Scientific Peer Review from USDA
Comments on the Interagency Science Discussion (Step 6)
Draft IRIS Toxicological Review of Formaldehyde—Inhalation
June 2024

Date: 07/22/2024

Peer reviewers from various USDA[1] agencies provided the following non-IRIS specific comments and IRIS-specific scientific comments for U.S. EPA's consideration.

Non-IRIS Specific Comments

USDA values and supports the efforts of EPA and other regulatory authorities to protect the health of workers and exposed individuals through the regulatory risk assessment process. Given the significance and ubiquity of formaldehyde in commerce and in production, and the sheer volume of information contained in this review, USDA would note that the time provided for review was very short. USDA requests a more formal process to address issues related to this chemical.

USDA also requests additional interagency conversations to discuss potential implications of this draft toxicological review on future regulatory actions for formaldehyde.

Related to the scientific comment below about use of sensory irritation as an endpoint, if this endpoint is maintained, risk assessors and risk managers using this endpoint for regulatory decisions should discuss the conservatism inherent in this endpoint and take it into account as part of their regulatory decision-making process. Similarly, we also encourage IRIS to clarify how the conclusions in its toxicological review can be/should be used, and what limitations should be kept in mind by regulatory scientists who may use the IRIS conclusions.

USDA notes that formaldehyde is both directly and indirectly very important in agriculture, including in applications that themselves impact human and environmental health (positively). If those uses are threatened due to an overly conservative toxicological assessment of formaldehyde, that assessment could have a net adverse impact on human health and the environment.

IRIS-Specific Scientific Comments for EPA's Consideration

USDA has concerns that recent reviews of formaldehyde are missing from the draft IRIS toxicological review of formaldehyde, such as a 2023 update of the CIIT Formaldehyde Biologically Based Dose Response (BBDR) model by Connelly et al. https://academic.oup.com/toxsci/article/193/1/1/7076626.

[1] The USDA offices participating in the interagency scientific peer review include: the Food and Nutrition Service, Office of Policy Support; the Food Safety and Inspection Service, Office of Public Health Science; the Office of the Chief Economist, Office of Risk Assessment and Cost-Benefit Analysis; and the Office of the Chief Economist, Office of Pest Management Policy.

Section ES.2.1 of the IRIS Toxicological Review of Formaldehyde states that, "The selected RfC is the midpoint of three osRfCs (0.006, 0.007 0.008 mg/m^3) representing a group of respiratory system-related effects (i.e., pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control) that were interpreted with the highest confidence and had the lowest UFCs." Please explain why this methodology was used to define the osRfC and why it is appropriate.

Please provide the scientific rationale and plausible pathway for why it is appropriate to conclude that formaldehyde causes lymphohematopoietic (LHP) cancers including acute myeloid leukemia when there is no evidence that formaldehyde enters the bone marrow or blood when inhaled.

USDA requests additional characterization about the use of sensory irritation as an endpoint and a rationale for the UFs for this endpoint. We request clarification on whether IRIS considers irritation itself an adverse effect, or if IRIS considers it to be indicative of a systemic effect. USDA notes that use of sensory irritation as an endpoint is conservative because it would protect against adverse effects from higher exposures.

Please provide more details about the likelihood of individuals staying in areas with high enough levels of formaldehyde to cause adverse effects, including carcinogenicity, when people are likely to leave areas when they experience sensory irritation such as eye irritation.

What evidence suggests that all of the nasopharyngeal cancers observed in the U.S. population are attributable to formaldehyde exposure?

USDA requests additional characterization regarding the use of age dependent adjustment factors (ADAFs). The 2005 EPA Guidelines for Carcinogen Risk Assessment indicate that "an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur." USDA is not certain that ADAFs are required because it is not clear that different doses were fully considered by EPA.

Given the importance of formaldehyde in many different business applications and sectors, including agriculture, we request that IRIS provide guidance for application of its RfC and inhalation unit risk (IUR) values in risk assessments for workers and all population subgroups. For example, if EPA maintains use of ADAFs, additional scientific explanation on how to correctly use the IRIS-selected endpoints for each age group is needed in order to ensure appropriate use of the selected value(s).