

Good morning, my name is Nicholas Chartres and I am the Associate Director of Science and Policy at the Program on Reproductive Health and the Environment at the University of California, San Francisco. My comments today will focus on the Human Health Toxicity Guidelines.

I want to state that I have no conflicts to disclose.

With regards to Charge question 2: *“Please comment on the scientific adequacy, completeness, organization and other relevant considerations regarding EPA’s list of proposed “common element modules” (See Table 1)”* my comments focus on the use of systematic review methods described in Module 2. These methods have not been adequately or completely described as they are 1) only included in module 2 and 2) only described as *“general principles associated with collecting potentially relevant studies including conducting a literature search”*.

Firstly, systematic review methods are critical for Modules 1, 2 and 3, not only Module 2. Systematic reviews have been recommended for evaluating the strength of evidence for environmental exposures and the relationship to adverse health outcomes. Secondly, the Institute of Medicine (IOM), which has 21 standards covering the entire systematic review process that, if adhered to, result in a scientifically valid, transparent, and reproducible systematic review, defines a systematic review as a:

*“scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies”*¹

If it is EPA’s intent to incorporate “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**” then EPA must implement a systematic review method that is compatible with empirically based existing methods and aligns with the IOM definition of a systematic review, including but not limited to, using explicit and pre-specified scientific methods **for every step of the review.**

There are multiple well-developed science-based, peer-reviewed and validated methods for conducting systematic reviews in environmental health that EPA could readily apply, including the National Toxicology Program’s Office of Health Assessment and Translation Method² and UCSFs Navigation Guide

¹ Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. Page 1. Washington, DC: The National Academies Press

² National Toxicology Program Office of Health Assessment and Translation. (2015). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Institute of Environmental Health Sciences; 2015

Systematic Review Method, which has been demonstrated in six case studies.^{3,4,5,6,7, 8,9,10} The National Academies of Science (NASEM) has cited both of these systematic review methods as exemplary of the type of methods EPA should use in hazard and risk assessment.^{11,12, 13,14} Further, the NASEM utilized both methods in its 2017 assessment of the potential health impacts of endocrine active environmental chemicals.¹⁵ Specifically, in its 2017 review the NASEM found:

“Both the OHAT and Navigation Guide methods include the key steps recommended by a previous National Academies committee (NRC 2014) for problem formulation, **protocol development**, specifying a study question, developing PECO statement, identifying and selecting the evidence, evaluating the evidence, and integrating the evidence.”¹⁶

To assess the harms in human studies, instead of conducting an entirely new review, the NASEM used the Navigation Guide published systematic review on PBDE flame retardant exposure and IQ and concluded that:

“To assess the human evidence, the committee critically evaluated the methods of a recent systematic review conducted by Lam et al... Judging that this existing review fulfilled the requirements of a systematic review and that there was **no evidence of risk of bias in the assessment**, the committee used the Lam et al. review as a basis for its own assessment.”¹⁷ (emphasis ours)

³Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environ Health Perspect.* 2014;122(10):1028-39. Epub 2014/06/27. doi: 10.1289/ehp.1307893. PubMed PMID: 24968388; PMCID: 4181929.

⁴Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. *Environ Health Perspect.* 2014;122(10):1015-27. Epub 2014/06/27. doi: 10.1289/ehp.1307177. PubMed PMID: 24968374; PMCID: 4181920.

⁵Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. *Environ Health Perspect.* 2014;122(10):1040-51. Epub 2014/06/27. doi: 10.1289/ehp.1307923. PubMed PMID: 24968389; PMCID: 4181930

⁶Vesterinen H, Johnson P, Atchley D, Sutton P, Lam J, Zlatnik M, Sen S, Woodruff T. The relationship between fetal growth and maternal glomerular filtration rate: a systematic review. *J Maternal Fetal Neonatal Med.* 2014;1-6. Epub Ahead of Print; PMCID: 25382561.

⁷Johnson PI, Koustas E, Vesterinen HM, Sutton P, Atchley DS, Kim AN, Campbell M, Donald JM, Sen S, Bero L, Zeise L, Woodruff TJ. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. *Environ Int.* 2016;92-93:716-28. doi: 10.1016/j.envint.2016.03.009. PubMed PMID: 27156197.

⁸Lam J, Sutton P, Halladay A, Davidson LI, Lawler C, Newschaffer CJ, Kalkbrenner A, Joseph J, Zilber School of Public Health, Windham GC, Daniels N, Sen S, Woodruff TJ. Applying the Navigation Guide Systematic Review Methodology Case Study #4: Association between Developmental Exposures to Ambient Air Pollution and Autism. *PLoS One.* 2016;21(11(9)). doi: 10.1371/journal.pone.0161851.

⁹Lam J, Lanphear B, Bellinger D, Axelrad D, McPartland J, Sutton P, Davidson LI, Daniels N, Sen S, Woodruff TJ. Developmental PBDE exposure and IQ/ADHD in childhood: A systematic review and meta-analysis. *Environmental Health Perspectives.* 2017;125(8). doi: doi: 10.1289/EHP1632.

¹⁰Lam J, Koustas E, Sutton P, Cabana M., Whitaker E., Padula A, Vesterinen H, Daniels N, Woodruff TJ. Applying the Navigation Guide: Case Study #6. Association Between Formaldehyde Exposures and Asthma. In preparation. 2019.

¹¹National Research Council. (2014). *Review of EPA's Integrated Risk Information System (IRIS) Process.* Washington, DC: The National Academies Press; 2014.

¹²National Academies of Sciences Engineering, and Medicine. (2018). *Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation.* Washington, DC: The National Academies Press; 2018.

¹³National 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, D.C.: The National Academies Press; 2011

¹⁴National Academies of Sciences, Engineering, and Medicine. 2019. *Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene.* Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

¹⁵National 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, D.C.: The National Academies Press; 2011

¹⁶National 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.* Page. 119. Washington, D.C.: The National Academies Press; 2011

¹⁷National 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.* Page. 8. Washington, D.C.: The National Academies Press; 2011

Additionally, The World Health Organization and International Labor Organization (WHO/ILO) are using the Navigation Guide method to conduct systematic reviews of occupational exposures and disease as part of assessing the global burden of work-related injury and disease due to exposure to occupational risk factors.¹⁸

Finally, in response to charge question 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?”*, EPA should prioritize the implementation of empirically based systematic review methods before proceeding with the development of the other modules as empirically based systematic review methods are the foundation for all risk assessments. Without the development of these methods the following steps of the risk assessment may be biased.

We have commented extensively with regard to the use of systematic review methods and that the current approach used by the Toxic Substances Control Act are not empirically based or consistent with the best available science. Our comments can be found here <https://bit.ly/PRHENAS>

¹⁸ Mandrioli, D., Schlünssen, V., Ádám, B., Cohen, R. A., Colosio, C., Chen, W. et al. (2018). WHO/ILO work-related burden of disease and injury: Protocol for systematic reviews of occupational exposure to dusts and/or fibres and of the effect of occupational exposure to dusts and/or fibres on pneumoconiosis. *Environment International*, Vol. 119, Pg. 174–185. <https://doi.org/10.1016/j.envint.2018.06.005>