

June 23, 2020

Public comments to EPA SAB re: Human Health Toxicity Guidelines

Good morning, my name is Tracey Woodruff and I'm a professor at the University of California, San Francisco's School of Medicine and the Director of the Program on Reproductive Health and the Environment. My comments today will focus on the Human Health Toxicity Guidelines.

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

A modular approach to the Human Health Toxicity Guidelines could successfully act as a unifying approach and single source of basic risk assessment approaches. It would allow for consistency in approaches across health endpoints, as has been recommended by the National Academy of Sciences, and is consistent with what we know about the science. However, it is **critical** that this approach build upon **existing guidelines and recommendations** from EPA and integrate **expert** recommendations from groups such as NAS, who have had several reports on this topic with recommendations, many of which EPA has yet to implement, such as the recommendations from Science and Decisions report.

With regard to charge question 1, there does not appear to be sufficient opportunity for public comment in this guideline. In fact the opportunity only appears after EPA review and approval of the draft module. Given the importance of these guidelines, there should be opportunities for the public to provide comment as early as the scoping to ensure module drafting takes into account all necessary considerations. There is also likely a need for multiple expert reviews. Therefore, we recommend that EPA adopt a similar process to the IRIS Review Timeline for public comment, which is 18-months for an individual chemical and is likely to be longer given the multiple modules and complexity of this task.

With regard to Charge Question number 2, we recommend that EPA utilize an already existing empirically-based systematic review methodology such as the OHAT Method developed by the National Toxicology Program, to framework Modules 1-3. Nick Chartres will be commenting on this in more detail.

In both Modules number 1 and 4, EPA references life-stage susceptibility, vulnerable populations, and cumulative risk.

Upgrading how EPA considers human variability considerations will be critical. Historically, EPA has relied on standard default values ("uncertainty" or "safety" factors) that have been applied across the board to various chemicals and health outcomes. Newer science demonstrates that EPA's typical safety factor of 10 is **insufficient** to account for variability due to life stage, genetics, underlying disease status, multiple exposures, and external stressors such as poverty or other non-chemical stressors. In fact, for cancer, the National Academy of Sciences recommended a factor of **25- to 50-** to account for the variability between the median individual and those with more extreme responses.¹

We recommend that EPA also consider the work done by state regulators, for example, the California EPA's work on early-life vulnerability to carcinogens. This approach incorporates differential susceptibilities to carcinogens and non-carcinogens, utilizing more recent science on increased susceptibility during the prenatal period **and** age-related susceptibility for non-mutagenic carcinogenic agents.² Its literature review on differential susceptibility to carcinogens and non-carcinogens is based on age **and** life stage derived age

¹ National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Pg. 168

² OEHHA. In Utero and Early Life Susceptibility to Carcinogens: [Internet]. 2009. Available from: <https://oehha.ca.gov/media/downloads/cnr/appendixjearly.pdf>

adjustment values for carcinogens, which include the prenatal period³, and increased the default intraspecies uncertainty factors for non-carcinogens to **30**, and to **100 for specific endpoints such as asthma or neurotoxicity**.⁴ The Cal EPA default factor can also be modified upwards or downwards depending on chemical specific information (*e.g.*, for benzene because of variability in metabolism and other sensitivities the non-cancer variability is 100).

At a minimum, EPA should start with Cal EPA's age adjustment values and intraspecies uncertainty factors for incorporating age/early life susceptibility. Cal EPA also developed child-specific risk values for chemicals (*e.g.*, atrazine, lead, nickel, manganese, heptachlor) that specifically address routes of exposure and differences in susceptibility unique to children compared to adults.⁵ EPA should review these additional evaluations and incorporate these values as appropriate to the baseline of 30 and 100.

Furthermore, a default guidance principle should be that animal findings **are** relevant to humans **unless there is sufficient and compelling scientific information to support otherwise**.

Finally, as part of this effort, the committee should recommend that EPA adopt the recommendation from the National Academy of Sciences that a unified approach to risks of cancer and other conditions **starts** with an assumption that **there is risk at low doses unless scientific data shows otherwise**. There are numerous reasons why this is scientifically appropriate, including that **many** harms from chemicals exposures continue to be shown at lower and lower exposures (*e.g.* lead, and particulate matter), and where background levels due to the background risk of health effects is **already** present or high (*e.g.* diabetes, neurodevelopmental outcomes).

There is also a wide range of human variability in response to chemical exposures. Some people are more vulnerable than others due to intrinsic and extrinsic factors. Intrinsic factors include age (*e.g.* such as early development, elderly), genetics, and preexisting conditions (such as diabetes, preexisting cardiovascular conditions or immune related diseases). Extrinsic factors include exposure to other industrial chemicals, which has been well documented, and the NAS has noted, can **increase** susceptibility compared to individual chemical exposures. Other factors that can increase susceptibility and external stress are things such as poverty, food insecurity and racism and discrimination. These factors vary across the population and mean that some groups are going to be at **higher risk at lower exposures** to the extent that it is **not possible** determine a threshold in the population.

Finally, an article we published in *Science* found that incorporating the most current scientific approaches to evaluate health risks can greatly improve the impact of economic benefit analyses utilized in environmental policy.⁶ Developing a framework that allows calculation of risk at any exposure level will aid EPA in decision making as it allows benefit/cost analysis among other analytic tools for decision makers.

³ California EPA 2009. Cal EPA 2009. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. <http://oehha.ca.gov/media/downloads/cnr/tdscancerpotency.pdf>

⁴ Cal EPA 2008. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document For the Derivation of Noncancer Reference Exposure Levels <http://oehha.ca.gov/media/downloads/cnr/noncancerstdfinal.pdf>

⁵ California Environmental Protection Agency. Office of Environmental Health Hazard Assessment (OEHHHA). Child-Specific Reference Doses (chRDs) Finalized to Date. Available from: <http://oehha.ca.gov/risk-assessment/chrd/table-all-chrds>

⁶ McGartland, A., Revesz, R., Axelrad, D. A., Dockins, C., Sutton, P., & Woodruff, T. J. (2017). Estimating the health benefits of environmental regulations. *Science (New York, N.Y.)*, 357(6350), 457–458. <https://doi.org/10.1126/science.aam8204>

We have commented extensively with regard to our concerns around EPA's incorporation of vulnerability and cumulative risk under TSCA, most recently on EPA's Scoping Documents for the next 20 chemicals. We will send these comments to the committee, but they can also be found at bit.ly/PRHE20Scope.