcher should consider and help make the connection between mechanistic, in-vitro and in-vivo data.

(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.

See response to charge question (1). It is recommended that priorities be guided by the overarching goal of reducing and eliminating animal testing.

*Dr. Tara Sabo-Attwood*

### *Consolidated Human Toxicity Assessment Guideline*

#### **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.

The modular approach is appropriate and working through modules seems like an effective way to prioritize and revise the workflow. If the end game here is risk/safety assessment then exposure assessment seems to be missing as a stand-alone module.

(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.

Vulnerable populations will need to be clearly defined across the modules as there are multiple variables that contribute to susceptibility that span molecular to social science contributions.

(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.

I recognize the importance of the immune system in assessing toxicity and support the addition of immunotoxicity to the endpoint specific module group. However, sub-modules for immunotox and the other endpoints would be helpful to better define whether the focus here is on the mechanism of action or some other 'endpoint' (i.e. inflammation, autoimmune, infection susceptibility). Note that inflammation is a process that can lead to cancer or other endpoints, and these will have to be somewhat detangled. Also, endocrine seems missing as an endpoint.

(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.

The mapped timeline and prioritization seems reasonable.

(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

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

- Methods that would harmonize the evaluation of dose-response for cancer and noncancer effects.

I would prioritize low-dose extrapolation approaches.

DO NOT CITE OR QUOTE.

***Dr. Mara Seeley***

**Charge Questions: Human Toxicity Assessment Guideline**

1. *Proposed modular approach*

The proposed approach seems reasonable

2. *Scientific adequacy, completeness, organization and other relevant considerations regarding EPA's list of proposed "common element modules"*

The list seems adequate, complete and well organized

3. *Scientific adequacy, completeness, organization and other relevant considerations regarding EPA's "endpoint-specific modules"*

Key endpoints, which are common critical effects for chemicals in EPA's IRIS database, are not included, e.g., hepatotoxicity and renal toxicity

4. *What modules should EPA work on first and why*

EPA should work on the Common Element Modules first, as it seems these modules would lay the foundation for understanding and interpreting the information in the Endpoint-Specific Modules. Within the Common Element Modules, Module 4 should be worked on first, as the information included in this module seems like it would be most likely to advance the state-of-the-art for conducting risk assessments.

5. *Prioritization of issues*

Methods to harmonize d/r evaluation for cancer/noncancer, and use of various dose-response modeling approaches would be higher priority (in that order).

DO NOT CITE OR QUOTE.

*Dr. Kimberly White*

**Charge questions for the SAB consultation on EPA activities to re-examine and consolidate EPA's Human Toxicity Assessment Guideline**

**1. Question: 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.**

Answer: I am encouraged that EPA has taken into consideration the 2019 feedback from the SAB and the numerous public comments in order to develop a more thoughtful approach to updating existing human health toxicity related guidelines. The agency has indicated that it intends to complete the design of the Consolidated Guideline and prioritize the modules to be developed in December 2020 and then it will initiate the development of the modules in January 2021. The Agency indicates that the Consolidated Guideline will focus only on hazard characterization and dose-response assessment. However, the Agency should include information regarding any future plans for addressing exposure assessment or risk characterization and how the plans for this Consolidated Guideline will be used along with those other elements of the risk assessment process. I would also encourage the Agency to include a list of all the existing Agency guidance documents that will be revised, updated or incorporated as part of this Consolidated Guideline, and update figure 1 to include the opportunities for public comment and peer review (in addition to the SAB consultations) associated with each phase of the process.

**2. Question: 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.**

Answer: The proposed "common element modules" appear to be reasonable starting points for development of various aspects of the Consolidated Guidelines. Below are some suggested recommendations for consideration on some of the identified modules.

- Module 1 Planning and Scoping a Human Toxicity Assessment – While the module description includes concepts like "fit for purpose" and problem formulation it should also include discussion of the application of the Consolidated Guidelines for various program office use. The program offices currently may be performing elements of risk assessment for varying regulatory purposes and that information should be discussed in this module. This module should also discuss where there are currently differences in program office approaches, and how the Consolidated Guidelines will seek to provide a unified or singular Agency approach.

DO NOT CITE OR QUOTE.

- Module 2 Identifying and Evaluating Toxicity Studies – Suggest this module be renamed “Identifying and Evaluating Scientific Data” and that it include three sub-categories or modules focused on animal toxicity data; epidemiology data; and mechanistic data. Each one of these modules should discuss the (1) literature search process associated with the identification of primary peer reviewed publications, peer reviewed reviews or meta-analysis of primary data, and grey literature and (2) the data quality assessment (e.g. quantitative or qualitative assessment) and how the data quality information will be used for interpretation within and between data streams.
- Module 3 Hazard Identification – This module should include case study examples of how data could/will be integrated across data streams for the purpose of hazard identification, including how to integrate positive, negative and null data points. The module should also include examples of adverse outcome pathways that the Agency will consider relying on and the level of data and confidence for plausible mode of action frameworks with relevant case examples.
- Module 4 Dose-Response Assessment – In addition to the areas included, this module should include a review and discussion of application of uncertainty factors.

**3. Question: 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.**

Answer: Modules 5 – 11 – Generally, these appear to be the appropriate endpoints for focus. The agency should consider focusing on endpoints identified in modules 5 – 10. The agency should include discussion or subcategories in Module 5. Developmental Toxicity related to maternal toxicity, mortality, structural abnormalities, alterations to growth and functional impairment. Module 6. Reproductive Toxicity should also include sub-categories for female fertility and male fertility toxicity endpoints. Additionally, the agency should also consider including an endpoint for systemic toxicity (e.g. liver, kidney) and separately solicit public and peer review input for other endpoints of focus.

**4. Question: 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.**

Answer: EPA has identified a number of modules for inclusion in the Consolidated Guideline. The agency should focus on development of Modules 1 -4 as they will provide the foundation for the overall process. For the endpoint specific modules, all of these items are important but if the agency is unable to do them in parallel, suggest the agency evaluate upcoming regulatory decisions where updated endpoint specific guidance would be most beneficial.

**5. Question: EPA received many comments from SAB members on dose-response issues.**

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

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

Answer: EPA has identified several issues above that would be important to address in the development of the Consolidated Guidelines. The use and application of dose-response modeling approaches and dose-response extrapolation including case study examples of how data can be used to inform the dose-response assessment should be priority areas of focus. Also, as an additional area of focus is understanding impacts of endogenous production in determining human health risk given that the agency may be currently evaluating substances that are produced endogenously.

DO NOT CITE OR QUOTE.

***Dr. Richard Williams***

In the summary of Recommendations, I see " • Reconsider the linear-no-threshold (LNT) approach as a default for low-dose extrapolation." Since I haven't been involved in this, I am just wondering "reconsider" is sufficiently strong. From research I have done with evolutionary biologists in the last several years, I have become convinced that there is a threshold for most chemicals and certainly one for ionizing radiation. In addition, should there be some mention of hormetic dose-response curves. A quick Google search reveals 3500 articles using "hormesis" or "hormetic." I know that the Department of Energy is looking into this as well. This may all be written up in a report somewhere or on the table for a future panel.

Second, it seems like there should be some emphasis on characterizing risks that can be used when an economic Regulatory Impact Analysis is needed. Three kinds of analyses are not helpful, safety assessments, risk assessments that only characterize risks to highly exposed or highly sensitive subpopulations or risk assessments that are conservative (I did see something about reconsidering the EPA position "never to knowingly underestimate risk.") This is also important when there are likely risk/risk or health/health trade-offs.

## **Comments from SAB Chemical Assessment Advisory Committee Members**

*Dr. Richard Belzer*

### **Preliminary Comments on SAB/CAAC Review of Proposed *Consolidated Human Toxicity Assessment Guideline*<sup>3</sup>**

June 19, 2020

**(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.**

A modular approach is sensible for establishing common rules and procedures with which all toxicity assessments conform. Only where there is a substantial, science-based distinction should toxicity assessments differ.

This change could have salutary effects throughout the risk analysis ecosystem if it is faithfully implemented. First, it would have beneficial spillover effects on USEPA's Quality System.<sup>4</sup> Second, it would reinvigorate the Agency's commitment to the information quality principles of transparency (through reproducibility), utility, integrity, and objectivity.<sup>5</sup> Third, it would improve the quality of Agency peer review so that time is not wasted on the perfunctory review of common elements.<sup>6</sup>

A key weakness of both the current and proposed framework is the extent to which toxicity assessments are de facto regulatory standards. Were this not so, few if any toxicity assessments would be controversial. There surely are scientific controversies over which scientists are quite prepared to wage war, but their intramural disputes are not what drives public controversy.<sup>7</sup> Rather, controversy arises because Agency toxicity assessments tend to predetermine regulatory outcomes. A Consolidated Guideline that fails to put an end to this is highly unlikely to succeed. An approach that translates scientific knowledge directly into estimates of benefits and costs may be a way to accomplish this, for at least that way the consequences of de facto regulation would be transparent, but that is not the direction implied by the proposed Consolidated Guideline.

---

<sup>3</sup> The charge to the committee is presented in U.S. EPA Science Advisory Board (2020).

<sup>4</sup> U.S. Environmental Protection Agency (2020b).

<sup>5</sup> Office of Management and Budget (2002), U.S. Environmental Protection Agency (2002).

<sup>6</sup> U.S. Environmental Protection Agency (2015).

<sup>7</sup> Several prominent individuals have been credited with the aphorism that academic politics are so vicious precisely because the stakes are so small.

DO NOT CITE OR QUOTE.

**(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.**

Proposed Module 1 (“Planning and Scoping a Human Toxicity Assessment”) appears to include most of the expected “key elements.” The Agency should clearly define all “key elements,” and adherence to these definitions must be both required and objectively refutable by third parties. Obviously, “key elements” that are not objectively defined, or are subjectively interpreted, would destroy a Consolidated Human Toxicity Guideline’s scientific foundation.

Some “key concepts” identified in Module 1 (e.g., “cumulative risk”) may be difficult to objectively define. Historically, cumulative risk has been constrained to co-occurring or coincident human health risks.<sup>8</sup> This scope is inherently incomplete. They systematically exclude indirect risks to human health and welfare, risks beyond the human health domain, and substitution risks.<sup>9</sup>

The rule in benefit-cost analysis is that every benefit and every cost should be counted, and each benefit and cost must be counted exactly once. This goal is unachievable in practice because not all benefits and costs can be quantified, and not all quantified benefits and costs can be monetized. But technical limitations do not justify abandoning the goal. Rather, they argue for concerted effort to better identify, quantify, and monetize what’s missing. It is unhelpful to devote resources toward adding yet another significant figure in the estimation of a well-understood benefit or cost while important benefits and costs remain unmonetized.

Economists may be especially familiar with the so-called “drunk and lamp post problem,” but it applies to all scientific disciplines:

A drunk loses his keys and is looking for them under a lamp post. A policeman comes over and asks what he’s doing.

“I’m looking for my keys,” he says.

“Where did you lose them?” the policeman asks.

---

<sup>8</sup> U.S. Environmental Protection Agency (2019) includes three definitions for “cumulative risk” and numerous related definitions. Each is context-dependent and domain-limited. Choosing which of these alternative versions of “cumulative risk” is likely to be driven by policy rather than science.

<sup>9</sup> U.S. Environmental Protection Agency (2019) does not define “substitution risk.” However, it is an essential concept in benefits assessment.

DO NOT CITE OR QUOTE.

“I lost them over there.”

The policeman looks puzzled. “Then why are you looking for them over here?”

“Because the light is so much better here.”<sup>10</sup>

USEPA should resist the temptation to look for its “keys” underneath the lamp post. Rather, the Agency should be guided by a rigorous evaluation of the value of information. Which has more social value: (1) marginal improvements in an existing endpoint-specific module, or (2) creating a module where none currently exists? For an existing endpoint-specific module, which has more social value: (1a) making marginal improvements within the existing structure, or (1b) overcoming the deadweight loss that has accumulated over decades of relentless drift in upward bias, excess precision, absent or understated characterization of uncertainty, and unsupported causality assumptions? It’s been said that “success consists of going from failure to failure without loss of enthusiasm.”<sup>11</sup> This is not a healthy path for risk assessment.

Some “key concepts” listed in Module 1 (e.g., “vulnerable populations”) may not be capable of objective definition. U.S. Environmental Protection Agency (2019) borrows definitions of “vulnerable population” from NLM, the Centers for Disease Control, and the Resilience and Adaptation in New England (RAINE) Glossary. All are subjective. Indeed, any difference within the population in toxicological hazard or exposure could be interpreted as a manifestation of “vulnerability.” Because the typical purpose of identifying “vulnerable populations” is to give them special (i.e., subjective) weight, it is hard to imagine how this concept could ever be defined objectively.

Module 1 should not include any purportedly “key elements” that are subjectively defined. If they are included, then the Common Element Module will not be scientific. Moreover, subjectivity in Module 1 invites subjectivity in Module 2 (“Identifying and Evaluating Toxicity Studies”), Module 3 (“Hazard Identification”), Module 4 (“Dose-Response Assessment”), and all of the Endpoint Specific Modules.

One of the “key concepts” listed in Proposed Module 1 is “fit for purpose” (elsewhere “fitness for purpose”).<sup>12</sup> A key purpose of risk assessment is the estimation of benefits for regulatory standard-setting, health-based guidance, and similar activities. But USEPA risk assessment is generally not fit for benefits assessment. This purpose requires expected value risk estimates, and USEPA risk assessment is neither designed nor implemented to obtain expected values.<sup>13</sup> Therefore, Module 1 of the Consolidated Human

---

<sup>10</sup> A representative version of the joke is related by Leaver (2014).

<sup>11</sup> Freedman (2010a), excerpted at Freedman (2010b), who attributes the aphorism to Winston Churchill.

<sup>12</sup> Office of Management and Budget (2019), U.S. Environmental Protection Agency (2020a).

<sup>13</sup> Expected values are required whenever the entire risk distribution is not objectively characterized. It has long been Agency staff policy to overestimate risk. See U.S. EPA Office of the Science Advisor (2004), p. 13: “[S]ince EPA is a health and environmental protective agency, EPA’s policy is that risk assessments should not knowingly

DO NOT CITE OR QUOTE.

Toxicity Guideline must include provisions sufficient to ensure that all modules strive for (and not eschew) expected value estimates of risk.

Adherence to information quality principles<sup>14</sup> is not included in the list of “key elements.” It should be. These principles apply to all influential information, and it should go without saying that Agency risk assessments are “influential.”<sup>15</sup> In addition, every Endpoint-Specific Module will have information quality concerns, and applicable information quality guidelines are neutral with respect to them all. USEPA must ensure that every module adheres to applicable information quality guidelines and includes effective procedures for pre-dissemination review and error correction.

Data quality is mentioned in proposed Module 4 (“Dose-Response Assessment”), but this is likely to be too late and too selective. The quality issues related to toxicological data are not unique; they exist in Module 2 (“Identifying and Evaluating Toxicity Studies”), Module 3 (“Hazard Identification”), and in every proposed Endpoint-Specific Module. It would be much better to incorporate information quality concerns in Module 1 so that all subsequent modules (and all implementations) are treated the same.

Finally, a key attribute absent from Proposed Module 1 is humility. Whether by self-selection, training, or experience, many scientists (and perhaps especially risk assessors) suffer a severe deficiency of this personal quality. Risk estimates – remarkably, including low-dose extrapolations orders of magnitude outside the boundaries of available data and across species, where scientific uncertainty and the temptations of mathematical delusion are the greatest – are routinely reported as if they are reliable, if not actually true. More than three decades ago, USEPA sensibly characterized low-dose cancer risk estimates with the caveat that the true risk could be as low as zero.<sup>16</sup> Long ago, the Agency abandoned this without scientific justification<sup>17</sup> and ratified a policy preference in favor of upward bias.<sup>18</sup>

It's worth discussing how to imbue Module 1 with a spirit of humility, for there is no obvious mechanism or internal regulatory procedure through which it can be ensured. Nonetheless, humility is likely to be a genuinely “key element.” Absent humility about the limits of scientific knowledge and the boundary between science and policy, Agency risk

---

underestimate or grossly overestimate risks. This policy position prompts risk assessments to take a more ‘protective’ stance given the underlying uncertainty with the risk estimates generated. Another framing policy position is that EPA will examine and report on the upper end of a range of risks or exposures when we are not very certain about where the particular risk lies.”

<sup>14</sup> Office of Management and Budget (2002), U.S. Environmental Protection Agency (2002).

<sup>15</sup> Office of Management and Budget (2002), p. 8460: “‘Influential’, when used in the phrase ‘influential scientific, financial, or statistical information’, means that the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions.”

<sup>16</sup> U.S. Environmental Protection Agency (1986). This caveat was abandoned when cancer risk assessments were incorporated as inputs to Agency benefits assessments.

<sup>17</sup> U.S. Environmental Protection Agency (1996), U.S. Environmental Protection Agency (2005).

<sup>18</sup> See footnote 13.

DO NOT CITE OR QUOTE.

assessment practice will continue to be plagued by controversy, conflict, and limited productivity – no matter how (or even if) the Agency implements its proposed Consolidated Human Toxicity Guidelines.

**(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.**

Endpoint-specific modules (Modules 5–11 in Table 1) should be selected and prioritized based on their relative practical utility for decision-making grounded in USEPA’s statutory authority. That means, as a threshold matter, they must be comprehensible to the public and susceptible to valuation. Endpoints that are not comprehensible to the public or susceptible to valuation cannot be used in benefits assessment. Without benefits assessment, decision-makers cannot ascertain or rank their relative importance. Among those endpoints that nonexperts can comprehend and value, preference should be given to endpoints with higher valuations.

Of course, risk assessors often have their own professional and personal preferences. For example, cancer risk assessors might reasonably believe that Module 8 (“Carcinogenicity”) is most important, whereas neurotoxicity risk assessors could think that Module 10 (“Neurotoxicity”) belongs at the top. Choosing among these modules based on the relative strength of preference among risk assessors makes the outcome dependent on which risk assessors are polled and who does the polling.

If instead endpoint-specific modules are ranked and selected based on their relative practical utility, their value to the public (which, let us remember, is supposed to guide Agency decision-making) can be taken into account.

This approach helps focus attention on research needs that could be both simultaneously hidden and urgent. Suppose risk assessors can agree that a particular endpoint is crucial for estimating human health risk, but currently it is not comprehensible to the public or susceptible to valuation. To aid rational regulatory decision-making, more must be learned (and quickly) to overcome these problems. Only then can Agency decision-makers properly elevate this endpoint to the stature it deserves in the risk management agenda.<sup>19</sup>

**(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**

---

<sup>19</sup> It is certainly possible to use political pressure to elevate a publicly incomprehensible endpoint to the top of the regulatory agenda. However, risk assessors should be wary of employing such tactics lest they lose their credibility as scientists.

DO NOT CITE OR QUOTE.

**may include commentary on the extent of update needed for each of the existing guidelines.**

As noted above in my response to Question 3, the only *scientific* way to set priorities among endpoint-specific modules is based on their relative practical utility. Note that practical utility is just a synonym for public health benefits. To allocate scarce Agency resources any other way means achieving fewer and less valuable reductions in human health risk.

**(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:**

*(a) Use of various dose-response modeling approaches (e.g., model averaging);*

Model averaging can be a valuable way to reduce bias, but it requires that the models being “averaged” (i.e., weighted) be independent. If they are not independent, then their biases are correlated; and if their biases are correlated, averaging them may increase total bias.

Model averaging (i.e., weighting) almost certainly cannot be done objectively. That means someone has to choose the weights, and all weights are subjective. Should it be a risk assessor or a policy official? If risk assessors are scientists, they have no business exercising policy judgment (even if they’d like to do so). If it is a matter of policy judgment, then the authority and responsibility belongs to duly appointed Agency officials (even if they’d prefer *not* to be responsible for their choices).

My sense is that a better approach, and one less fraught with peril to the risk analysis profession, is to report all available models along with the available evidence for and against each. Similar reporting schemes elsewhere have faltered because of biased reporting. One way to reduce biased reporting is to establish a peer review system in which conflicts of interest (fully reported) are expressly encouraged, with the objective being to secure agreement among competing interests as to how evidence is presented.<sup>20</sup>

*(b) Further consideration of the use of low-dose extrapolation approaches;*

---

<sup>20</sup> The conventional peer review model see, e.g., The National Academies (2003), Office of Management and Budget (2005), U.S. Environmental Protection Agency (2015) treats conflicts of interest as liabilities rather than assets. But those with conflicts of interest tend to be the most motivated peer reviewers; as long as they are not anonymous, they can responsibly hold their intellectual “foes” to the most rigorous scientific standards. When each “side” does this to the other, the quality of everyone’s science improves.

DO NOT CITE OR QUOTE.

Low-dose extrapolation (more generally, extrapolation outside the bounds of available data) is always scientifically perilous. It has been done so often and for so long in human health risk assessment that we are desensitized to the peril.

Recent experience with SARS-CoV-2 (“COVID-19”) has shown just how damaging such extrapolation can be. On March 16, 2020, the Imperial College London (ICL) COVID-19 Response Team predicted that an “unmitigated epidemic” “would result in 2.2 million U.S. fatalities and 510,000 U.K fatalities, “not accounting for the potential negative effects of health systems being overwhelmed on mortality.” Almost all of these fatalities would occur before August 20, with a peak daily death rate of about 17 per 100,000 forecast for about June 20.<sup>21</sup>

The data tell a very different, and much less dramatic, story. As of June 16, approximately 112,000 U.S. deaths associated with COVID-19 have been reported (5% of the ICL forecast); the 3-day moving average number of confirmed cases is increasing in only 13 states; and the daily death rate is very low.<sup>22</sup>

Experience with COVID-19 is different for many reasons, but the reason most relevant here is that the predictions ICL made beyond the boundary of the data were testable after the fact and USEPA low-dose risk assessments generally are not. Based on this experience, however, the Agency should reconsider how much confidence in low-dose extrapolation is scientifically justified; do more to accurately characterize uncertainty on key margins, including causality; and develop a practice of scientific humility.<sup>23</sup>

*(c) Additional consideration of endogenous production of environmental contaminants; and*

The endogenous production of potentially toxic substances (e.g., formaldehyde) is an excellent example of the more general problem I discussed in my response to Question 2. When “cumulative risks” are purportedly taken into account, the domain is always Gerrymandered. Not all risks are included, including some chemical risks. This bias undermines the scientific credibility and integrity of cumulative risk accounting, as well as benefits assessment that relies on its outputs. The only distinguishing feature raised by the endogenous production of environmental contaminants, and their exclusion from (cumulative) risk assessment, is irony.

---

<sup>21</sup> Ferguson, et al. (2020), p. 7 [Figure 1]. They also estimated 1.1–1.2 million U.S. fatalities “even if all patients were able to be treated” (p. 16).

<sup>22</sup> Johns Hopkins University Coronavirus Resource Center (2020). It’s likely that some deaths caused by COVID-19 are not included. It’s certain that many deaths attributable to COVID-19 were not caused by COVID-19.

<sup>23</sup> Benefit estimates are not proportional to point estimates of risk. Point estimates, especially at low doses where they are most uncertain, may benefits even if they aren’t upwardly biased. The public is less willing to pay for goods and services that may not be realized, including risk reductions.

DO NOT CITE OR QUOTE.

*(d) Methods that would harmonize the evaluation of dose-response for cancer and noncancer effects.*

There is no justification for making any conceptual distinction between cancer and noncancer dose-response. A biological phenomenon is adverse if and only if an optimally informed person is willing to pay to avoid it. The nature of a risk is relevant only insofar as it affects a health endpoint. The severity of a risk is fully captured by risk magnitude, and the value of risk avoidance or prevention is determined by willingness-to-pay (WTP).<sup>24</sup> Thus, the purpose of risk assessment is to estimate *first* the loss imposed by a risk on human welfare, and estimate *second* the welfare gain expected to be realized by reducing it. The purpose is never to derive a “worst case,” or some variant thereof, nor is it to divine an exposure which is “safe.” Those objectives are inherently nonscientific.<sup>25</sup>

A major problem remains because WTP depends on the quality of lay risk comprehension. Some risks (e.g., premature mortality, financial harm) are readily comprehended by nonexperts, but many (maybe even most) others are not. There surely are phenomena (some biological) that scientists and risk assessors are able to understand sufficiently well to comprehend them as adverse. But for a republican government in a democratic society, the authority for making risk-reduction decisions cannot be delegated to an unelected scientific clerisy. It is our job as scientists and risk assessors to develop ways to translate complex and presumably risky phenomena into popularly understandable forms that enable nonexperts to credibly value reduction or prevention. And we must do so without embedding *our* risk preferences along the way.

With this in mind, it is my view that USEPA should focus the development of endpoint-specific modules where nonexperts already have sufficient knowledge and insight to value risk reduction. The Agency should postpone the development of modules where this is lacking until technologies have been developed, tested, and validated that effectively and objectively translate complex endpoints into language nonexperts can comprehend. This task is tractable, not impossible; rather, we have to date devoted virtually no effort to solving it. We can make substantial progress by paying more attention to it.

## References

Ferguson NM, Daniel Laydon, Gemma Nedjati-Gilani, Natsuko Imai, Kylie Ainslie, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Zulma Cucunubá, Gina Cuomo-Dannenburg, Amy Dighe, Ilaria Dorigatti, Han Fu, Katy Gaythorpe, Will Green, Arran

---

<sup>24</sup> Willingness-to-pay (WTP) is the maximum price at which a person will voluntarily engage in an exchange. This is the foundation of welfare economics. Benefit-cost analysis (and USEPA’s practice of Regulatory Impact Analysis) is built on this concept. It is over 150 years old.

<sup>25</sup> “Safety” has no scientific definition. It is inherently controlled by policy preferences, on which members of the public hold diverse but equally legitimate views. Thus, the entire safety assessment edifice is unsustainable as scientific risk assessment.

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

Hamlet, Wes Hinsley, Lucy C Okell, Sabine van Elsland, Hayley Thompson, Robert Verity, Erik Volz, Haowei Wang, Yuanrong Wang, Patrick GT Walker, Caroline Walters, Peter Winskill, Charles Whittaker, Christl A Donnelly, Steven Riley, Ghani AC. 2020. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. London UK: Imperial College COVID-19 Response Team.

Freedman DH. 2010a. Wrong: Why Experts Keep Failing Us -- and How to Know When Not to Trust Them. New York NY: Hachette Book Group of Little, Brown.

Freedman DH. 2010b. "Wrong". New York Times (New York NY) June 10.

Johns Hopkins University Coronavirus Resource Center. 2020. Cumulative Cases Available: <https://coronavirus.jhu.edu/data/cumulative-cases> [accessed June 16, 2020].

Leaver S. 2014. The Drunk Neo-classical Economist and the Lamp Post. The misBehaving Economist. Vol. 2020.

Office of Management and Budget. 2002. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies; Notice; Republication. Federal Register 67:8452-8460.

Office of Management and Budget. 2005. Final Information Quality Bulletin for Peer Review. Federal Register 70:2664-2667.

Office of Management and Budget. 2019. Improving Implementation of the Information Quality Act. M-19-15. Washington DC: OMB.

The National Academies. 2003. Policy on Committee Composition and Balance and Conflict of Interest. Washington DC: National Academies Press

U.S. Environmental Protection Agency. 1986. Guidelines for Carcinogen Risk Assessment. Federal Register 51:33992-34003.

U.S. Environmental Protection Agency. 1996. Proposed Guidelines for Carcinogen Risk Assessment. Federal Register 61:17960-18011.

U.S. Environmental Protection Agency. 2002. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency EPA/260R-02-008. Washington DC: USEPA.

U.S. Environmental Protection Agency. 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Washington DC: EPA Risk Assessment Forum.

U.S. Environmental Protection Agency. 2015. Peer Review Handbook. EPA/100/B-15/001. Part 4th. Washington DC: USEPA/Science and Technology Policy Council.

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

U.S. Environmental Protection Agency. 2019. Terms & Acronyms. Available: [https://iaspub.epa.gov/sor\\_internet/registry/termreg/searchandretrieve/termsandacronyms/search.do](https://iaspub.epa.gov/sor_internet/registry/termreg/searchandretrieve/termsandacronyms/search.do) [accessed June 16, 2020].

U.S. Environmental Protection Agency. 2020a. Guidelines for Preparing Economic Analyses (SAB Review Draft). Washington DC: USEPA/NCEE.

U.S. Environmental Protection Agency. 2020b. Agency-wide Quality System Documents. Available: <https://www.epa.gov/quality/agency-wide-quality-system-documents> [accessed June 16, 2020].

U.S. EPA Office of the Science Advisor. 2004. An Examination of EPA Risk Assessment Principles and Practices; Staff Paper EPA/100/B-04/001. Washington DC: USEPA Risk Assessment Task Force.

U.S. EPA Science Advisory Board. 2020. Charge to the SAB on the Consolidated Human Toxicity Assessment Guideline. Washington DC: USEPA/SAB.

**Dr. Tiffany Bredfeldt**

### **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<sup>26</sup>. 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<sup>27</sup>, 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<sup>28</sup> in case- or location-specific circumstances, support risk assessment.<sup>29</sup>

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.<sup>30</sup> 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 approaches for characterization

---

<sup>26</sup> <https://www.epa.gov/risk/risk-assessment-guidelines#tab-1>

<sup>27</sup> [https://yosemite.epa.gov/sab/sabproduct.nsf/357DC7E5C59BA9AD85258438005BA457/\\$File/EPA-SAB-19-003+.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/357DC7E5C59BA9AD85258438005BA457/$File/EPA-SAB-19-003+.pdf)

<sup>28</sup> See *Guidelines for Human Exposure Assessment* <https://www.epa.gov/risk/guidelines-human-exposure-assessment>

<sup>29</sup> 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>

<sup>30</sup> <https://www.epa.gov/expobox/about-exposure-factors-handbook>

DO NOT CITE OR QUOTE.

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

DO NOT CITE OR QUOTE.

members would recommend EPA consider? This can include comments on Figure 1, Process/Timeline.

- a. *The choice to consolidate guidelines is one for which EPA can be applauded. This should improve efficiency and transparency of approaches. The decision to utilize a modular approach to the consolidated guidelines is also favorable as it should be a more focused and efficient way to tackle the challenge of consolidating the guidelines.*
- b. *The proposed approach is reasonable and appears to be a very logical path forward. The process as shown in Figure 1 is also very logical, particularly in prioritization of modules to be developed first. The timeline appears to be ambitious, but I do believe it to be achievable.*

(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.

- a. *The organization and adequacy of the common elements modules is generally well thought out. It seems that the order and prioritization of the first four*

DO NOT CITE OR QUOTE.

*modules is defensible and covers key elements of systematic review and WOE integration in a chemical-specific assessment.*

- b. In the common elements, EPA should consider adding guidelines for the evaluation of human studies as they are critical to many assessments. The intent of such guidelines would be to add clarity and transparency for how EPA uses human studies, particularly epidemiological studies. Epidemiological studies are mentioned as a part of Module 2, but so critical are these study types to assessments, they deserve stand alone guidance.*
- c. The guideline modules list NAMs as a part of Module 2. However, given that these are evolving methods that do not have guidelines as yet it may be important to enable them to be represented in a major sub-section of Module 2 or have a separate standalone document to accompany these guidelines, a likely outcome.*
- d. Alternatively, NAMs or high throughput screening and genomic POD's may be better suited to be placed in an endpoint-specific module.*

(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.

6/24/20 Preliminary comments from individual members of the Chartered SAB and SAB Chemical Assessment Advisory Committee. These comments do not represent consensus SAB advice or EPA policy.

DO NOT CITE OR QUOTE.

- a. *The subsections are well thought out and encompass many traditional endpoints.*
- b. *With the adoption of new methods, these subsections may need to be expanded to include the following: epigenetics, HTP screening, genomic PODs or aberrant gene expression changes that serve as POD.*
- c. *DART studies should cover endocrine disruption, or it should be a standalone module.*

(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.

- a. *The first four modules serve as the core for the guidelines and should be considered first.*
- b. *With the paradigm shift to using NAMs, guidelines should cover these areas early in the process so that they may be modified as additional input is given from public and scientific communities over time.*

(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);

DO NOT CITE OR QUOTE.

- 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.

- a. *I see further consideration of the use of low-dose extrapolation approaches and methods that harmonize the evaluation of dose-response for cancer and noncancer effects as the top highest priorities of those listed above.*
- b. *Various dose-response modeling approaches is important, but of higher importance is how we deal with low-dose or biologically relevant doses.*
- c. *The additional consideration of endogenous production of environmental contaminants is important, but represents a rarer event and, as such, should be the lowest priority of the above list.*

**Dr. Karen Chou**

## **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<sup>31</sup>. 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<sup>32</sup>, 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<sup>33</sup> in case- or location-specific circumstances, support risk assessment.<sup>34</sup>

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.<sup>35</sup> 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

---

<sup>31</sup> <https://www.epa.gov/risk/risk-assessment-guidelines#tab-1>

<sup>32</sup> [https://yosemite.epa.gov/sab/sabproduct.nsf/357DC7E5C59BA9AD85258438005BA457/\\$File/EPA-SAB-19-003+.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/357DC7E5C59BA9AD85258438005BA457/$File/EPA-SAB-19-003+.pdf)

<sup>33</sup> See *Guidelines for Human Exposure Assessment* <https://www.epa.gov/risk/guidelines-human-exposure-assessment>

<sup>34</sup> 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>

<sup>35</sup> <https://www.epa.gov/expobox/about-exposure-factors-handbook>

DO NOT CITE OR QUOTE.

are common across endpoints and consideration of state-of-the-science 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.

DO NOT CITE OR QUOTE.

The module approach is carefully considered and formed. It is very helpful conceptually when dealing with such a complex issue. There is no further comment currently on the 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.

Many of the methods applied in NAMs are likely to change the uncertainties in toxicity assessment. The guidance for the application of interspecies and intraspecies extrapolation factors should be reconsidered accordingly. Existing UFs may need to be redefined and new categories of UFs may be added when the endpoints and dose-response relationship are assessed using alternative approaches.

(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.

There is currently no recommendation for any changes.

(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.

Harmonizing guidelines for cancer and noncancer effects should be the priority because extensive amount of knowledge from reliable sources supports the threshold assumption of dose-response relationship of cancer-causing substances. Harmonization of cancer and noncancer assessment approaches would significantly decrease the burden of toxicity testing, reporting, and document review.

(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.
- Model averaging may be applied to minimize model uncertainty. If the current guidelines do not prevent the application of the model averaging approach, there is no need to set it as a priority item.
- Low-dose extrapolation is necessary when results for rare diseases are observed in laboratory studies, because of the limited number of observations. Harmonizing the assumption of dose-response relationship for cancer and noncancer effects may eliminate the use of low-dose extrapolation approach. It is therefore a top within the harmonization effort.
- Biotransformation products from exposure to exogenous substances have always been a major concern in toxicology and risk assessment. This concern is supported by solid toxicological

DO NOT CITE OR QUOTE.

database. If toxicity testing studies will be limited to *in-vitro* or non-mammalian species, this should be set as a top priority when drafting new risk assessment guidelines.

- Incidences of cancer diseases are rare events. Quantitative problems associated with analyzing and modeling rare events data must be solved before the toxicity and risk assessment approaches for cancer and noncancer assessment can be harmonized. This is a top priority within the harmonization effort.

**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.

<p><b>Common Element Modules</b> <i>These proposed modules would address common elements of an assessment that pertain to all health endpoints</i></p>	<p><b>Module 1. Planning and Scoping a Human Toxicity Assessment</b> 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.</p>
	<p><b>Module 2. Identifying and Evaluating Toxicity Studies</b> 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.</p>
	<p><b>Module 3. Hazard Identification</b> 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.</p>
	<p><b>Module 4. Dose-Response Assessment</b> This module will cover a comprehensive set of issues including but not necessarily limited to:</p> <ul style="list-style-type: none"> <li>• Consideration of a unified approach for dose-response assessment;</li> <li>• Absorption, distribution, metabolism, and excretion (ADME) considerations;</li> <li>• Toxicodynamic versus toxicokinetic considerations;</li> <li>• Data quality considerations;</li> </ul>

DO NOT CITE OR QUOTE.

	<ul style="list-style-type: none"> <li>• Types of dose-response data: animal tests; human chamber tests; epidemiological studies; occupational studies; high throughput testing; virtual tissue modeling;</li> <li>• Benchmark dose modeling including choosing a response rate, identifying a point-of-departure (POD) and extrapolation of dose-response to exposures lower than POD;</li> <li>• Deriving a POD, reference value, or margin of exposure;</li> <li>• Probabilistic modeling;</li> <li>• Model averaging;</li> <li>• Characterization of lifestage and population variability and vulnerability;</li> <li>• Physiologically Based Pharmacokinetic (PBPK) and Biologically Based Dose-Response (BBDR) modeling;</li> <li>• 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 <math>\frac{3}{4}</math>-power); and</li> <li>• Cumulative risk considerations.</li> </ul>										
<p><b>Endpoint Specific Modules</b>  <i>These proposed modules would focus on aspects of the hazard characterization and dose-response issues and methods that are specific to that endpoint</i></p>	<table border="1"> <tr> <td data-bbox="605 1018 1101 1087"> <p><b>Module 5. Developmental Toxicity</b></p> </td> <td data-bbox="1101 1018 1427 1738" rowspan="5"> <p>These proposed modules would cover definitions, critical concepts, test systems, data interpretation, and endpoint specific dose-response and exposure assessment considerations as needed.</p> </td> </tr> <tr> <td data-bbox="605 1087 1101 1123"> <p><b>Module 6. Reproductive Toxicity</b></p> </td> </tr> <tr> <td data-bbox="605 1123 1101 1207"> <p><b>Module 7. Immunotoxicity</b>  <i>(no EPA guideline currently exists)</i></p> </td> </tr> <tr> <td data-bbox="605 1207 1101 1249"> <p><b>Module 8. Carcinogenicity</b></p> </td> </tr> <tr> <td data-bbox="605 1249 1101 1438"> <p><b>Module 9. Mutagenicity</b>  <i>(mutagenicity as a mode-of-action would be addressed in both Module 3 – Hazard Identification &amp; Module 4 – Dose-Response Assessment)</i></p> </td> </tr> <tr> <td data-bbox="605 1438 1101 1480"> <p><b>Module 10. Neurotoxicity</b></p> </td> <td></td> </tr> <tr> <td data-bbox="605 1480 1101 1738"> <p><b>Module 11. Other Endpoints?</b>  <i>(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)</i></p> </td> <td></td> </tr> </table>	<p><b>Module 5. Developmental Toxicity</b></p>	<p>These proposed modules would cover definitions, critical concepts, test systems, data interpretation, and endpoint specific dose-response and exposure assessment considerations as needed.</p>	<p><b>Module 6. Reproductive Toxicity</b></p>	<p><b>Module 7. Immunotoxicity</b>  <i>(no EPA guideline currently exists)</i></p>	<p><b>Module 8. Carcinogenicity</b></p>	<p><b>Module 9. Mutagenicity</b>  <i>(mutagenicity as a mode-of-action would be addressed in both Module 3 – Hazard Identification &amp; Module 4 – Dose-Response Assessment)</i></p>	<p><b>Module 10. Neurotoxicity</b></p>		<p><b>Module 11. Other Endpoints?</b>  <i>(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)</i></p>	
<p><b>Module 5. Developmental Toxicity</b></p>	<p>These proposed modules would cover definitions, critical concepts, test systems, data interpretation, and endpoint specific dose-response and exposure assessment considerations as needed.</p>										
<p><b>Module 6. Reproductive Toxicity</b></p>											
<p><b>Module 7. Immunotoxicity</b>  <i>(no EPA guideline currently exists)</i></p>											
<p><b>Module 8. Carcinogenicity</b></p>											
<p><b>Module 9. Mutagenicity</b>  <i>(mutagenicity as a mode-of-action would be addressed in both Module 3 – Hazard Identification &amp; Module 4 – Dose-Response Assessment)</i></p>											
<p><b>Module 10. Neurotoxicity</b></p>											
<p><b>Module 11. Other Endpoints?</b>  <i>(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)</i></p>											
<p><b>Appendix</b></p>	<p><b>Glossary</b>  <i>(update after each module is developed)</i></p>										

**Dr. Harvey Clewell**

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

**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.

*I believe that the proposed modular approach is a significant improvement over the previous approach, which lacked coherence.*

- (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.

*Overall, I believe the list of common element modules is appropriate and includes the key elements of toxicity assessment.*

*Identifying Planning and Scoping (Module 1) as the initial step in Toxicity Assessment is an important step forward compared to much of the previous guidance on human health assessment and continues the progress made in this area by the IRIS program. Part of this step should also be a preliminary evaluation of Mode of Action based on data for similar compounds identified by QSAR and Read-Across analysis. This can now be easily conducted using apps on the EPA and OECD websites.*

*The description of Module 2 (Identifying and Evaluating Toxicity Studies) is consistent with the recent efforts by the IRIS program to implement systematic review of toxicity studies.*

*I am somewhat concerned, however, that the description of Module 3 (Hazard Identification) does not provide a clear statement of the criticality of mode of action (MoA) analysis in the toxicity assessment process. Evidence integration has not typically been performed well in EPA risk assessments. In particular, there has been a tendency to focus hazard identification on the selection of the critical studies that should go forward for dose-response assessment based primarily on a comparison of the associated points of departure, and only apply MoA considerations in the. Despite the emphasis of the current cancer guidelines on the use of MoA evaluation to direct the risk assessment*

DO NOT CITE OR QUOTE.

*approach, recent assessments have generally failed to adequately incorporate MoA information. There also appears to be an unwillingness to try to apply some form of systematic review to evaluate mechanistic studies, rather than cherry-picking studies to support going forward with a default approach in the Dose-Response Assessment. This reluctance is certainly driven in part by the potential difficulty of the process, which would involve the review of a wide variety of data, only part of which would be studies conducted on the chemical being assessed. However, the recent inability of the agency to gain NAS acceptance of its toxicity assessments is to a large extent due to the failure to adequately implement a MoA-directed risk assessment approach. In the case of the dioxin cancer assessment, the agency repeatedly resisted NAS requests to show the results of dose-response assessments based on both the linear default and a more scientifically plausible nonlinear approach. This resistance was supported by an evaluation of mechanistic data that appeared to be specifically selected to support the default linear approach, and ignored data to the contrary. Recent risk assessments for arsenic and formaldehyde have also failed to adequately use available data informing the mode of action, and have relied solely on default dose-response approaches, despite strong MoA information supporting alternative approaches. The description of this module needs to provide a clear call for MoA-directed toxicity assessment, regardless of the difficulty of conducting a systematic review of mechanistic data.*

*In Module 4 (Dose-Response Assessment), it is not clear where inhalation dosimetry (e.g., the 1994 RfC Dosimetry Guidance) fits. Dosimetry is particularly important in the case of aerosol/particle exposures.*

*There does not appear to be a Module for Risk Characterization. Is that no longer considered to be part of the Toxicity Assessment? I realize that the EPA's position in recent years is that their Toxicity Assessments are not Risk Assessments because they do not include the Exposure Assessment (which they generally have). However, Module 1 would have to include an evaluation of potential exposures in the population of concern in order to put together an appropriate description of the scope and focus of the Toxicity Assessment. Moreover, a Characterization Module is critical to convey the uncertainty in the Toxicity Assessment to the Risk Assessors. Where else could the Characterization go? Are the Risk Characterization Guidelines being withdrawn?*

*It is crucial that toxicity assessments should include a transparent and comprehensive Characterization Module that is consistent with the OMB Memorandum "Updated Principles for Risk Analysis" (OMB 2007, M-07-24). Important characteristics include:*

- Characterizations of risks and of changes in the nature or magnitude of risks should be both qualitative and quantitative, consistent with available data. The characterizations should be broad enough to inform the range of policies to reduce risks.*

DO NOT CITE OR QUOTE.

*- Judgments used in developing a risk assessment, such as assumptions, defaults, and uncertainties, should be stated explicitly. The rationale for these judgments and their influence on the risk assessment should be articulated.*

- (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.

*Modules 5 – 11 represent a good start. Where does general noncancer organ toxicity (liver, kidney, skin, etc.) fit – Other Endpoints?*

- (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.

*Module 3 (Hazard Identification) should be worked on first, to clearly set out the principals of MoA-directed toxicity assessment, including the need for a transparent and objective review of mechanistic data to support an MoA evaluation process that includes relevant studies performed on other chemicals with structural or toxicological similarity.*

- (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:

- a. Use of various dose-response modeling approaches (e.g., model averaging);

*Lowest priority.*

*Bayesian meta-regression (e.g., model averaging) is a powerful approach for analyzing multiple studies, but it is highly susceptible to unintended bias associated with the selection of dose-response models and the definition of quasi-informative prior distributions for model parameters. In addition, due to the unavoidable impact of exposure error in the studies, the observed dose-response can differ significantly from the true dose response, with a tendency toward linearization of the apparent dose-response (Crump 2006, Rhomberg et al. 2011).*

*An additional challenge with Bayesian meta-regression with epidemiological data is the minimal influence of limited, and often negative, data at low concentrations on the predicted dose-response, which is dominated by the stronger dose-response data at higher concentrations. As a result, even an analysis "within the*

DO NOT CITE OR QUOTE.

*range of the data” can in fact represent a significant extrapolation below the range of the informative data.*

- b. Further consideration of the use of low-dose extrapolation approaches;

*Highest priority.*

- c. Additional consideration of endogenous production of environmental contaminants;

*Third highest priority.*

*EPA Guidance currently does not adequately deal with situations where a compound is present endogenously, either as an essential nutrient (e.g., manganese) or as a product of normal metabolism (e.g., formaldehyde, acetone).*

- d. Methods that would harmonize the evaluation of dose-response for cancer and noncancer effects.

*Second highest priority.*

DO NOT CITE OR QUOTE.

***Dr. Michael Jayjock***

My primary expertise is in the evaluation of human exposure in the context of human health risk assessment. As such, I understand that the proper evaluation of hazard or toxic effect is fully half of the risk assessment process. To that end, I have endeavored to study the science of toxicology as it relates to human health risk assessment. That process has caused me to voice opinions and advice to my toxicology colleagues over the years. The strongest effort in that regard is a paper I did with colleagues almost 20 years ago and attached to this email (Jayjock, Lewis and Lynch, Quantitative Level of Protection Offered to Worked by ACGIH Threshold Limit Values Occupational Exposure Limits, AIHA Journal, (62), January/February 2001). This argues for the combination of cancer and non-cancer risk and the use of models to provide quantitative estimates (with uncertainty) of the risk extant at any level of exposure including any exposure limit. Although, not mentioned in this paper, I did suggest, in a subsequent paper, a few year later (Jayjock, How much is enough to accept hormesis as the default?..., Human & Experimental Toxicology, 24, 245-247, 2005) that the emerging science of 'omics would hold the key to actually understanding what might be happening in human tissue at environmentally relevant exposures. It is indeed heartening to see that approach being used within these 2020 draft guidelines.

I was very impressed with the comments and points made by Dr. Fenner-Crisp in response to the charge questions. She has been on the front lines as a very credible, dedicated and capable scientist and public servant relative to these critical issues. I heartily endorse all of her comments, especially her prominent assertion that the NAS become wholly involved at every stage of these deliberations and decisions. From my perspective, the Agency definitely sits within the shadow of public mistrust. I cannot state it better than Dr. Fenner-Crisp:

*... Given the lingering concerns about the politicization of the SAB and its committees, it is incumbent upon the agency to engage a broader swath of the scientific community to assure that its outputs reflect an objective view of the state of the science. Consultation with the NAS should begin soon with a conversation similar to that which is occurring now with the SAB and continue at key points along the pathway as illustrated in Figure 1.*

DO NOT CITE OR QUOTE.

***Dr. Wayne Landis***

EPA reviews June 23-24 2020 SAB Committee meetings  
Wayne G. Landis

My reviews are focused on the Consolidated Human Toxicity Assessment Guideline and the New Approach Methods and Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Testing document. These reviews match my expertise in toxicology and risk assessment. During my career I have also been the Chair of my university's Institutional Animal Care and Use Committee (IACUC). Reduce, refine and replace has been an important consideration for several decades and is discussed in the current textbooks in the field.

I applaud the consideration of probabilistic risk assessment in decision making. By definition, it is not risk assessment unless it is probabilistic. However, there are a number places where the legacy of non-probabilistic approaches exist. One is the continued use of NOAELs and similar measures based on the outcomes of hypothesis testing. The issues with such point estimates can easily be found with a google search. The same can be said of taking a point estimate, even the lower confidence interval, from a regression model. Often, we are attempting to extrapolate to the effects at very low doses because the standard experimental designs are not asking the questions appropriate for risk assessment. Experimental designs need to be altered to answer the key questions in risk assessment, not risk assessment being compromised attempting to accommodate outdated methods.

I have long been a proponent of the use of exposure-response curve fitting instead of hypothesis testing to describe toxicity. I have co-authored several papers on the topic. For a decade I have also worked to integrate causality into a risk analysis and have become increasingly skeptical of many approaches claiming to be weight of evidence. I downloaded the EPA guidance document for exposure-response to evaluate its application as a Module.

During my long stint on several SAB subcommittees from the mid 2000s to the early 2010s and with several administrators. I was used to extensive documentation and having time to conduct our own analysis when necessary to answer the charge questions. In comparison this process resembles a rapid screening review than a careful consideration and analysis. I also discourage EPA from referencing documents published behind paywalls in journals in their documentation. Such an example is “ ([Cumulative risk assessment lessons learned: A review of case studies and issues](#))”. My understanding is that work produced by a U. S. agency cannot be copyrighted by a third party. I also examined several other documents that were available to document different modules.

***Consolidated Human Toxicity Assessment Guideline  
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.

- I consider a modular approach to eventually be a useful approach. It is not clear what the key risk assessments are that these modules support. In the are highlighted in Table 1, Module 2, it sounds as if these items are only being considered as factors in a literature review. My experience in evaluating studies for a variety of agencies is that

DO NOT CITE OR QUOTE.

many toxicity studies were conducted as screening studies were a NOAEL or LD50 were the goals. These legacy designs have a number of failings, among them the lack of reported test doses, effects data, minimum effect size, and so on. If the original observations are available, they may be analyzed using current techniques, but often exposures were not conducted at low doses.

- The approaches are often frequentist in design and analysis. Bayesian statistics, curve fitting and Bayesian networks are being adopted in many other fields and have proven useful. A suggestion to use Bayesian curve fitting was in the 2000 "*Benchmark Dose Technical Guidance Document*". I have noted that Bayesian curve fitting is now being applied to toxicity data ([https://cfpub.epa.gov/si/si\\_public\\_record\\_report.cfm?Lab=NCEA&dirEntryId=343986](https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NCEA&dirEntryId=343986)) and welcome the move.

(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.

#### Module 1

- Modules 1 and 2 do not seem to address ideas of causality-A key first step in any analysis is the construction of at least a proposed cause-effect pathway. Those endpoints based on genotoxicity are likely to have pathways very different from narcosis, endocrine disruption, or interaction with a specific key protein such as AChE. This is one area where the use of adverse outcome pathways may be very beneficial. The relative lack of quantitative AOPs is an issue in making specific predictions, but the framework is a good place to start. When the discussion comes to specific effects it should also bring to mind causal pathways similarities and differences in pathways.
- Be specific on genders and the varied distributions of exposure-response relationships that occur. I do not see that specifically noted in the modules or I missed the implied inclusion.
- Bayesian networks and other tools can be applied to evaluate different lines of influence. While BNs are relatively new, the approach can be traced to S. Wright in the early 20<sup>th</sup> century. Thinking at the beginning of the study of the data analysis framework is key in deciding about the kinds of data that can be addressed.
- The mindset does not address probabilistic factors in so much of the discussion. Toxics and exposure change the probability of physiological responses. Risk –still seems stuck in HQs and divide for a threshold. Even if the HQ is defined probabilistically that limits the kinds of analysis that can be done on the factors contributing to the answer. The tools are now taught to seniors and first year graduate students so they are ready for wider adoption. These tools should also be applied to experimental design and descriptions of causality.

Module 2-I have already identified my preference for exposure-response analysis.

- Module 2 –how do the data from different studies correspond to a proper analysis of exposure response? Again, a conceptual model that describes causality would be useful here. Given an appropriate analysis and datasets a proper uncertainty and

DO NOT CITE OR QUOTE.

sensitivity analysis can provide insights into the key variables (nodes) in making a prediction.

- Module 2 also seems like a good place for an explicit consideration of an AOP. It is likely that only few key events are necessary to make reasonable predictions of toxicity.
- Dose-response descriptions need to be improved. Even with the BMD approach a point is being presented to describe an exposure response by using the lower confidence interval of the regression. In examining the Guidance Documents it appears that the confidence interval is for the most likely outcome from the dataset. However, the most likely outcome does not necessarily provide protection to the tails of the cause-effect interactions. Prediction intervals should be considered as an additional tool in the decision-making process. Prediction intervals estimate the value of a new observation given the existing model. New observations (effects) can occur far from the boundary of the confidence intervals.
- Discussion of uncertainty and sensitivity in the analysis. In my risk assessment world these are two key characteristics of any evaluation. I do not see a discussion in any of the modules of how important these aspects are in contributing to the risk assessment process.
- Model averaging should take into account prior knowledge—Bayesian model averaging. I am wary of a simple averaging taking place when the outputs of curve-fitting models are discussed. My assumption in this discussion is that Bayesian model averaging is what is being discussed. In this instance weights are assigned to the various model outputs depending on how well they describe the exposure-response relationship. Since the commonly used regression models have little connection to the toxicokinetics of the interaction the equations are more convenience than being based on first principles. It has been demonstrated that when the concentration-response experiment covers the entire range of exposure-response that the various models converge (Moore and Caux 1997). My observation is that experiments designed for hypothesis testing often do not include sufficient observations at doses at which decisions will be made. Hence the different models are not constrained within this region and divergence occurs.
- Testing the accuracy and precision. So, when are we going to test our process for its eventual accuracy and precision? After the modules are produced and in use how do we know they work?
- The discussion around cumulative effects has been around a very long time. See NRC 2010, Chapter Cumulative effects can be addressed, see NRC 2010. Science and Decisions : Advancing Risk Assessment , Chapter 13, page 213. Note that many of the issues I have discussed in this review are discussed in this keystone publication.

Moore DRJ, Caux P-Y. 1997. Estimating low toxic effects. Environmental Toxicology and Chemistry 16:4 794-801.

(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.

Genders???

Differences in socio-economic class?

DO NOT CITE OR QUOTE.

Ethnic/Racial differences in access to healthcare, nutrition, etc? will impact susceptibility to stressors.

(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.

It does not seem that there is a clear indication that the experimental design should be amenable to current data analysis tools and that they should describe causality. There has been a growing literature on describing causality and on the fact that the world is both deterministic and probabilistic. The field has advanced considerably since the formulation of many of the EPA guidance documents.

(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:

I covered several of these topics above. It is imperative that EPA does a better job of describing exposure-response. I have a few additional comments.

- Use of various dose-response modeling approaches (e.g., model averaging);-- *Model average is a tool for reconciling multiple regression assumptions. If the data were adequate throughout the entire exposure-response relationship (in other words, good experimental design) the models should converge. Replication is not as important as having more observations along the exposure-response continuum.*
- Further consideration of the use of low-dose extrapolation approaches--*in other words attempting to have statistical tools save poor experimental design? I am always wary of such attempts; it generates further poorly done experiments. Extrapolation beyond datasets is generally something we teach students as something not to attempt.*
- Additional consideration of endogenous production of environmental contaminants;--*(no comments on this item)* and
- Methods that would harmonize the evaluation of dose-response for cancer and noncancer effects. *First step build conceptual models that describe the various steps in the generation of cancer and non-cancer effects. What are the commonalities? Those commonalities should be the initial steps for consideration of harmonization.*

#### **Table 1: Proposed Modules**

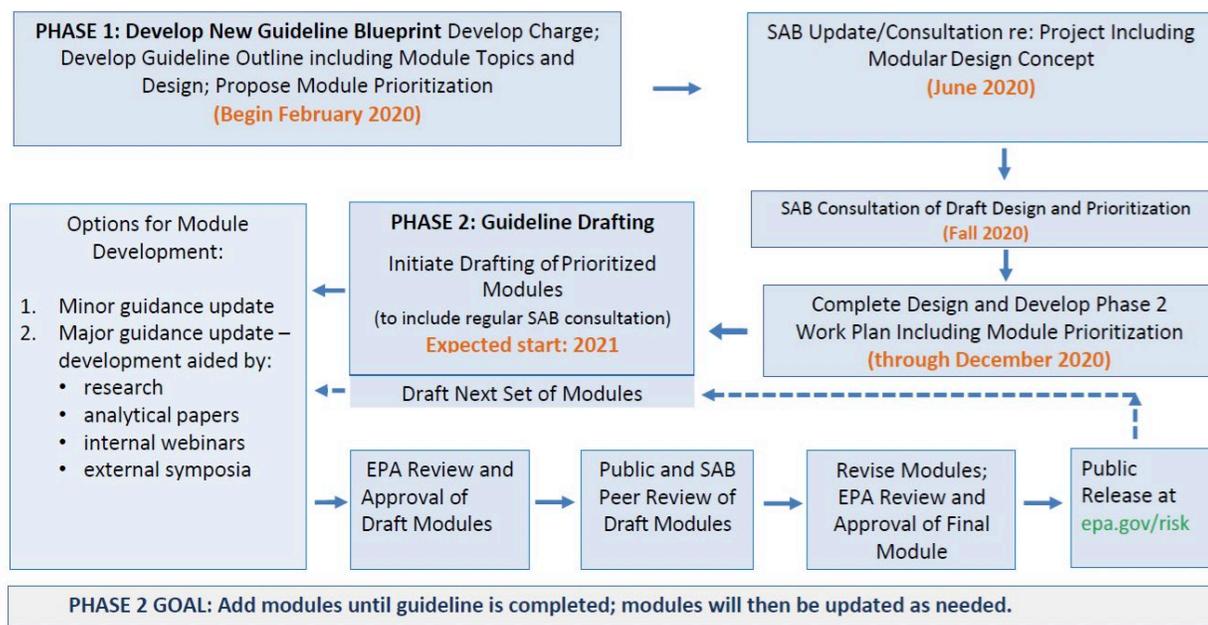
Modules are in order of how the Consolidated Guideline could potentially be organized, but not necessarily the order in which they would be written.

DO NOT CITE OR QUOTE.

<p><b>Common Element Modules</b></p> <p><i>These proposed modules would address common elements of an assessment that pertain to all health endpoints</i></p>	<p><b>Module 1. Planning and Scoping a Human Toxicity Assessment</b></p> <p>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.</p>
---	--

<p><b>Module 2. Identifying and Evaluating Toxicity Studies</b></p> <p>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.</p> <p><b>Module 3. Hazard Identification</b></p> <p>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.( wgl-of humans or test species??)</p>
--

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



DO NOT CITE OR QUOTE.

Comments on Figure 1.

Phase 1.

I have a number of questions regarding the diagram.

- What are the goals?
- What kind of accuracy will be required?
- How new are the tools, is this a 21<sup>st</sup> century process?
- Will the data analysis and decision science be current?
- Are we limited to frequentist approaches to data analysis? I sure hope not. See the references to the Carriger et al papers below.
- Where is the preliminary conceptual cause-effect framework? Answers to these questions would assist my ability in evaluating the overall process.

Phase 2. How is priority understood if the biggest drivers are not determined in a quantitative fashion? I try to discourage hand-waving.

What are the goals and what are the financial and other design constraints? These societal constraints will limit what the toxicologists and data analysts can do. This can be estimated and provides a context on what EPA is asking the SAB to accomplish.

*Dr. Ted Simon*

**Charge Questions on Toxicity Assessment:**

1) This process of guidance development is appropriate to the task. I would, however, include exposure assessment as a tool for prioritization. Dr. John Wambaugh, an EPA staffer in RTP, has written eloquently on this topic and I cite his relevant papers in regard to the NAMs. If a specific chemical can be given a lower priority, smart allocation of the resources for development of toxicity reference values can occur. Perhaps this is included in the “overarching considerations” in Module 1. Maybe a separate module for “exposure prioritization” is needed.

2) As part of module, please include some language that indicates that problem formulation should be viewed as a “voyage of discovery.” I found this phrase in the NATO Code of Best Practice for Command and Control Assessment at (<https://apps.dtic.mil/dtic/tr/fulltext/u2/a457898.pdf>). The point is to ensure the problem formulators keep an open mind.

3) I applaud the idea of an immunotoxicity module but have mixed feelings about including it, as doing so may significantly increase the uncertainty in the process. I would expect most environmental stimuli have some effect on the immune system. The hygiene hypothesis suggests that the current state of autoimmune disease is due to the elimination of so-called “old friends;” these “old friends” are commensal organisms (invertebrates and protists) from earlier times in human history that provided health benefits and were eliminated as part of a response to other public health goals. The response of medicine now is biologic drugs such as adalimumab or infliximab, monoclonal antibodies against tumor necrosis factor-alpha (TNF- $\alpha$ ), a key molecule in the immune response. Testament to how little is known about the immune system is the current misperception that pre-existing asthma increases the risk of COVID-19. Whilst both are respiratory diseases, the extant data argues otherwise [1].

Hence, I would admonish care in developing toxicity factors based on the level of understanding of the portion of the immune system affected. I agree with the goal but a sufficient scientific knowledge base to achieve this goal may not yet be developed. Nonetheless, exploration of immunotoxicity endpoints is worth taking on.

4) I would start module 1 first because lessons learned by doing so may alter the timing and development of the other modules. Thinking hard about planning and scoping should also be a “voyage of discovery.”

5) I would agree with all these suggestions. I would prioritize consideration of endogenous production of chemicals, low-dose extrapolation, and harmonization in that order.

*Dr. Eric Smith*

## **Comments from E.P. Smith**

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

#### **Discussion/Charge Questions**

- (6) 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.

The module approach seems reasonable as a general approach going forward. Having a flowchart might help move through the process.

- (7) 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.

Module 1: Should qualitative uncertainties be part of this module?

Module 2: Would it be valuable here to identify critical uncertainties and if there is adequate information to reduce some of these uncertainties. It seems the goal here is to build the framework for the weight of evidence model. Is there a flowchart that would help?

Module 3: Again it would seem uncertainty plays a role here.

Module 4: This module seems to be much more specific than others. Perhaps this makes it an easier one to complete first. Some of these topics can take a considerable amount of effort (model averaging, probabilistic modeling). I presume most of the tools will be frequentist however model averaging and probabilistic modeling can be approached using Bayesian approaches. Will these be considered?

- (8) 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.

These seem reasonable. Is it worth having study design as part of each of these modules since there is a data interpretation component. Evaluation of strength of evidence is worthwhile (ie uncertainties). Is there a need for a module that relates to "strength of conclusions" or combining all the information and evaluation of importance. Perhaps identify what is needed to strengthen conclusions.

DO NOT CITE OR QUOTE.

- (9) 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.

I do not have an opinion as to the ordering as it seems laid out in a sequence for modules 1-4.

Modules 5-11 seem independent of the others so could be done at any time. The only issue would be the information that would be linked to the other modules and if there is standardization (format/content) but this could be adjusted through editing.

- (10) 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:
- a. Use of various dose-response modeling approaches (e.g., model averaging);

Model averaging is one method for reducing some of the uncertainty associated with choice of model. There are of course other ways to reduce uncertainty. It would be valuable to give guidance on how much uncertainty can be reduced through model uncertainty, what are the necessary ingredients for successful model averaging and if there are other ways that might also be effective. It is not clear how all of the evidence will be combined to provide an estimate of critical dose levels. Is this worth a separate module?

Is there a retrospective study that could illustrate the approaches and compare them to the historical approach?

- b. Further consideration of the use of low-dose extrapolation approaches ;
- c. Additional consideration of endogenous production of environmental contaminants;

Could this be done using case studies?

and

- d. Methods that would harmonize the evaluation of dose-response for cancer and noncancer effects.

Could this be done using case studies?