

May 29, 2019

To: EPA Scientific Advisory Board

Re: Updating EPA Guidelines for Carcinogen and Noncancer Assessment

We are scientists, academics and health professionals engaged in environmental health and write in response to the announcement that EPA is planning to update the 2005 Guidelines for Carcinogen Risk Assessment,¹ and create guidelines for non-cancer assessment.

We recognize that scientific advances in the fields of cancer and non-cancer risk assessment may support the need for updates to EPA guidelines and policies, and we are happy to offer our expertise and support to help guide this endeavor. We are also pleased that the SAB is being asked to provide its expert recommendations to EPA on this issue.

Every day, the public may come in contact with myriad chemicals and pollutants that can harm health, through air, water, food and consumer products. EPA is mandated to evaluate chemicals and ensure the protection of public health from those that are toxic, and risk assessment is a key part of this process. EPA's risk assessment guidelines play a critical role in informing how the Agency will analyze the evidence on chemicals and ultimately, its policy decisions. Thus it is vital that EPA's guidelines are accurate, reflect current science, and support evidence-based decision making that will protect people's health, especially our most vulnerable populations.

If EPA will move forward with a guidelines update, it needs to put in place a transparent process that provides opportunities for meaningful public engagement throughout.

First, it is important to identify what areas of the guidelines require updates, based on current science. EPA should engage the National Academies of Sciences (NAS) to conduct a review and provide recommendations. EPA should then use this information to develop a scoping plan for the guidelines update and solicit public comment on the plan. The NAS has recommended seeking public comment early in a process to ensure that the project is appropriately scoped and for the Agency to receive, up front, relevant information that it can incorporate.²

Second, for major guideline updates, EPA typically follows a process that includes internal Agency review, interagency review, external peer review, expert input and public comment. For example, the *Draft Guidelines for Human Exposure Assessment* notes:

“EPA's Risk Assessment Forum obtained broad participation in its efforts to update the 1992 document. The Risk Assessment Forum convened a colloquium of EPA exposure assessment scientists in 2005 to assess the state-of-the-science, discuss Agency practice and identify emerging issues. This colloquium was followed by meetings with scientists from EPA, state agencies and the broader scientific community... In 2006, the Agency consulted with the EPA Science Advisory Board, describing its approach to the update and summarizing comments

¹ US EPA (2005) Guidelines for Carcinogen Risk Assessment. Available from:

https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

² 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. <https://doi.org/10.17226/25086>.

received from Agency scientists, the scientific community and the public. This update, the *Guidelines for Human Exposure Assessment*, benefits from many additional years of experience with exposure and risk assessments across the Agency, conversations with the broader scientific community and products from the Science Advisory Board and the National Research Council of the National Academy of Sciences.”³

Subsequent to these activities, the draft guidelines were released for public comment and external peer review.⁴ Any cancer and non-cancer guidelines drafts should follow a similar process, and would additionally benefit from NAS peer review.

Finally, for all of the above, experts engaged throughout this process should be free of conflicts of interest that have been empirically found to affect bias. Specifically, financial links to a regulated industry, whether as a direct representative or as a consultant, is such a conflict of interest.^{5, 6} Importantly, as stated by the Office of the Inspector General, receipt of a federal grant is *not* a financial conflict of interest.⁷

While a comprehensive scientific review is needed to determine guideline areas requiring updates, we have some initial recommendations based on well-established science of two major areas for consideration:

1. Implement the NAS recommendation for a unified approach to analyzing health effects from chemical exposures that applies the methods used for mutagenic carcinogens to non-mutagenic carcinogens and non-cancer health effects.

NAS has recommended that the default approach to the dose-response for all mechanisms of action (MOAs) be linear.⁸ The current EPA practice for assigning “nonlinear” MOAs does not account for mechanistic factors that can create linearity at a low dose, such as when an exposure contributes to an existing disease process.⁹ Specifically:

- Chemical exposures that add to existing (background) processes, endogenous and exogenous exposures lack a threshold if a baseline level of dysfunction occurs without the toxicant and the toxicant adds to or augments the background process.¹⁰
- Human variability with respect to the individual thresholds for a nongenotoxic cancer mechanism can result in linear dose-response relationships in the population.¹¹

³ EPA (2016) Guidelines for Human Exposure Assessment. Risk Assessment Forum, Peer Review Draft. Available: <https://www.epa.gov/risk/guidelines-human-exposure-assessment>

⁴ 81 FR 774

⁵ Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev.* 2017(2:MR000033.). doi: 10.1002/14651858.MR000033.pub3.; PMID: 28207928.

⁶ White J, Bero LA. Corporate manipulation of research: Strategies are similar across five industries. *Stanford Law & Policy Review.* 2010;21((1)):105-34. .

⁷ EPA OIG (2013) EPA Can Better Document Resolution of Ethics and Partiality Concerns in Managing Clean Air Federal Advisory Committees. Report No. 13-P-0387. Pg. 9-10

⁸ National Research Council. *Science and Decisions: Advancing Risk Assessment.* Washington, D.C.: National Academies Press; 2009. Ch.5

⁹ Id. pg. 129

¹⁰ Id. pg. 130

¹¹ Id.

- In animal tests, a specific chemical may cause cancer through a nonlinear dose-response process. But for the human population, the dose-response relationship for the same chemical is likely a low-dose linear one, given the high prevalence of pre-existing disease and background processes that can interact with a chemical exposure, and given the multitude of chemical exposures and high variability in human susceptibility.¹²

Historically EPA has assumed a linear dose-response with no threshold of effect only for carcinogens that are mutagens or that have high human body burdens. But as detailed above, the science indicates that this linear presumption with no threshold is appropriate for mutagenic carcinogens, non-mutagenic carcinogens, and non-cancer health effects.

2. Science indicates greater susceptibility of early life stages to cancer and non-cancer health effects; the guidelines should add or increase factors to account for this.

While EPA does account for increased susceptibility to genotoxicants, it does not include the prenatal period or chemicals that can influence cancer through other mechanisms. California EPA's guidance incorporates factors to account for increased susceptibility for exposures that occur prenatally for carcinogens, non-mutagenic carcinogenic agents and non-carcinogens. Their literature review on differential susceptibility to carcinogens and non-carcinogens based on age and life stage derived age adjustment values for carcinogens which include the prenatal period¹³ and increased the default intraspecies uncertainty factors for non-carcinogens to 30 and 100 for specific endpoints such as asthma or neurotoxicity.¹⁴

In general, developmental life stages, including the fetus, infancy, and childhood, are more vulnerable to chemical exposure and toxicity. However, typical EPA age-dependent adjustment factors account for other life stages but NOT fetal exposures. Recent studies have demonstrated differential expression and activity of metabolic enzymes such as Cytochrome P450 in fetal versus adult tissue, indicating potential life stage-dependent variability in metabolic capabilities and greater vulnerability during fetal development not accounted for in current risk assessment practices.¹⁵ This is a critical point to address, as disruptions during fetal development have implications for health and disease in adulthood. The guidelines process should evaluate this rich body of literature to identify the most up-to-date scientific knowledge regarding human variability and susceptibility and incorporate these scientifically-based default values unless there are chemical-specific data supporting departing from the defaults. California EPA also developed child-specific risk values for chemicals (e.g., atrazine, lead, nickel, manganese,

¹² Id.

¹³ 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/crnrtsdscancerpotency.pdf>

¹⁴ 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/crnrtsdscancerpotency.pdf>

¹⁵ Sadler, N.C., Nandhikonda, P., Webb-Robertson, B.J., Ansong, C., Anderson, L.N., Smith, J.N., Corley, R.A. and Wright, A.T., 2016. Hepatic cytochrome P450 activity, abundance, and expression throughout human development. *Drug Metabolism and Disposition*, 44(7), pp.984-991.

heptachlor) that specifically address routes of exposure and differences in susceptibility unique to children compared to adults.¹⁶

We are appreciative of the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

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¹⁶ California Environmental Protection Agency. Office of Environmental Health Hazard Assessment (OEHHA). Child-Specific Reference Doses (chRDs) Finalized to Date. Available from: <http://oehha.ca.gov/risk-assessment/chrd/table-all-chrds>

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