Message from the EPA IRIS Program

August 2024

The following slides were presented at a virtual meeting held on July 29, 2024 between EPA and representatives from other federal agencies/departments and the Executive Office of the President (EOP). EPA convened this meeting to discuss interagency comments received on the draft IRIS Toxicological Review of Formaldehyde – Inhalation (Interagency Science Discussion Draft; Step 6). The following federal agencies and departments were represented at the meeting: EPA, EOP (OMB and CEQ); USDA; DoD; DoE; OSHA; CPSC; NASA; SBA; ATSDR; FDA; and NIEHS. The slides summarize comments received and EPA's responses. The verbatim comments from EOP, other federal agencies and departments on the Step 6 Interagency Science Discussion Draft are posted to the EPA IRIS website and in the docket (EPA-HQ-ORD-2010-0396).

EPA
United States
Environmental Protection
Agency

Interagency Comments on the Toxicological Review of Formaldehyde-Inhalation

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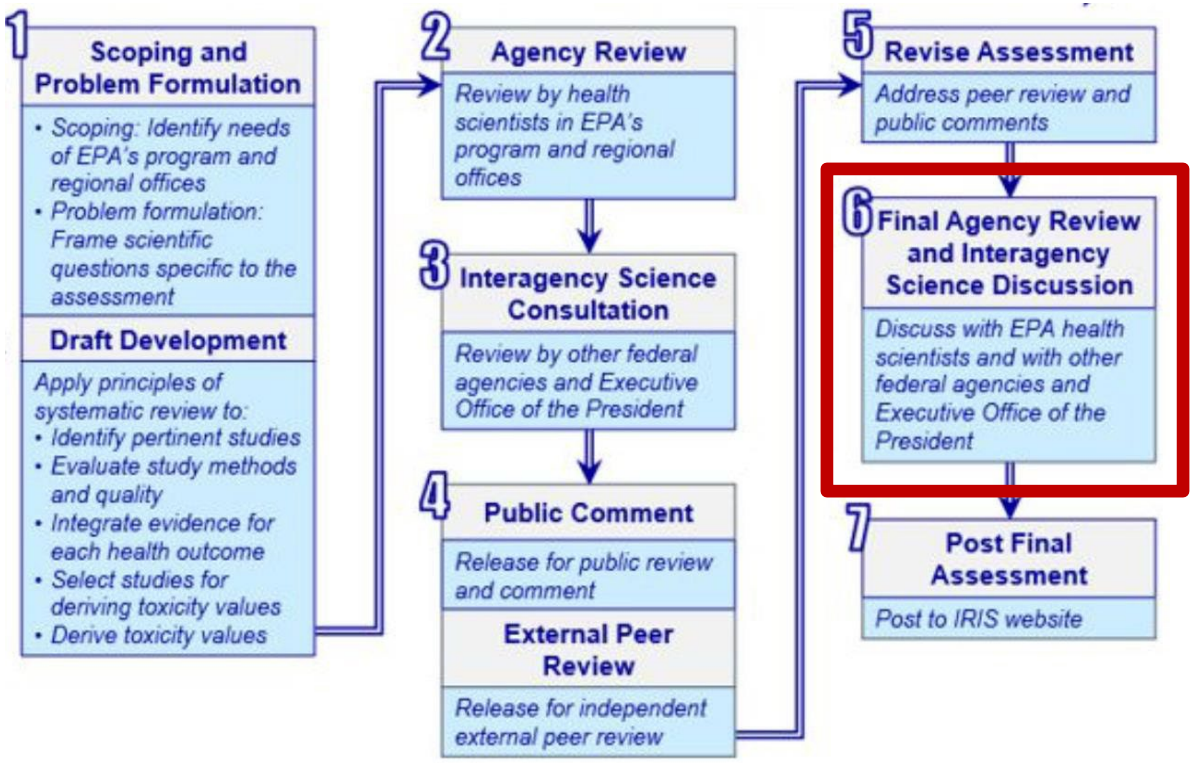
Interagency Science Discussion



- Focus is on EPA's disposition of peer review and public comments
- IASD comments become part of the public record of the assessment
- Scientific comments were received from ATSDR, USDA, and NIOSH (OMB, NIEHS and NASA indicated they did not have comments)

General clarifications

- ATSDR: Comments related to incorrect callouts and numbering, and organizational revisions.

EPA notes: Incorrect callouts and numbering have been being checked and addressed. As noted in the Step 6 email to partners, a technical editing review was performed in parallel with the Step 6 review (thus, the email requested comments be focused on scientific content). Extensive organizational changes were made in response to the Tier 1 recommendation from the NASEM panel, which caused significant changes to callouts.

- USDA: Comments related to potential future regulatory actions and requests for interagency discussions on such potential future actions.

EPA note: IRIS assessments address hazard ID and dose-response analyses. They are not risk assessments. The regulatory applications of the final IRIS assessment are not the purview of ORD or IRIS, nor does ORD direct assessors on how the strengths and uncertainties of the toxicity values impact their regulatory decision-making. Such inquiries should be directed to the relevant EPA programs or regional offices.

- ATSDR: Comments on EPA guidelines and potential cross-agency differences in approaches (e.g., MOA; epidemiology).

EPA notes: These comments are not specific to the IRIS formaldehyde assessment. It is important to note, however, that a lack of understanding of MOA is not considered in EPA guidelines as a reason to reject causality and epidemiology studies are routinely used by EPA and other international health assessors to support causal conclusions.

General clarifications

- ATSDR: Comments related to preliminary assessment materials (e.g., protocol).

EPA notes: In 2011, NAS recommended IRIS should not stop developing assessments as it was developing and implementing systematic review methods, such as releasing protocols. The draft formaldehyde assessment was already very mature when the protocol practice was implemented within IRIS in 2018. Thus, in 2023, NASEM's resultant conclusion was that "pre-published protocols are essential for future IRIS assessments," and EPA agrees with this conclusion. These points are covered in Appendix F.

- ATSDR: "Many responses from EPA are not addressed directly after the comment but in later comment responses, such as… In this respect the Reviewer is indicating they could not find a separate response from EPA for several NASEM findings. However, response for many of them were found under different comments..."

EPA notes: EPA did not respond to every NASEM Finding. The NASEM Findings were not committee recommendations, but rather conclusions that typically did not warrant a response. When recommendations were associated with a Finding, NASEM provided Tiered comments. EPA responded to Findings when there were clarifications made in light of those Findings.

General clarifications

- ATSDR: "EPA does not provide any substantial response to the 16 public comments received [in Appendix F.5] (Note: "EPA has provided responses as necessary on topic areas addressed by the IRIS assessment" does not suffice). It is suggested that the footnote be moved to the main text of the document as a response to some of the comments. Further, as the footnote does not address all comments (e.g., lack of transparency, consistency with international scientific agencies, lack of impartiality), it is recommended that the main issues … be parsed out to provide adequate responses to each of the issues."

EPA Notes: An expanded explanation for why responses are not provided for the general ("we appreciate the evaluation") or IRIS formaldehyde assessment-nonspecific ("…hazards associated with formaldehyde applications in the animal agriculture section.") public comments included in Appendix F.5 is now provided (footnote was retained): "Note: EPA has provided responses in Appendix F.1 to F.4 on topic areas addressed by the IRIS assessment. The comments below are either general comments not needing an EPA response, or they are not relevant to the scientific analyses in the IRIS formaldehyde assessment [footnote text: IRIS assessments are not risk assessments and they do not address exposure assessment or risk management considerations. These are the purview of other EPA program and regional offices, and thus responses are not provided to these comments. Responses are also not provided to comments related to EPA, IRIS, or NASEM processes or policies. EPA draws independent scientific conclusions based on the evidence, which can differ from conclusions by others (see Appendix G for a summary). IRIS assessments do not include evaluations of such potential differences, and thus, responses to comments of this nature are also not provided.]"

Response to comments on NRC (2011) review

- ATSDR: “Two public comments received from University of California San Francisco and Troy Corporation both felt that EPA did not address the 2011 NAS recommendations (pg F-4). Though EPA responds with peer review findings that EPA met the “broad intent” of the recommendations, EPA does not substantively respond to a significant Troy Corporation public comment which was also from NAS. Specifically, the comment states that “EPA did not identify modes of action…[for cancer and] nervous system effects and systemic toxicity”. It is recommended that EPA add to the response by summarizing the additional details added to the ToxReview that addresses modes of action for the endpoints.”

EPA notes:

- To clarify, the quoted text is from the Troy Corporation and the comment from UCSF did not pertain to the above; rather, it reflected that they may have missed the Step 4 draft Appendix responding to each specific recommendation in the 2011 NRC review.
- When comments are received on the same topic, EPA prioritizes findings from the consensus peer review over individual public comments.
- Extensive analysis and discussion of the NPC cancer MOA and its application can be found in Sections 3.2.5 and 5.2.
- EPA did not identify MOAs for LHP cancers, nervous system effects, or other systemic effects due to the lack of an evidence-based explanation for such MOAs; however, the evidence that does exist, with an assumptions of no systemic distribution, was evaluated.
- EPA guidelines do not require MOA understanding to identify a hazard.

Response to comments on assessment methods and literature

- USDA: "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."

EPA notes: The IRIS Program formally reviews the literature through the time of release for Step 4 external review (2022). After this time, studies are recommended for incorporation by the external peer review panel if the studies "significantly alter key conclusions such as the draft RfC or IUR" [see peer review charge questions]. For this study, public comments (in writing and orally) on this update were provided to the NASEM committee and the publication was available (March 2023) well in advance of the committee's report. No recommendation to incorporate it was provided. Regardless, as the IUR is based on the human data, this update applicable to the animal data would not alter the IUR.

- ATSDR: "There are numerous comments concerning additional literature that EPA did not appear to include in the ToxReview. EPA did review the suggested studies and tagged some of the literature as supplemental and determined 7 studies met PECO criteria … "

EPA notes: EPA checked and verified that the noted studies were considered (Appendix F).

- ATSDR: Comments related to supplemental tagging practices in the IRIS Program.

EPA notes: Supplemental studies are not excluded, and the Handbook describes how categories of supplemental information are collated for additional review. Note that EPA does not include tables of supplemental studies; studies are tracked in HERO.

Response to comments on assessment methods and literature

- ATSDR: "EPA's response to a comment by American Forest and Paper Association indicated that at least three of the bulleted comments "are not specific to the content of the assessment and thus no response is provided." The Reviewer disagrees with the lack of response to these other bullets (e.g., failing to incorporate relevant literature, use of uncertainty factors, lack of transparency) as they do impact the formaldehyde specific assessment. Further, more than one commenter (Tox Strategies) noted similar literature failures. This issue could detract form the confidence in the entire ToxReview."

EPA notes: As outlined in Appendix F, the two studies identified by the commenter were considered by EPA. The other two were generalized comments (i.e., "EPA failed to discuss studies accurately and transparently"; "EPA is overly conservative in its use of uncertainty factors"). It is noted that such broad statements were presented without a scientific basis, and in the presence of extensive discussions of studies and detailed rationales for uncertainty factors applied. These topics were part of the peer review charge.

- NIOSH: "Epidemiological evidence is slight for oropharyngeal/hypopharyngeal cancers, …": NIOSH suggests replacing the word "slight" with "limited." Use of the phrase "slight evidence" in an epidemiological context is unusual."

EPA notes: "Slight" evidence is the phrasing used in the IRIS Handbook to describe one of the five evidence synthesis judgment categories (for human and animal evidence).

Response to comments on noncancer hazard identification

- USDA: “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.”

EPA notes: As described in Sections 3.2.1 and 5.1, sensory irritation (e.g., “burning eyes”), at the magnitude and severity reported in most studies, is considered a minimally adverse outcome. During the extensive review of the apical and mechanistic studies relevant to this outcome, EPA did not identify evidence to support considering this response as indicative of a systemic effect, nor to support that protecting individuals from developing sensory irritation would be expected to protect against other adverse effects, particularly when considering human variability. Quantitatively, PODs for sensory irritation were not the most sensitive.

Response to comments on noncancer hazard identification

- USDA: "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."

EPA notes: The evidence supporting several well-established health effects of formaldehyde inhalation includes long-term human observational studies in homes and workplaces where the exposed individuals continued to be exposed to formaldehyde, possibly at levels lower than those that causing overt sensory irritation. The conclusions drawn are based on the available evidence and do not address the hypothesis that individuals can move homes or jobs when facing adversity.

- ATSDR: "EPA indicates, in a response to a commentor, that Ozen (2002) is cited for testes endpoints and Ozen (2005) for testosterone endpoints in the ToxReview. Yet, the Reviewer checked the ToxReview and on page 3-346 line 5, EPA is citing Ozen 2005 for testes findings. It is recommended to correct this error or to add that testes histology uses Ozen (2005) and testes weight cites Ozen (2002)."

EPA notes: In rechecking, while no instances of citing Ozen 2005 for testes weight was found, an error in citing Ozen 2002 for seminiferous tubule measures was corrected.

Response to comments related to the RfC

- ATSDR: "…EPA has used new methodology to combine dose response assessments (e.g., Hanrahan et al. 1984 and Liu et al. 1991) to address deficiencies in the individual studies which then created a new BMCL and cRfC. It is noted that EPA elected to use the Hanrahan et al. 1984 and Liu et al. 1991 (combined study) to develop the osRfC for sensory irritation when the Andersen, 1983 study resulted in a lower cRfC (0.01 mg/m^3 vs 0.02 mg/m^3), this even though the Andersen study was a controlled exposure study therefore having more informative exposure estimates. EPA based this selection on the overall confidence in higher confidence in the combined study (medium-low) and it has less of a composite uncertainty factor (3 vs 10). It is recommended that EPA allow for another round of interagency, peer review, and public commenting on this ToxReview to provide the scientific community time to assess whether they agree with this methodology and resultant cRfCs and osRfCs. This sentiment is echoed by public commenters."

EPA notes: It is standard practice to make changes to assessments in response to peer review comments (here, a Tier 2 suggestion) without additional peer review. A few points:

  - NASEM's consensus Finding 10 concluded that favoring well conducted observational studies over controlled exposure studies was justified for this outcome.
  - The methodology used is not new. The dose-response modeling approach for the combined data is the same as that previously used to model Hanrahan et al. alone. The methods for estimating results from Liu et al. parallel those of NASEM (2023, Appendix D).
  - The osRfC for sensory irritation is no longer used in the RfC. Thus, this revised value does not represent a key assessment conclusion.

Response to comments on the RfC

- USDA: "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."

EPA notes: The methodology used to select the RfC is in accordance with considerations in EPA guidelines and follows the approaches outlined in the IRIS Handbook (see Chapter 8). This approach emphasizes the preference to consider confidence in the reliability and certainty of the toxicity value over sensitivity of the value itself (e.g., for formaldehyde, several lower osRfCs were more uncertain and thus not selected).

- ATSDR: "In response to a comment about Figure 2-3 needing to accurately show…outdoor and indoor formaldehyde concentrations, EPA indicates the figure is in Section 5.1.5; however, it would be more accurate to respond that the figure no longer exists and to not identify any section (of the ToxReview) where it would have been located. Additionally, since the figure was removed, it is suggested that a reason be provided as to why a public comment to show accurate ranges resulted in not keeping the figure."

EPA notes: To clarify, the figure was not removed. The ranges of exposure levels were removed from the figure and a description in the text of median indoor and outdoor levels was added for context. This clarification has been added to the response to comments.

[Aside: despite different decisions, the ATSDR MRL and IRIS RfC are near-identical]

Response to comments on respiratory tract pathology and cancer

- NIOSH: "Although an explanation was added to explain why Horton et al. [1963] is still considered (in relation to the anatomical location of lesions), the explanation does not state clearly that the nasal epithelium was not examined. Absence of neoplasms even after exposure to a very high concentration of formaldehyde for 35 weeks could be explained by several mechanisms. However, a mechanism cannot be determined without nasal epithelium examination. The authors might want to state clearly what useful information is derived from this study."

EPA Notes:

- The commenter refers to neoplasms; however, this study was classified as *not informative* for respiratory tract cancers and thus not synthesized in the context of neoplasms (or the absence thereof).
- The study is mentioned in the noncancer effects section in relation to the anatomical location of lesions only as a brief commentary that it may take very high exposure levels to cause lesions in more distal regions of the respiratory tract. Statements about lack of lesions in the nasal epithelium are not associated with this study.
- We agree this study is not useful to nasal cancer interpretations.

Response to comments on respiratory tract cancer

- NIOSH: "Although the bioassays in mice, hamsters, and rats represent similar exposure concentrations and duration of exposure, clear species differences in the severity of lesions are present."…The sentence mentions differences in toxicity outcomes in difference species and within sex, when exposed to similar concentration of formaldehyde and for the same duration. If the evidence is collected from different experimental animal studies, and there is a clear indication of differential toxicity due to anatomical and metabolism related differences, NIOSH recommends stating how this issue has been addressed when extrapolating to human adverse outcomes (not just application of uncertainty factors).

EPA notes: Of these studies, only those in rats could be used in the dose-response modeling and quantitative extrapolation to humans, so there are no applicable animal species-specific quantitative differences. The cited sentence does contribute to the hazard conclusion at the end of the paragraph that "… inhalation exposure to formaldehyde in experimental animals induces nasal cancer and dysplasia with increasing incidence as a function of exposure duration and concentration at the POE."

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

EPA notes: See Section 5.2.1, which provides an estimate of the number of nasopharyngeal cancer cases at different lifetime formaldehyde exposure levels and compares it with the total incident cases of NPC per year.

Response to comments on respiratory tract cancer MOA

- NIOSH: "'Although uncertainties remain, the nasal cancer MOA, including mutagenicity, is interpreted as relevant to this cancer type.' This statement is not clear. Are the uncertainties pertaining to the entire MOA(s) or to mutagenicity alone? The sentence could be rewritten to provide clarification."

EPA notes: The quoted sentence builds from the prior sentence: "This evidence is supported by the apical and mechanistic evidence for nasal cancers across multiple animal species, although some uncertainty remains in the interpretation of the animal nasal data as wholly applicable to interpreting sinonasal cancer (and thus, the animal evidence is reflected as *moderate* for the purpose of interpreting human SNC). Although uncertainties remain, the nasal cancer MOA, including mutagenicity, is interpreted as relevant to this cancer type ."

The highlighted sentence has been revised: "Despite some uncertainty in the applicability of the animal data to human SNC, the identified nasal cancer MOA, including mutagenicity, is interpreted as relevant to this cancer type."

Response to comments on respiratory tract cancer MOA

- ATSDR: "It is recommended that EPA's respond fully to ToxStrategies bulleted comments in their response, even if that is to point the Commenter to other EPA responses addressing the same issues. It is unclear that the statement "studies with no primary data…" addresses failure to integrate relevant science and other bulleted comments."

EPA notes: Additional text has been added to the response to comments for bullets with specific questions as follows: "… Please also see the specific descriptions in the Toxicological Review that describe how the relevant information was identified (Section 2) and how EPA guidelines were adhered to in evaluating the respiratory cancer MOA (Section 3.2.5), as well as the consideration of nonlinear approaches to addressing one MOA contributing to upper respiratory tract cancers, including derivation of an RfC (Section 5.2.1). EPA has updated the BMDS modeling, as described in responses to NASEM and public (including from ToxStrategies) comments below, primarily in Appendix F.3.8."

Response to comments related to LHP cancer and MOA

- USDA: "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."

EPA notes: Extensive analyses and discussion supporting the LHP cancer hazard conclusions can be found in Section 3.3.3). This was also a science topic in the peer review charge questions; the conclusion was supported by the NASEM panel.

- NIOSH: " During Step 3 NIOSH recommended including key evidence provided by the three studies listed below. In EPA's response to the comment, the non-English study (Chebotarev et al. 1986) was mentioned to have been removed because its contribution was not significant to the evaluation. It is not clear why the other relevant studies were not considered…Chromosomal aberrations are evidence of potential genotoxic effects of formaldehyde. Please cite Yager et al. [1986] which looked at an average increase in sister chromatid exchange (SCE) and formaldehyde exposure and Vasudeva and Anand [1996] which evaluated chromosomal aberrations in medical students exposed to formaldehyde."

EPA notes: The studies by Yager et al. (1986) and Vasudeva and Anand (1996) were considered by EPA and included in the assessment. These studies are included in the Appendix Genotoxicity tables (Appendix C.3.6).

Response to comments related to LHP cancer MOA

- ATSDR: “EPA responded to public comments related to systemic effects with “ lack of understanding of how inhaled formaldehyde can cause systemic effects without systemic distribution is insufficient to outweigh the formaldehyde-specific evidence that those effects are happening.” This response seems insufficient to address the underlying issues (e.g., no systemic distribution and the types of studies providing the “evidence”). As EPA notes in a response, epidemiological data were the basis of supporting their lymphohematopoietic cancer assessment when no mechanism of action has been hypothesized. Suggest EPA add scientific detail to multiple responses.”

EPA notes: Understanding of MOA is not required to identify a human health hazard, per EPA guidelines. However, the evidence that is available to inform potential MOAs for systemic effects under the strict assumption that formaldehyde is not distributed beyond the respiratory tract was evaluated and discussed in detail within each synthesis section, including for LHP cancers (Section 3.3.3).

Response to comments related to ADAF application to the IUR

- USDA: "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."

EPA Notes: Per EPA cancer 2005 guidelines and the supplemental guidance, ADAFs are applied for cancers for which there is sufficient evidence to conclude that the chemical operates, at least in part, through a mutagenic MOA. There is robust evidence supporting this conclusion for formaldehyde, and it was endorsed by the consensus peer review.

Clarifying that the text quoted by USDA is in relation to dose-response modeling not ADAFs (in the example, it is illustrating a low-dose linear extrapolation below doses at which cytotoxicity can be experimentally defined), EPA notes that the assessment includes detailed analyses of the two contributing cancer MOAs, mutagenicity and cytotoxicity-induced regenerative proliferation, and outlines and evaluates extensive attempts to experimentally define the exposure levels relating to both.

Other Submitted Comments Requiring Discussion?

Current/Ongoing IRIS Activities

- PFHxS
  - Final peer review report released July 2024
- PFNA
  - Peer Review Meeting July 30 – August 1
- Hexavalent Chromium
  - Anticipating finalization August 2024 (Step 7)
- Inorganic Arsenic
  - Ongoing peer review activities. Public meetings were held on July 8 and 16 for discussion of draft report by SAB Inorganic Arsenic Review Panel
  - Final report expected Fall 2024, after quality review by chartered SAB

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And "Thank You!" to many other contributors