

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 New Approach Methods and Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Testing

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My name is Wendy Heiger-Bernays and I'm a Clinical Professor of Environmental Health at Boston University School of Public Health. My expertise is in toxicology and risk assessment, with an emphasis on research translation.

Thank you for the opportunity to provide comments on the topic of EPA's New Approach Methods and Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Testing.

I have no conflicts to disclose.

The progress made on testing key characteristics of environmental chemicals using New approach methodologies (NAMs) is very impressive. Tox21 was the catalyst for reduction, replacement and refining with collaboration between regulatory agencies, regulated entities, NGOs and academics towards moving these methods forward as decision making tools for hazard and risk assessment. Beginning in 2015, the use of NAMs served as alternatives for assays in the Endocrine Disruptor Screening Program (EDSP)¹ battery, allowing the screening of thousands of chemicals for hazard assessment purposes.

It is time to move forward and EPA is to be commended on seeking to do so. There remain significant obstacles and budget restrictions on animal testing should coincide with thoughtful data-driven methodologies. Complex linkages of in vitro systems do not make a human and definitely do not make a population of humans. The challenges of modeling susceptible humans who experience complex disorders that occur at different life stages with environmental chemical contributors are extensive - think about infertility, autism, adverse neurobehavioral outcomes, and metabolic disease and cancers in addition to underlying disease status. The National Academy of Sciences 2017 report 'Using 21st Century Science to Improve Risk-Related Evaluations'² identified the limitations and concerns of relying only on NAMs – stating that NAMs should not be used by themselves to explain away potential adverse effects, or classify chemicals as 'safe'. This is particularly important as we move from using NAMs for hazard assessment to risk assessment.

¹ <https://www.federalregister.gov/documents/2015/06/19/2015-15182/use-of-high-throughput-assays-and-computational-tools-endocrine-disruptor-screening-program-notice>

² National Academies of Sciences, Engineering, and Medicine 2017. Using 21st Century Science to Improve Risk-Related Evaluations. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24635>.

As Ginsberg et al (2019)³ note, “Although these approaches hold the promise of protecting public health and the environment by identifying safer alternatives, we caution that lack of evidence of hazard does not necessarily mean the preferred alternative is completely safe but, rather, that it does not show evidence of known hazard potential.”

I emphasize the importance of relying on external expert review, public comment and the work of the National Academies moving forward. This will be particularly important when evaluating how decisions will be made with regard to a risk-based approach for waiving chronic/carcinogenicity studies. It will be important to clearly describe how much data are available when waivers are requested, when animal models will be retained; and how Mode of Action, read across, and gene expression data will be evaluated. In addition, it is critical that methods incorporate susceptibilities and variabilities, as well as cumulative risk.

A clearly described, well vetted and well communicated process for selection of Points of Departure is necessary. EPA needs to provide examples of chemicals where low-dose effects may be challenging to predict the POD; here EPA should rely on the work of the 2017 NAS on Evaluating Low-Dose Toxicity from Endocrine Active Chemicals⁴.

Risk assessment must protect the public’s health while adopting new scientific approaches. Thank you for the opportunity to share my comments today.

³ Ginsberg GL, Pullen Fedinick K, Solomon GM, Elliott KC, Vandenberg JJ, Barone S Jr, Bucher JR. New Toxicology Tools and the Emerging Paradigm Shift in Environmental Health Decision-Making. *Environ Health Perspect.* 2019 Dec;127(12):125002. doi: 10.1289/EHP4745. Epub 2019 Dec 13. PMID: 31834829; PMCID: PMC6957281.

⁴ National Academies of Sciences, Engineering, and Medicine 2017. *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals.* Washington, DC: The National Academies Press. <https://doi.org/10.17226/24758>.