Agency for Toxic Substances and Disease Registry (ATSDR)
Comments on the Interagency Science Discussion (Step 6)
Draft IRIS Toxicological Review of Formaldehyde—Inhalation
June 2024

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Most of the changes made in response to the external peer review and public comments by EPA in the external review draft IRIS Toxicological Review of Formaldehyde dated June 2024 are satisfactory. It should be noted that EPA indicates "some [public] comments were truncated for brevity" (pg F-2) and encourages the reader to review the EPA docket for the full comments. ATSDR reviewed the Supplemental Information for the ToxReview, specifically Appendix F which details the response to public comment. When necessary, ATSDR consulted with the updated (June 2024) IRIS Toxicological Review of Formaldehyde (Inhalation) and other appendices in the Supplemental Information document to ensure that changes were made. ATSDR did not refer to the full docket in completing this review.

It is also noted that in multiple responses EPA used the NASEM committee (peer review) as the primary resource in counteracting scientific public comments (e.g., pg F-32 line 20-25; pg F-40, line 10; pg F-46, line 37-38; pg F-92, line 12-13;, F-99, line 31-32; F-113, line 4-6) from other entities.

Below are comments provided by ATSDR to EPA to assist them in improving or clarifying some of the responses provided in the Supplemental Information document of the Formaldehyde Toxicological Review (ToxReview).

F.1. NASEM REPORT CHAPTER 2: "METHODS AND ORGANIZATION"; CHARGE QUESTION 1: ASSESSMENT DEVELOPMENT METHODS AND ORGANIZATION

F.1.2. Response to Prior National Research Council (NRC) Reports

- 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.

F.1.3. Alignment of the Assessment Methods with the State of Practice

- EPA responded to the tier 1 recommendation to revise the assessment to ensure that users can find and follow methods…(pg F-5 to F-8). EPA then added a chapter called "Assessment Overview" to address the comment. The outline for Chapter 3 has been much improved now

that an endpoint (e.g., nasopharyngeal cancer under Section 3.2.5) contains subsections for all the systematic review processes (e.g., evidence, associations) and then leads to a conclusionary statement for the endpoint. However, the need to place a document map (Table 2-1) into the assessment for health effect endpoints that jump around within the ToxReview, highlights the challenges a reader and reviewer has with following an effect endpoint to conclusion. For instance, sensory irritation has two continuous sections in chapter 2 (2.2.2, 2.2.3) but then jumps to Section 3.2.1 and finishes at Section 5.1. It is suggested that EPA consider changing their ToxReview outline to contain a health effect endpoint within one chapter and under one heading to allow readers continuity. This issue was echoed multiple times in public comments (e.g., pg F-17, line 5-8; pg F-32 line 27-30) and though some revision occurred, it is still a challenge for reviewers to follow and understand the content.

EPA might also like to consider, in future, separating (i.e., making a separate document for it) the peer review (Response to External Comments) from the other appendices that pertain to the ToxReview methodology. This Reviewer and probably others, lose their place in Appendix F when having to consult one of the other appendices to ensure that a change has been made to them.

It has been an ongoing challenge with reviewing EPA IRIS ToxReview Step 6 responses, as comments made to the original draft ToxReview will have sections, appendices and tables that are not the same as the updated review. For instance, pg F-9, lines 24-36 indicates Appendix E in the comment, yet Appendix E of the Supplemental Information document is "Quality Assurance for the IRIS Toxicological Review of Formaldehyde" and this appendix does not have figures and tables mentioned in the comment, therefore it becomes unclear whether EPA addressed the comment because the Reviewer cannot easily locate the revision. It would benefit EPA and the reviewers if the response indicated the name and location of the revision that was made in the updated ToxReview. Another words, the suggestion is to provide reviewers a crosswalk of the original comment name and location with the updated name and location.

Continuing with this example to communicate the point, a comment, on pg F-29, line 27 indicates that callout for Figures A-24 to A-26 were not cited in the main document and this comment was made in Appendix E of the original draft ToxReview. However, as noted earlier Appendix E is no longer the same in the updated ToxReview. The Reviewer then had to use the search feature on a newly created copy of the Supplemental Information (so as not to lose my Appendix F place) document to find "Figures A-24 to A-26" and it was only then that the Reviewer was able to confirm EPA's response that the callouts were added (these are now part of Appendix C, Section C.5.3, line 1). The ToxReview document contains no appendices so a callout to the figures has not occurred there.

Using the search feature on the Supplemental Information for "Figure A-36" and "Table A-93" which had inconsistent counts reported (pg F-9, line 28-32) by the commenter, returns no results within appendices A-E (Appendix F is the peer review comments which does not apply); therefore it is unclear how EPA "reviewed and clarified…inconsistences" unless they deleted the inconsistent figures and tables. If that was the solution then the Reviewer

recommends that EPA specify, especially for the commented figure and table, that the solution was to delete them, hopefully after obtaining consistent results.

- In response to a comment about Figure 2-3 needing to accurately show…outdoor and indoor formaldehyde concentrations (pg F-9, lines 35-36), EPA indicates the figure is in Section 5.1.5 (pg F-10 line 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.

- The response EPA has (pg F-11, line 27-29) for a comment received by the American Chemistry Council, (pg F-10, line 37 to pg F-11 line 2) seems to be misunderstood. It is believed that the Commenter recommended problem formulation and scoping activities be added to the ToxReview; not that NAS (2011) recommended it. EPA might consider adding text to the ToxReview indicating basic problem formulation and scoping activities, maybe in summary form, or indicating the systematic review processes of scoping and problem formulation were not guidelines when EPA began the formaldehyde assessment.

- EPA's response to a comment by American Forest and Paper Association (pg F-12, lines 16-34), 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 pg F-13 lines 7-9) noted similar literature failures. This issue could detract form the confidence in the entire ToxReview.

- There are numerous comments (pg F-12 to F-16) 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 (pg F- 14, line 24-32). Supplemental literature is not often discussed in the ToxReview so commenters would be unaware that EPA did review the suggested studies, even though a table identifying supplemental studies is often in appendices. EPA's indicates studies without "primary data" (e.g., pg F-12, line 37, pg F-16, line 33-34) are tagged supplemental. The Reviewer defines primary data as data that is published the first time (i.e., earliest in time). However, the epidemiological field has advanced with more refined statistical analyses being used by researchers; limiting to only "primary data" studies, especially for epidemiology, can therefore unnecessarily remove studies with secondary analysis of primary data that have valid results which need consideration. For instance, meta-analyses of epidemiological studies do not contain "primary data" (as the data were previously published), but it would be unwise to systematically remove these studies from consideration in developing ToxReviews. It is suggested that EPA reconsider the "primary data" limit placed on epidemiological studies and perhaps revise the response for their intended meaning.

- In reviewing the response to public comment (Appendix F of Supplemental Information) and determining whether EPA responses did indeed make changes to the ToxReview, there are multiple instances where the ToxReview callout to an appendix does not produce the desired information. In reviewing page F-18, line 11, the following was noted in the ToxReview: Page 5-10, Table 5-2 "d" footnote has "see Appendix C3.4" but when searching for Alexandersson, 1989, 31014 in the Supplemental Information it is on page B-125 which means it is in Appendix B. On page F-36, line 34-38, EPA notes footnotes were added to tables, however in consulting the ToxReview, footnotes were not added about flux to the specified tables, especially as chapter 2 is assessment methods which does not appear to align with specified discussive content. On page F-38, line 7-8 EPA indicates revision of tables that do not coincide with the tables containing modeling content. On page F-44, line 33 EPA refers to figures numbers that are not in the supplemental D-section, nor the ToxReview. It is recommended that EPA review and fix all callout errors prior to final publication of the ToxReview.

- Multiple comments were received (pg F-23 to F-26) regarding downgrading findings based on lack of mechanistic data and about mode of action (pg F-26 to F-27). A commenter provided information that makes it seem that EPA was the first agency to develop guidance (EPA 2005a) (pg F-24, pg 1). Further EPA developed guidelines indicating lack of data is not a reason for downgrading evidence findings (pg F-26, line 19). These actions create the appearance that EPA decided U.S. scientific policy that perhaps needed more consideration from a larger scientific community.

  Based on Figure 2-1 of the ToxReview, it also appears that one of the reasons EPA might not like to downgrade evidence findings for lack of mode/mechanism of action support is that RfCs and RfDs are not derived for evidence findings at or below "evidence suggests". In essence, EPA first developed guidance in 2005 to obviate the need of mechanistic data for any health effect and this is especially concerning when using epidemiological data for developing RfCs and RfDs since the population studied is exposed to mixtures and therefore a health effect may result from the mixture and not a sole substance exposure. Secondly, EPA restricted themselves to only creating RfCs and RfDs with "evidence demonstrates" and "evidence indicate" judgments. Because EPA developed the guidelines, the larger scientific community is no longer able to suggest the downgrading of evidence judgments and specifically for a scientific issue (i.e., mode/mechanism of action) that forms the basis of scientific rigor and judgment. Further, while the EPA response indicates application of the Hill considerations for causality (pg F-26, line 19-24), it should be noted that at least two criteria (temporal sequence and experimental evidence) are not possible to evaluate in most epidemiological studies and especially without mode/mechanism of action experimental evidence. Additionally, other Hall considerations are also very difficult to apply to most epidemiological studies to arrive at causality judgments. It is suggested that EPA convene discussions from the larger scientific community (such as scientific international workshops, panels, or other non-governmental panels/reports) regarding the issue of mode of action and the impact that it could have on evidence findings in systematic review.

- It is recommended that EPA's respond fully to ToxStrategies bulleted comments (pg F-27, line 22-28) 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…" (pg F-27, line 35-37) addresses failure to integrate relevant science and other bulleted comments.

- In this updated formaldehyde ToxReview, 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 (pg F-29 line 23-30) which then created a new BMCL and cRfC (ToxReview pg 5-50, Table 5-15). 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, 22932) 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) (ToxReview pg 5-53 to 5-55). 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 c (candidate) and os (organ specific) RfCs. This sentiment is echoed by public commenters (e.g., pg F-170, line 4-9; F-172, line 4-6).

- The following provides ATSDR and EPA derivations leading to differences in the health guidance value. EPA's overall RfC is 0.007 mg/m^3 which is the median of three osRfCs for respiratory system effects (pulmonary function [peak respiratory flow rate], allergy [rhinoconjunctivitis], and asthma [current prevalence or degree of control]) that provide high confidence and the lowest uncertainty (ToxReview pg 5-65 line 4-9). The studies used for the overall RfC (ToxReview pg 5-68, Table 5-24) are Annesi-Maesano et al. (2012), Krzyzanowski et al. (1990), Matsunaga et al. (2008), and Venn et al. (2003). The study osRfCs ordered from highest to lowest are, 0.008, 0.007, 0.006, or 0.004 mg/m^3. The Venn et al. 2003 study value (0.004 mg/m^3) for asthma degree of control was designated interchangeable with the current asthma prevalence value (0.006 mg/m^3) of Krzyzanowski et al. (1990) (ToxReview pg 5-65, line 7). EPA did not select the lowest cRfCs that were derived for the overall RfC. In selecting the median of these health conditions, EPA in effect selected pulmonary function which was derived based on a $BMCL_{10}$ for peak expiratory flow rate, a POD of 0.021, and composite UF of 3 (Kryzyzanowki, 1990, 27351; ToxReview pg 5-50; Table 5-15).

  ATSDR's formaldehyde chronic inhalation minimal risk level (MRL) was finalized in 1999. Like, EPA, respiratory effects were selected as the critical effect. The ATSDR inhalation chronic MRL for formaldehyde is 0.008 ppm (0.01 mg/m^3) based on eye and upper respiratory tract irritation and damage to the nasal epithelium in workers exposed for 10.4 years to an average TWA concentration of 0.24 ppm (Holmstrom et al. 1989c). The minimal lowest observable adverse effect level (LOAEL) was identified as 0.24 ppm. The minimal LOAEL was divided by uncertainty factors of 30 (3 for use of a minimal LOAEL and 10 for human

variability). When the Toxicological Profile for Formaldehyde was completed, ATSDR was not consistently using benchmark dose modeling in deriving a point of departure for the MRL.

F.2. NASEM REPORT CHAPTER 3: TOXICOKINETICS; CHARGE QUESTION 2: TOXICOKINETICS

F.2.2. Distribution of Inhaled Formaldehyde; Metabolism, Binding, and Removal of Inhaled Formaldehyde

- EPA responded to public comments (pg F-34 line 25 to F-35 line 17) 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 on page F-49, line 29-30, 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.

F.3. NASEM Report Chapter 4: Noncancer Health Effects; Charge Question 3: Respiratory System (Portal-of-Entry) Health Effects, Charge Question 4: Systemic Health Effects, and Charge Question 5: Noncancer RfC

F.3.2. Sensory Irritation

- The Reviewer could not identify Tables A-31 (pg 933, line 29), - 34, -35, and -36 (pg 934, line 1-2) in the documents.
- Many responses from EPA are not addressed directly after the comment but in later comment responses, such as: Pg 935, line 22, finding (1); Pg 1035, line 13, finding (15); Pg 1036, line 33, finding (20). 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. For example, finding (1) as noted to be on page 935 can be found under EPA's response to a tier 2 suggested revision (#4.2), on pg 936; line 38.

F.3.6. Reproductive and Developmental Toxicity

- 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).

F.3.7. Nervous System Effects

- Per controlled human exposure studies and EPA's response (pg F-97, line 10), it is unclear where the revisions were made as the cited, "Table A-85" does not exist in the Supplemental

Information and is not consistent with the ToxReview outline. Recommend that in responding to comments, EPA use the updated draft table identification to assist Reviewers in finding information; in this specific case, it was Table B-49 of the supplemental document but it may also be in the ToxReview tables too.

F.4. NASEM REPORT CHAPTER 5: CANCER ; CHARGE QUESTION 6: CANCER AND CHARGE QUESTION 7: IUR FOR CANCER

F.4.1. Hazard Identification

- EPA states "…that knowledge of MOA is not a pre-requisite for identifying a hazard in EPA guidelines or the IRIS Handbook" (pg F-146, line 33-35). It is recommended that EPA specifically cite the IRIS handbook on this statement and that EPA further clarify, scientifically, why having a hypothesized mechanism of action is not a prerequisite.

F.4.2. Dose-Response Analysis of Cancer Effects of Formaldehyde

- As noted previously (see F.3.2 Sensory Irritation comments), throughout the document, EPA responded to multiple NAESEM findings and public comments in one response (e.g., F-152, line 18), often these were not directly under the finding or comment but pages away in response to another comment. This practice is challenging for a Reviewer to verify that all comments have been addressed. The Reviewer recommends that EPA individually respond to findings and comments. If this is not possible, the Reviewer recommends that when EPA is responding to multiple findings/comments to then make it clear that finding/comment for x and y are in the response. When EPA is addressing a similar comment multiple times then the Reviewer asks that EPA identify in the current response the location of the full response. Also, best practice in responding to comments is to put the full text of the revision (or quoted excerpt) made to the ToxReview or Supplemental Information into the response along with the location of the revision.

F.5. GENERAL PUBLIC COMMENTS AND PUBLIC COMMENTS NOT ADDRESSED UNDER THE TOPIC AREAS ABOVE

- EPA does not provide any substantial response to the 16 public comments received (pg F-170 to F-176) and the line (pg F-170, line 2) ""[Note: EPA has provided responses as necessary on topic areas addressed by the IRIS assessment[46]]" does not suffice. It is suggested that the footnote (#46) on page F-170 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 [pg F-170, line 24-28; F-171, line 4-9 and line 28-31]; consistency with international scientific agencies [pg F-173, line 34 to F-174, line 8 and line 10-15], lack of impartiality [pg F-174, line 36-38; F-173, line 29-31; F-172, line 33 to F-173, line 14; F-170, line 24-28], it is recommended that the main issues received in these public comments be parsed out in order to provide adequate responses to each of the issues.