Toxicology Excellence For Risk Assessment
Cincinnati, Ohio

Regarding: Formaldehyde IRIS Toxicological Review of Formaldehyde – Inhalation (Draft Review)

June 9, 2022

Dear Colleagues

We applaud EPA for tackling this complex undertaking and allowing us to assist. However, although several aspects of EPA's formaldehyde text are well done, other aspects appear to suffer from lack of erudite judgment, adherence to EPA's guidelines, and missed opportunities to work with outside parties such as our European colleagues. The overall impression EPA's formaldehyde text makes is that formaldehyde is toxic at levels below what it often found indoors, or in outdoor air, or that is sometimes found in human breath. This begs credibility.

It is difficult to understand how EPA can propose safe levels for chemicals such as formaldehyde that are otherwise naturally occurring and endogenous produced in humans, often in metabolic pathway that are essential for human life, especially when external/exogenous exposures do not upset homeostasis of internal/endogenous concentrations. That EPA has proposed such safe levels however suggests to us that EPA has failed to bring to bear the erudition within much of their staff. This lack of erudite judgment is surprising because many of EPA's scientists have won the Lehman award from the Society of Toxicology, an award sometimes referred to as the Nobel prize for risk assessment. Two of EPA's current employees possess this award, Annie Jarabek and Edward Ohanian, and two recent EPA employees Rory Conley and Michael Dourson also possessed this award. More importantly, Rory Connolly has published extensively on formaldehyde and is heavily cited in EPA's text. Yet he has not been approached by IRIS staff for his opinion on the developing formaldehyde assessment since the early 2000's. The lack of using these EPA scientists, who are recognized world wide for their knowledge and experience with the toxicity of formaldehyde and other chemicals, defies explanation.

Well, what can EPA do to improve its draft?

First, EPA should focus on the area of critical effect and not belabor effects that are clearly well advanced in formaldehyde's underlying mode of action. For example, estimating a Reference Concentration (RfC) for a pathological endpoint that only occurs well above a No Observed Adverse Effect Level (NOAEL) for tissue irritation is non-sensical. Furthermore, EPA has some exquisite human data in hand including data in sensitive subgroups. EPA needs to recognize that a NOAEL for such data are, in effect, the RfC, as per its own definition of RfC. In such cases, no additional uncertainty factors are needed for within-human variability, as

readily demonstrated by prior EPA judgments found on its Integrated Risk Information System (IRIS).

Second, EPA should follow its own guidelines and develop a low dose cancer extrapolation based on a dual mode of action. The proposed hockey-stick approach of EPA's own award winning scientist, Rory Conolly, would like approximate the end result, but other approaches might be considered, such as that suggested by Dourson et al. (2008) for acrylamide, or published by McGregor et al. (2006) or by Thompson et al. (2020) for formaldehyde, the latter effort which was adopted by the European Union.

Third, EPA's choice of dosimeter for its cancer modeling, that is cumulative exposure, is wrong. EPA's own text indicates that that the choice of dosimeter for the formation of tumors, either nasal pharyngeal or leukemia, is related more to the peak concentration rather than the cumulative exposure. Thus, EPA needs to develop a low dose response extrapolation on the basis of peak exposure, despite the apparent difficultly in doing so. Otherwise, EPA's projected lifetime cancer risks are not credible.

Fourth, EPA should consider the recent findings of the Alliance for Risk Assessment (*ARA*) Beyond Science and Decisions workshop XIII, where formaldehyde was used as an example of a new approach to dosimetry that may offer some insights.[1] Simply put, this case study suggests that formaldehyde cannot penetrate the cell nucleus at low concentrations, thus supporting the threshold approach suggested by Thompson et al. (2020). In such cases, EPA (2005) cancer guidelines dictate the use of RfDs or RfCs as the basis of the low dose extrapolation rather than a linear low dose modeling.

We attached several texts that highlight our comments and should provide clarity to EPA's revision. We would be happy to work with EPA on specific aspects of these comments.

Sincerely,

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[1] See: https://tera.org/Alliance%20for%20Risk/WorkshopXIII/Workshop_Final_Report_22.pdf, case study 3, page 34.