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**Oral Comments from Dr. Nicholas Chartres, Director of Science and Policy at the Program on Reproductive Health and the Environment at the University of California, San Francisco to the Science Advisory Board (SAB) on the Report on EPA's Proposed Rule "Increasing Consistency and Transparency in Considering Benefits and Costs in the Clean Air Act Rulemaking Process"**

My comments focus on point 2.2 *Estimating Benefits and why EPA should adhere to best practices for the development of the BCA*.

We strongly support the SAB's major comment and recommendation that "*EPA should clarify and strengthen the estimation of benefits in the proposed rule by incorporating systematic review approaches"*, however better defining the strength of the relationship between exposure and outcomes with clear terms that have been predefined and include a range, such as suggestive, likely and known should be used.

Further, all health effects for which there is some evidence of a relationship, which includes suggestive, likely and known should be quantified as there is some evidence that there is risk and to not estimate the benefits would assume there are zero benefits which is not scientifically supported.

In 2.2.1, the SAB states that "*if feasible, inclusion in the benefits analyses of effects for which the relationship may be less certain (e.g., possibly causal), but the impact would be substantial, could provide a more complete perspective accounting for uncertainties"* and cites McGartland, et al., 2017).

As discussed by McGratland, 'Willingness to Pay' for reducing risks is higher for more severe health effects (e.g., cancer, cardiovascular disease, chronic health effects in children). As a result, the benefits of reduced exposure to a chemical with a "suggestive" relationship to serious heath endpoints may be higher than the benefits of reduced exposure to a chemical with a deemed "known" relationship to less serious health endpoints. It may be therefore incorrect to take account of the latter but not of the former.

Therefore we strongly support the SABs recommendation that Modification of the language in Section 82(a)(7) should allow such analyses, as the current language appears to exclude them.

However, as also highlighted in the review by McGartland, health effects with less certain evidence or without a clear summary statement of the strength of the evidence are usually excluded from benefits analysis, even though it is highly likely that there is some positive value to reduction of those risks. Therefore, including these less certain effects requires changes in both risk assessment and economics and an important first step is to provide greater clarity on the strength of evidence of each health effect.

We therefore recommend using Strength of Evidence statements to summarize health effects evidence for all health outcomes, not only cancer endpoints, such as those used by the National Toxicology Program's Office of Health Assessment & Translation and UCSFs Navigation Guide, which are systematic review approaches that have been endorsed by the National Academies of Science (NAS).

UCSFs strength of evidence ratings are based on a combination of four criteria: (1) Quality of the entire body of evidence; (2) Direction of the effect estimate; (3) Confidence in the effect estimate; and (4) Other compelling attributes of the evidence that may influence certainty. This leads to ratings off: Sufficient evidence of harmfulness, Limited evidence of harmfulness, Inadequate evidence of harmfulness, Evidence of lack of harmfulness are a supported by explicit description of what each rating indicates.

Further, these are both well-developed science-based, peer-reviewed and validated methods for conducting systematic reviews in environmental health that EPA could readily apply, for determining if there is a clearly causal or likely causal relationship between an exposure and a health outcome. [1,2,3,4,5,6,7,8,9] The NAS has cited both of these systematic review methods as exemplary of the type of methods EPA should use in hazard and risk assessment.[10,11, 12,13]

Further, the NAS utilized both methods in its 2017 assessment of the potential health impacts of endocrine active environmental chemicals.[14] 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."** [15]

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[1] 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

[2] Johnson 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.

[3] Koustas 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.

[4] Lam 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

[5] Vesterinen 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.

[6] Johnson 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.

[7] Lam 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.

[8] Lam 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. Environmenal Health Perspectives. 2017;125(8). doi: doi: 10.1289/EHP1632.

[9] Lam 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.

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

[11] National 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.

[12] 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, D.C.: The National Academies Press; 2011

[13] National 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.

[14] 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, D.C.: The National Academies Press; 2011

[15] 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. Page. 119.Washington, D.C.: The National Academies Press; 2011

Finally, we have commented extensively with regard to the use of systematic review methods that are not empirically based or consistent with the best available science under the Toxic Substances Control Act or the Integrated Risk Information Program that can be found here https://bit.ly/PRHENAS and https://bit.ly/35HE9H4

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