

Comments submitted to the EPA Chartered Science Advisory Board for consideration at its June 23-24, 2020, public meeting on the topic of EPA's plans for Re-examining and Consolidating its Human Toxicity Assessment Guideline

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I appreciate the opportunity to provide written and oral comments to the EPA Chartered Science Advisory Board for consideration in its discussion of EPA's plans for Re-examining and Consolidating its Human Toxicity Assessment Guideline.

I have been a risk practitioner for more than 40 years, over half of that time at EPA. Both during and following my tenure at the agency, I have had a hand in the preparation or peer review of hundreds of human health and ecological hazard and risk assessments and many of the agency's risk assessment guidance documents.

Before I dive into the details of the current proposal, I want to reinforce the view I expressed a year ago on how critical it is to engage the National Academies in this initiative to revisit, update and improve the agency's approach to human health risk assessment. 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.

Charge Question #1:

At the Science Advisory Board's June, 2019, meeting, I expressed concern that the Administrator was asking that updated cancer and new non-cancer guidelines be issued before the end of 2020. Needless to say, I am relieved to see that the agency now appears to be committed to a far more sensible approach and timeline that can allow for robust and credible science policy to be developed and for the full engagement of the SAB, the National Academies and other stakeholders in its review. I still hold to my prediction that any plan will take at least four to six years to be fully implemented, that is, to reach the Phase 2 Goal. Bear in mind that one year has already gone by.

A year ago, I also argued that EPA should NOT write separate guidelines for cancer and non-cancer, given that the idea of "separate" was driven primarily by the dichotomous approach the agency has taken historically in conducting dose response

assessments. I am pleased to see that the agency is acknowledging the many commonalities in cancer and non-cancer assessment, and now is opting to develop a Consolidated Guideline which will include assessment of both cancer and non-cancer endpoints. It makes sense –to quote EPA—“to include approaches that are common across endpoints and consider state-of-the-science approaches for characterization of dose-response, in addition to the incorporation of new approach methodologies (NAMs).” Including separate modules describing elements specific to each endpoint of concern and other relevant topics is a wise, efficient and practical path forward.

Charge Question #2: Common Element Modules:

Modules 1-3 collectively describe the elements of a systematic review process, an approach now widely recommended and increasingly applied in the field of environmental risk assessment. Since there is an expectation that the Consolidated Guideline and its components will represent an agency consensus and be applied agency-wide, I see these three modules as serving as the agency’s *one-and-only* approach to systematic review, thus resolving the current situation of there being two different agency approaches competing on separate tracks. Neither the ORD IRIS nor the OCSP TSCA systematic review process has been fully developed as yet. While the development of the ORD IRIS approach has been guided by consultation with, and recommendations from, the National Academies of Sciences (NAS) over the past several years, the heavily-criticized and flawed TSCA systematic review guidance was developed and has been used for roughly two years in the TSCA Existing Chemicals Risk Evaluation program without the benefit of any external expert peer consultation or review. Only recently has the Office of Pollution Prevention and Toxics (OPPT), the office responsible for managing the Existing Chemicals Risk Evaluation program, begun consultation with the NAS. I would hope that this will serve as the pathway to resolving each approach’s deficiencies and disparities in the near future.

It is not completely clear from the charge paper at what stage EPA will be addressing the major unresolved issues from the 2009 NRC report *Science and Decisions: Advancing Risk Assessment*. Module #4 seems to encompass much of an envisioned approach to *dose response assessment*, and to include discussion of general default and chemical-specific *adjustment factors* to account for *uncertainty* and *variability*, but there is only a passing reference to cumulative risk assessment in Modules 1 and 4. I would posit that the requisite more extensive discussion of cumulative risk assessment should be forthcoming *soon* in a separate, stand-alone document. Furthermore, there is no mention of aggregate (exposure) assessment in any of the four Common Element modules. Presumably, the agency can provide evidence that this aspect of risk assessment is adequately addressed in the 2019 Guidelines for Human Exposure Assessment. Nonetheless, it needs to be cited as a key concept in risk assessment

here as is cumulative assessment. Fleshing out the contents of Modules 1-4 in some greater detail would be helpful and clarifying.

To the list of Common Element Modules should be added:

Priority #1: Epidemiology. Evaluation of human data transcends endpoints. There is no existing guideline. With the exception of the assessment of human studies that serve as the foundation for the NAAQS criteria and ISAs, EPA does not do a very consistent job of assessing human data. Nevertheless, human data are playing an increasingly prominent role in the assessment of many high profile chemicals across its legislative mandates.

Priority #2: Endocrine disruption. Endocrine disruption is a phenomenon with consequences for all to-be-evaluated endpoints of concern. EPA needs to be clear on whether and, if so, how, it will acknowledge and incorporate low dose non-monotonicity into its risk assessments or consider non-monotonicity only to be a high dose phenomenon, manifesting itself only once cytotoxicity and cell death kick in.

Charge Question #3: Endpoint-specific Modules

All six endpoints listed in Table 1 are relevant and should be the subject of module development, in the following order of priority:

Priority #1: Mutagenicity. A guideline was a whisker away from being issued just a few years ago so it is the most up-to-date and would require the least revision. In addition, the increased clarification of the distinctions between, and consequences of, direct and indirect interactions with DNA mandate a near-term re-visit of the science policy choices related to dose-response assessment, especially for carcinogenic outcomes.

Priority #2: Immunotoxicity. There is no existing guideline and the endpoint is garnering a high level of attention, given our burgeoning understanding of the role of the immune system in virtually every aspect of biology.

Priority #3: Frankly, a toss-up among the remaining four, all of which have existing guidelines (*i.e.*, reproductive toxicity, developmental toxicity, neurotoxicity and carcinogenicity). While they may be considered quite long in the tooth (between 15 and 30 years old), they all contain still-relevant and sustaining scientific principles that can serve the agency well until their turn in the updating queue comes along. Updating should not be seen as an excuse to jettison long-standing policies that are generally sound and beneficial. EPA should tread cautiously here.

One might determine priorities by beginning with the endpoint that has the most robust body of information comprised of traditional animal and human data and, more importantly, relevant results from the application of validated new(er) assessment tools.

Bottom line: Don't throw the baby out with the bathwater!



Charge Question #4: Order of Priority for Module Development

I would argue that the agency already gets it right in listing the first four modules in their current order and designating them as the highest priorities:

Module 1. Planning and Scoping a Human Toxicity Assessment

Module 2. Identifying and Evaluating Toxicity Studies

Module 3. Hazard Identification

Module 4. Dose-Response Assessment

Absent a substantive detailed exposition of the key elements that are common to the assessment of all endpoints of toxicity, which these four modules presumably are designed to convey, we will remain in our current state, beset by redundancy, contradiction, uneven state of currency and confusion when attempting to articulate principles specific to an endpoint.

Charge Question #5: Priority of issues related to dose response:

I see Priority #1 as being *Methods that would harmonize the evaluation of dose-response for cancer and non-cancer effects*. This is the principal driver for creating a consolidated guideline in the first place and should be given immediate attention.

I would place *Additional consideration of endogenous production of environmental contaminants* last, not because it is not an issue worthy of attention eventually but because it is relevant only to a small number of substances in the universe of chemicals that EPA must assess.

I see the other two as a toss-up for Priority # 2 and 3.

In summary:

1. Consultation with NAS is critical to success. It should begin now.
2. The proposed scope to create a consolidated guideline over a multi-year timeline is far more sensible than that presented a year ago.
3. Common Modules 1-4 are key to success. Other common modules to be added include Epidemiology and Endocrine Disruption. Cumulative Risk Assessment should be addressed in a stand-alone document.
4. All six endpoints listed in Table 1 are relevant and should be the subject of module development. Order of priority: Mutagenicity, Immunotoxicity, the remaining four- a toss-up.
5. Order of Priority for Module Development: 1) Modules 1-4, 2) Mutagenicity, 3) Immunotoxicity, 4) Epidemiology, 5) Remaining four endpoint-specific, 6) Endocrine disruption
6. Priority of issues related to dose response: 1) *Methods that would harmonize the evaluation of dose-response for cancer and non-cancer effects*, 2) A toss-up between *Use of various dose-response modeling approaches (e.g., model averaging)* and *Further consideration of the use of low-dose extrapolation approaches*, 4) *Additional consideration of endogenous production of environmental contaminants*.

Thank you for your attention.