Submitted Via Email

March 31, 2023

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Committee Chair
Committee on Review of EPA's 2022 Draft Formaldehyde Assessment
National Academies of Science Engineering and Medicine
Board on Environmental Studies and Toxicology
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Re: Inconsistencies Between EPA's 2022, Draft Formaldehyde Assessment and EPA's December 22, 2022, Final IRIS Handbook

Dear Dr. Samet:

On behalf of the American Chemistry Council ("ACC") Formaldehyde Panel ("Panel"), I am writing to provide the accompanying document that delineates the Panel's feedback on EPA's written responses ("EPA's Responses") to the NASEM Committee's January 6, 2023, questions. As I noted previously, neither the Panel nor any other public stakeholder had an opportunity to review those written responses before the January 30th meeting.[1] Although the Committee actively discussed EPA's written responses during the public session, the public was effectively excluded because no one, other than the Committee and NASEM staff, was privy to EPA's written responses before the meeting and stakeholders were excluded from engaging in discussion with EPA and NASEM.

As described in detail in the accompanying document:

- EPA Did Not Follow its Own IRIS Handbook in Developing the 2022 Draft Assessment
- None of the NASEM Committee's Tier 1 Recommendations for the IRIS Handbook are Reflected in the 2022 Draft Assessment
- The 2022 Draft Assessment Failed to Fully Consider Key Studies

[1] https://www.americanchemistry.com/content/download/12904/file/2023-Letter-to-NASEM-Post-Jan-30th-Public-Meeting.pdf

- Study Evaluation Was Not Conducted Independently by Reviewers

- EPA's Integration Judgment for Myeloid Leukemia Does Not Incorporate Inferences Drawn from Available Scientific Information

Given that EPA has been developing the IRIS formaldehyde assessment for over two decades, the Panel would have expected the most recent 2022 Draft Assessment to reflect the best available systematic review approaches and best available science. Regrettably, that is not the case. In light of the fundamental deficiencies in *how* EPA developed the 2022 Draft Assessment, the NASEM Committee should recommend that EPA reissue a new draft that relies on the best available systematic review approaches, including the Tier 1 recommendations offered by the NASEM Committee that peer-reviewed the draft IRIS Handbook in 2022.[2]

Should you have any questions regarding this submission, I can be reached at sahar_osman-sypher@amerianchemistry.com.

Sincerely,

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On Behalf of the ACC Formaldehyde Panel

cc: Marcia McNutt (NASEM), Audrey Mosley (NASEM), Elizabeth Eide (NASEM), Clifford Duke (BEST), Kathryn Guyton (NASEM Staff Officer), formaldehyde@nas.edu

[2] National Academies of Sciences, Engineering, and Medicine. 2022. A Review of U.S. EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version. Washington, DC: The National Academies Press. https://doi.org/10.17226/26289.

Inconsistencies Between EPA's 2022 Draft Formaldehyde Assessment and EPA's December 22, 2022, Final IRIS Handbook

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The American Chemistry Council ("ACC") Formaldehyde Panel ("Panel") sets forth in this document the Panel's feedback on EPA's written responses ("EPA's Responses") to the NASEM Committee's January 6, 2023, questions. EPA's Responses address the NASEM Committee's systematic review related questions. At times, EPA's Responses refer to EPA's recently finalized IRIS Handbook ("IRIS Handbook"), which describes the sequential tasks involved in developing an IRIS assessment. These tasks include, among others, scoping, problem formulation, and developing a systematic review protocol. How IRIS assessments are developed, including in particular, the 2022 draft IRIS formaldehyde assessment ("2022 Draft Assessment") has been a keen focus of multiple NASEM committees starting from the 2011 NASEM Committee's review of the previous 2010 draft IRIS formaldehyde assessment.

The current NASEM Committee's focus on how the 2022 Draft Assessment was developed included a presentation and discussion involving Dr. Lisa Bero, Chair of the NASEM Committee to Review EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version ["IRIS Handbook"], during the NASEM Committee's first partially public meeting held on October 12, 2022.[1] Subsequently, EPA's final IRIS Handbook was issued on the afternoon of December 22, 2022,[2] at the same time as the NASEM Committee's second partially public meeting.[3] The existence of the NASEM Committee's written questions[4] and EPA's responses[5] were only made public during the third partially public meeting held on January 30, 2023[6] (EPA's responses were subsequently updated on February 8[7]). As such, the public has not had a meaningful opportunity to correct the record regarding mischaracterizations of the relationship between the 2022 Draft Assessment and the final IRIS Handbook.

Based on the questions posed to EPA during the January 30th public meeting, the NASEM Committee reviewing the 2022 Draft Assessment is clearly focused on *how* EPA developed its assessment. The NASEM Committee's focus on the *how* EPA developed its assessment is, of course, entirely appropriate given that IRIS assessments inform not only EPA

[1] https://www.nationalacademies.org/event/10-12-2022/review-of-epas-2022-draft-formaldehyde-assessment-meeting-1.
[2] https://www.epa.gov/newsreleases/epa-publishes-iris-handbook-and-final-iris-assessment-perfluorobutanoic-acid-pfba-and.
[3] https://www.nationalacademies.org/event/12-22-2022/review-of-epas-2022-draft-formaldehyde-assessment-meeting-2.
[4] https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D5C079283E383260F91B1C142061F7E12530EF165D0A?noSaveAs=1.
[5] https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D68387109D2AC09286D94B621C4C6E83410005858BE3?noSaveAs=1.
[6] https://www.nationalacademies.org/event/01-30-2023/review-of-epas-2022-draft-formaldehyde-assessment-meeting-3.
[7] https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D3A22C29743668E583CD8759F633481333EE3E7ECF54?noSaveAs=1.

risk assessment and risk management decisions, but are also relied upon by "federal, state, local, and tribal agencies, as well as community organizations and agencies in other countries."[8]

Although EPA's Responses note that "the methods used to develop the draft IRIS formaldehyde assessment were foundational to the development of the methods presented in the IRIS Handbook" and that "the underlying methods in the evolving and posted IRIS Handbook and the current draft assessment are fundamentally the same,"[9] EPA's Responses make clear that the 2022 Draft Assessment falls short of the IRIS Handbook and the best available systematic review approaches.[10] Inconsistencies in the approaches between the 2022 Draft Assessment and IRIS Handbook are perhaps unsurprising when one considers that the 2022 Draft Assessment was released months before the IRIS Handbook was finalized in December of 2022. Nonetheless, EPA must still ensure that the 2022 Draft Assessment comports with the best available systematic review approaches, including the Tier 1 recommendations offered by the NASEM Committee that peer-reviewed the draft IRIS Handbook.

In addition to the specific issues identified below, EPA's claims that "[t]he methods in the IRIS Handbook were directly informed by and responsive to guidance and recommendations received across an array of inputs to the IRIS program between 2012 and 2020 … including NAS reviews in 2011, 2014, and 2018; public workshops on systematic review … and peer review feedback of draft assessments incorporating evolving aspects of systematic review" lacks important context.[11] According to EPA, "[t]hese various engagements, reviews, and inputs… directly shaped" key methods in the 2022 Draft Assessment.[12] But that characterization differs from the historical record. The Panel has already identified specific examples where EPA's approach to developing the 2022 Draft Assessment does not comport with the NASEM Committee's 2011 review of the 2010 Draft Assessment, or with interagency and public comments on both the 2010 Draft Assessment and 2022 Draft Assessment.[13] Moreover, none of the NASEM reviews or public workshops from 2012 – 2020 addressed previous drafts of the formaldehyde assessment or how well it reflected the evolving IRIS Handbook.

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[8] National Academies of Sciences, Engineering, and Medicine. 2022. A Review of U.S. EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version. Washington, DC: The National Academies Press. https://doi.org/10.17226/26289

[9] https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D3A22C29743668E583CD8759F633481333EE3E7ECF54?noSaveAs=1 (pg. 5 and 23)

[10] A NASEM Committee peer-reviewed the draft 2020 IRIS Handbook and in 2022 issued its report that included no fewer than 28 Tier 1 recommendations, which are defined as the "Highest priority recommendations the committee believes are critical to improve the scientific rigor and/or clarity of the document." *Id*. at 16. None of the NASEM Committee's Tier 1 recommendations, let alone Tier 2 and 3 recommendations are reflected in the 2022 Draft Assessment because the assessment was issued *before* the NASEM Committee's 2022 report and *before* the IRIS Handbook was finalized.

[11] https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D68387109D2AC09286D94B621C4C6E83410005858BE3?noSaveAs=1 (pg. 23).

[12] https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D68387109D2AC09286D94B621C4C6E83410005858BE3?noSaveAs=1 (pg. 25).

[13] Comments from ACC have been shared with the NAS committee and are also available in EPA's docket at: ACC Formaldehyde Panel Comments: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103, and ACC Formaldehyde TSCA Risk Evaluation Consortium Comments: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0100

As noted above, the NASEM Committee's January 30th public meeting evidenced the Committee's appropriate focus on *how* EPA developed the 2022 Draft Assessment, which is entirely consistent with the Committee's task to: "assess whether EPA's draft document adequately and transparently evaluated the scientific literature, used appropriate methods to synthesize the current state-of-the science, and presented conclusions regarding the hazard identification analysis and dose-response analysis of formaldehyde that are supported by the scientific evidence."[14]

A recent letter to the Panel by the NASEM Study Director, however, suggests that the Committee's focus on *how* EPA developed its 2022 Draft Assessment may be outside the scope of the Committee's charge.[15] As we have previously documented to EPA and NASEM, the Study Director's rigid and narrow view of the Committee's task is inconsistent not only with the Committee's own scope of work but with the Committee's and EPA's legal requirements, including under Section 15 of the Federal Advisory Committee Act, EPA guidance regarding peer review and information quality, as well as the 2011 NASEM Committee's peer review of the 2010 Draft Assessment.[16]

EPA Did Not Follow Its Own IRIS Handbook in Developing the 2022 Draft Assessment

The IRIS Handbook underscores the importance of the scoping exercise, the results of which "are communicated across EPA and with other federal or state agencies, tribes, and the public via the IAP [IRIS Assessment Plan] … which is released for public comment to provide additional opportunities for input early in the assessment process." [17] Similarly, initial problem formulation also takes into account stakeholder input during public comments on the IAP. EPA convenes "a public science meeting to solicit scientific and stakeholder input."[18] Typically, EPA identifies experts to provide feedback on the IAP, and especially on the key science issues, during the meeting.[19]

Regrettably, during the development of the 2022 Draft Assessment, EPA failed to develop any of these work products – the IAP, systematic review protocol, or key science issues – or convene a public science meeting. EPA's deviations from its IRIS Handbook are not trivial

[14] https://www.nationalacademies.org/our-work/review-of-epas-2022-draft-formaldehyde-assessment#sectionProjectScope.
[15] "The committee's charge is to review the assessment prepared by EPA, and not to conduct their own assessment of formaldehyde. The committee is also not charged to comment on other interpretations of scientific information relevant to the hazards and risks of formaldehyde, nor does the statement of task call on the committee to review alternative opinions of EPA's formaldehyde assessment. Any other topics that do not fall within the committee's charge are not within the purview of the committee's review" - NAS March 6, 2023 Letter to ACC: https://americanchemistry.com/media/files/acc/industry-groups/formaldehyde/files/nasem-review-of-epa-s-2022-formaldehyde-iris-assessment
[16] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment.
[17] *Id*. at 2.
[18] *Id*. at 4.
[19] *Id*. Science issues as well as "predefined mechanistic analyses … help[] frame the approach used for organizing the literature inventory." EPA Responses to NASEM panel questions for the January 30, 2023, public meeting at 35.

or inconsequential. On the contrary, the systematic review protocol "is a central component of systematic review."[20]

EPA readily admits in EPA's Responses that it neither developed nor released a systematic review protocol, but that "the description of methods included within the draft assessment has been available for comment throughout the 7-Step IRIS Process."[21] EPA is mistaken. The Panel provided extensive comments to EPA and to the NASEM Committee describing in great detail both its scientific and procedural concerns with the 2022 Draft Assessment.[22]

The Panel also alerted the NASEM Committee to these concerns in an October 25, 2022, letter to Dr. Guyton, in which the Panel stated, in part:

> In developing the 2022 draft assessment, however, EPA failed to implement Step 1 of the IRIS process; EPA never released an IRIS assessment plan, which would have included scoping and problem formulation materials. Inexplicably, formaldehyde is the only one of the eighteen chemicals under review by the IRIS Program for which EPA **has not** developed an IRIS Assessment Plan or Systematic Review Protocol. Perhaps most significantly, five chemical assessments were suspended in 2019 and then reprioritized in 2021 (formaldehyde, chloroform, ethylbenzene, naphthalene, and uranium). Yet all of them, except formaldehyde, have involved public comment on an IRIS assessment plan and systematic review protocol.[23]

EPA also asserts that because "a complete Step 1 draft had been developed by 2017, EPA did not consider it appropriate (or a pragmatic use of resources) to develop and release a protocol for a finished draft."[24] Additionally, EPA asserts that the "IRIS 'Preamble' approach …is consistent with the advice from NAS Panels in 2011 and 2014."[25] But once again, EPA is mistaken. Several years before EPA had developed "a complete Step 1 draft" EPA was fully aware that a 2014 NASEM report on the IRIS Program had explicitly recommended: "After the systematic-review questions are specified, **protocols for conducting the systematic reviews** to address the questions should be developed."[26] Nor can EPA's failure to issue protocols be

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[20] *Id.* at 9.

[21] EPA's Responses, *supra* note 5, at 3. EPA's Responses include a response to the NASEM Committee's question whether EPA can "provide protocols for the multiple reviews of the various non-cancer outcomes and cancer types…?" *Id*. at 7. EPA's longwinded, multipage response essentially boils down to simply: *no protocols were developed for any endpoint.*

[22] Panel's June 2022 comments to EPA on the 2022 Draft Assessment, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103.

[23] Panel's October 25, 2022 NASEM letter, available at: https://www.americanchemistry.com/content/download/12170/file/Letter-to-NASEM-on-Procedural-Issues-and-Attachment.pdf

[24] EPA's Responses, *supra* note 5, at 3. Step 1 of the IRIS process entails all the sequential stages involved in developing a draft IRIS assessment.

[25] *Id.*

[26] National Academy of Sciences, Review of EPA's Integrated Risk Information System (IRIS) Process, 2014, at 6. (emphasis added).

rectified by pointing out that "the methods used to develop the draft IRIS formaldehyde assessment were foundational to the development of the methods presented in the IRIS Handbook…."[27]

Elsewhere in EPA's Responses, EPA emphasizes the role of the 2011 NASEM Committee's report on the 2010 draft IRIS formaldehyde assessment as "[t]he primary guidance used to develop the current draft IRIS assessment."[28] This is a particularly perplexing statement. The NASEM report should not be viewed as a substitute, even partly, for a systematic review protocol developed by EPA and reflecting public input, as prescribed by EPA's IRIS Handbook.

In sum, EPA's attempts at post-hoc rationalizations to justify its substantial deviation from its own IRIS Handbook miss the fundamental point that the IAP and the systematic review protocol for the development of any IRIS assessment, including in particular the 2022 Draft Assessment, must be developed *before* an IRIS assessment is drafted.

The 2022 Draft Assessment Failed to Fully Consider Key Studies

The IRIS Handbook acknowledges the possibility that literature searches for IRIS assessments may miss studies, but that "the IRIS process provides overlapping workflows to ensure key literature is identified, including … multiple opportunities for public comment."[29] In developing the 2022 Draft Assessment, however, EPA offered only one opportunity for public comment on the 2022 Draft Assessment, and that was only *after* the 2022 Draft Assessment was issued. The lack of multiple opportunities for public input undoubtedly contributed to EPA missing key studies in the 2022 Draft Assessment.[30]

The process for inclusion and exclusion of studies from the 2022 Draft Assessment also diverges from the IRIS Handbook. For example, the 2022 Draft Assessment provides a broad generic Population (including animal species), Exposure, Comparator, and Outcomes (PECO) statement as well as outcome-specific inclusion and exclusion criteria provided in Appendix A.5 of the 2022 Draft Assessment. The initial 2012-2016 search and selection process discussed in Appendix A.5 generally follows typical systematic literature review methods with an important exception – some of the studies were excluded after the full-text review for PECO relevance, but the specific studies and reasoning are not documented. In particular, for human studies of upper respiratory and lymphohematopoietic malignancies published through 2016, 59 articles were included through the initial title and abstract screen followed by the full-text screening; of these 59 studies, 47 were included and 12 were excluded without explanation. This is not an acceptable systematic review practice.

Appendix F of the 2022 Draft Assessment details the process for literature published between 2016 and 2021. In brief, studies from this time period that met the PECO criteria were further reviewed to determine if **"they could potentially be impactful to the assessment with**

[27] EPA's Responses, *supra* note 5, at 5.
[28] *Id*. at 23.
[29] EPA's Responses, *supra* note 5, at 15.
[30] See Appendix A on the Panel's October 25, 2022 NASEM letter, available at: https://www.americanchemistry.com/content/download/12170/file/Letter-to-NASEM-on-Procedural-Issues-and-Attachment.pdf

respect to changing hazard conclusions or toxicity values presented in the 2017 draft."[31] The criteria for determining whether the studies were "impactful" are vague and subjective, and thus EPA's process for reaching these decisions remains unclear. Perhaps most importantly, determination of a new study's impact was clearly tied to previously drawn hazard conclusions in the 2017 draft IRIS formaldehyde assessment. Thus, EPA's evaluation of what was "impactful" was biased in that decisions were made based on findings in the 2017 draft IRIS formaldehyde assessment.

Study Evaluation Was Not Conducted Independently by Reviewers

In responding to the NASEM Committee's question 1b, EPA states, "The evaluation of each study involved an initial review by a primary topic-specific expert and a secondary review by a second expert who also reviewed the extracted domain-specific details for accuracy (the secondary reviewer was not blinded to the primary review.)"[32] EPA's study evaluation process for the 2022 Draft Assessment appears at odds with IRIS Handbook, which explicitly notes that "as part of quality assurance, each study evaluation is conducted *independently* by at least two reviewers…."[33] Study evaluation represents a crucial part of the systematic review process. Importantly, the study reviewers "assign ratings for each domain (good, adequate, deficient, critically deficient) and for the overall study confidence (high, medium, low, or uninformative).[34]

EPA's Integration Judgment for Myeloid Leukemia Does Not Incorporate Inferences Drawn from Available Scientific Information

The IRIS assessment development process involves the "integration of the separate evidence streams to identify health hazards plausibly associated with the agent."[35] This entails combining "[t]he animal and human evidence judgments to draw an overall evidence integration judgment(s) that incorporates inferences drawn on the basis of information on the human relevance of the animal evidence, coherence across evidence streams, potential susceptibility, understanding of biological plausibility and MOA…."[36]

EPA asserted that its causal conclusion regarding myeloid leukemia was "based on multiple epidemiologic studies that found associations with different exposure metrics, and which were supported by mechanistic studies in exposed humans that provided biological support for genotoxic and immunologic changes in peripheral blood cells."[37] EPA's conclusion is at odds with the IRIS Handbook, which lists numerous scientific considerations in interpreting

[31] 2022 Draft Assessment (Appendix) at F-5. (emphasis added).
[32] EPA's Responses, *supra* note 5, at 16.
[33] U.S. Environmental Protection Agency, ORD Staff Handbook for Developing IRIS Assessments, 2022, at 4-4. (emphasis added).
[34] *Id*. at 4-30. EPA also notes that during the time-frame 2012-2015, "Each health effect-specific section was formally reviewed internally by topic-specific workgroups …." The IRIS Program at that time included disciplinary workgroups. What is not conveyed in EPA's Responses, however, is that during at least part of this time-period Dr. Kathryn Guyton served as one of the disciplinary workgroup co-chairs.
[35] IRIS Handbook, *supra* note 19, at xvi.
[36] *Id.* at 6-2. Later in the IRIS Handbook EPA inexplicably contradicts this statement by parenthetically asserting that "(consideration of biological plausibility will not influence the evidence integration judgment.)" *Id.* at 6-29.
[37] 2022 Draft Assessment (Appendix) at D-30.

mechanistic evidence, including whether "the hypothesized MOA(s) [are] biologically plausible, considering the chemical's pharmacokinetic processes, the biological processes known to contribute to the health effect, and the biological or experimental support for connections between mechanistic events?" EPA should also "[c]onsider consistency with established MOAs for related agents."[38]

As the Panel discussed in its comments to EPA on the 2022 Draft Assessment, however, the human evidence is neither consistent nor strong, there are no lymphohematopoietic cancers observed in animals, and there is no biologically plausible MOA. Ironically, elsewhere in the 2022 Draft Assessment, EPA appears to agree with the Panel's conclusions:

> Generally, evidence supporting the development of LHP cancers after formaldehyde inhalation has not been observed in experimental animals (i.e., rodents), including a well-conducted, chronic cancer bioassay in two species, a similar lack of increased leukemias in a second rat bioassay, and multiple mechanistic evaluations of relevant biological changes, including genotoxicity (i.e., inadequate evidence). The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.[39]

Contrary to the available scientific information, EPA nonetheless concludes that, "the evidence demonstrates that formaldehyde inhalation causes myeloid leukemia in humans given appropriate exposure circumstances."[40]

Conclusion

Given that EPA has been developing the IRIS formaldehyde assessment for over two decades, the Panel would have expected the most recent 2022 Draft Assessment to reflect the best available systematic review approaches and best available science. Regrettably, that is not the case. In light of the fundamental deficiencies in *how* EPA developed the 2022 Draft Assessment, the NASEM Committee should recommend that EPA reissue a new draft that relies on the best available systematic review approaches, including the Tier 1 recommendations offered by the NASEM Committee that peer-reviewed the draft IRIS Handbook.[41]

[38] IRIS Handbook, *supra* note 19, at 6-30.
[39] 2022 Draft Assessment at lv.
[40] 2022 Draft Assessment at 1-542.
[41] National Academies of Sciences, Engineering, and Medicine. 2022. A Review of U.S. EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version. Washington, DC: The National Academies Press. https://doi.org/10.17226/26289