

6/20/20 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.

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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 20, 2020)

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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 description 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.

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- 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.

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- 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.

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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

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for nongenotoxic chemicals should be a nonlinear, threshold approach. With regard to animal models, it 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 α 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

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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.

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

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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.

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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.

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- 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.

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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.

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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*¹

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.² Second, it would reinvigorate the Agency's commitment to the information quality principles of transparency (through reproducibility), utility, integrity, and objectivity.³ Third, it would improve the quality of Agency peer review so that time is not wasted on the perfunctory review of common elements.⁴

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.⁵ 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.

¹ The charge to the committee is presented in U.S. EPA Science Advisory Board (2020).

² U.S. Environmental Protection Agency (2020b).

³ Office of Management and Budget (2002), U.S. Environmental Protection Agency (2002).

⁴ U.S. Environmental Protection Agency (2015).

⁵ Several prominent individuals have been credited with the aphorism that academic politics are so vicious precisely because the stakes are so small.

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(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.⁶ This scope is inherently incomplete. They systematically exclude indirect risks to human health and welfare, risks beyond the human health domain, and substitution risks.⁷

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.

⁶ 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.

⁷ U.S. Environmental Protection Agency (2019) does not define “substitution risk.” However, it is an essential concept in benefits assessment.

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“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.”⁸

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.”⁹ 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”).¹⁰ 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.¹¹ Therefore, Module 1 of the Consolidated Human

⁸ A representative version of the joke is related by Leaver (2014).

⁹ Freedman (2010a), excerpted at Freedman (2010b), who attributes the aphorism to Winston Churchill.

¹⁰ Office of Management and Budget (2019), U.S. Environmental Protection Agency (2020a).

¹¹ 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

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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 principles¹² 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.”¹³ 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.¹⁴ Long ago, the Agency abandoned this without scientific justification¹⁵ and ratified a policy preference in favor of upward bias.¹⁶

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.”

¹² Office of Management and Budget (2002), U.S. Environmental Protection Agency (2002).

¹³ 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.”

¹⁴ U.S. Environmental Protection Agency (1986). This caveat was abandoned when cancer risk assessments were incorporated as inputs to Agency benefits assessments.

¹⁵ U.S. Environmental Protection Agency (1996), U.S. Environmental Protection Agency (2005).

¹⁶ See footnote 11.

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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.¹⁷

(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

¹⁷ 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.

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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.¹⁸

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

¹⁸ 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.

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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 20.¹⁹

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.²⁰

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.²¹

(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.

¹⁹ 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).

²⁰ 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.

²¹ 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.

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(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).²² 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.²³

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.

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²² 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.

²³ “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.

6/20/20 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.

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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.

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 give 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 indicate 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 spate 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 adaimumab or infliximab, monoclonal antibodies against tumor necrosis factor-alpha (TNF- α), 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

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

- (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: 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?

- (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.

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.

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- (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.

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.

- (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 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?