Submitted Via Email

July 16, 2024

The Honorable Michael Regan
Administrator U.S. Environmental Protection Agency
William Jefferson Clinton Building
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Washington, D.C. 20460
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RE: Potential Finalization of U.S. EPA's Draft Integrated Risk Information System (IRIS) Assessment of Formaldehyde

Dear Administrator Regan,

The American Chemistry Council's (ACC) Formaldehyde Panel (the Panel) would like to provide comments to the Environmental Protection Agency's (EPA) Office of Research and Development (ORD) in reference to the 2022 Draft Integrated Risk Information System (IRIS) Toxicological Review of Formaldehyde-Inhalation. Since 2022, the Panel has extensively commented on the numerous procedural and scientific flaws with EPA's 2022 Draft Assessment. Given the assessment has moved into the critical step of final agency review/interagency science discussion,[1] the Panel reiterates calls made since 2021 for EPA to address key scientific, legal, peer review, and procedural issues with the underlying IRIS assessment which require the Agency to go back to the drawing board on the 2022 Draft Assessment.

It would be highly inappropriate and demonstrate that resulting regulations based on the assessment are not best available science if the Agency was to finalize the assessment based on the following defects and failure to address key comments outlined in this communication:

- Failure to identify, incorporate, and address highly relevant peer review comments from committees of the National Academies (NAS), including formaldehyde-focused reports from 2011 and 2023[2], as well as recommendations from EPA's Human Studies Review

[1] See EPA IRIS website for formaldehyde, available at: https://iris.epa.gov/document/&deid=248150. In June 2024, the "Quick Check" tracker indicated that the assessment moved into step six – final agency review/interagency science discussion.

[2] ACC has documented significant concerns around independence/balance/transparency with the 2023 NASEM reviews. See ACC letter regarding FACA violations, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0264; and ACC Comments on Scientific and Legal Issues with EPA's Forthcoming Peer Review of Draft Evaluation of Formaldehyde under the Toxic Substances Control Act (TSCA) and Federal Insecticide,

Board (HSRB) in 2023, and the Science Advisory Committee on Chemicals (SACC) expected later this month. The need to incorporate robust peer review findings and recommendations is clear in EPA and White House policies on peer review, scientific integrity, and information quality as well as scientific standards under the Toxic Substances Control Act (TSCA), Clean Air Act, and other laws.

- Failure to rectify major issues with the robustness, independence, balance, and transparency of aspects of peer reviews related to the draft IRIS Assessment.

- Failure to incorporate and respond to the significant public comments received by EPA, NAS, HSRB, and SACC since 2021.[3]

- Failure to conduct a full, open, and documented interagency consultation process on the draft or final assessment. Consistent with calls from a group of dozens of bipartisan members of Congress, Executive Order 12866 and other White House guidance, and interagency requirements under environmental statutes, this coordination should last at least 60 days, and include all federal agencies.

- Failure to fix fundamental methodological and procedural defects with the assessment. For example, EPA's June 2024 IRIS Outlook confirms that, contrary to the Agency's 7-step IRIS process, IRIS handbook, statutory or regulatory requirements, and clear peer review recommendations, formaldehyde is the only IRIS assessment which has not issued and/or taken public comments on a pre-established systematic review protocol.[4]

- Failure to fully incorporate the latest peer reviewed publications on formaldehyde. Just this year, several important studies and reviews have been published that are highly relevant to the assessment.[5]

Fungicide, and Rodenticide Act (FIFRA), Mar. 8, 2024, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0007.

[3] The Panel provided detailed information on why these public comments to EPA and peer reviewers must be incorporated in a November 2023 letter to the Agency: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0130.

[4] https://www.epa.gov/system/files/documents/2024-06/iris-program-outlook-june-2024-508.pdf.

[5] For example: Vincent, Melissa J., Seneca Fitch, Lauren Bylsma, Chad Thompson, Sarah Rogers, Janice Britt, and Daniele Wikoff. "Assessment of associations between inhaled formaldehyde and lymphohematopoietic cancer through integration of epidemiological and toxicological evidence with biological plausibility." *Toxicological Sciences* (2024); Goyak, Katy, and Stewart Holm. "Sensory irritation and use of the best available science in setting exposure limits: Issues raised by a scientific panel review of formaldehyde human research studies." *Regulatory Toxicology and Pharmacology* (2024): 105587; Lauer, Daniel J., Anthony J. Russell, Heather N. Lynch, William J. Thompson, Kenneth A. Mundt, and Harvey Checkoway. "Triangulation of epidemiological evidence and risk of bias evaluation: A proposed framework and applied example using formaldehyde exposure and risk of myeloid leukemias." *Global Epidemiology* 7 (2024): 100143; Salthammer, Tunga. "The reliability of models for converting formaldehyde emissions from wood-based materials to different environmental conditions." *Building and Environment* 247 (2024): 111041.

This letter covers the following points that are directly relevant to the 2022 Draft IRIS Assessment:

I. Interagency science consultation process for EPA's 2022 Draft Assessment undermines transparency and did not elicit information from potentially impacted agencies

II. Diverse group of stakeholders, experts and peer reviewers identify major issues with EPA's reliance on the Draft Formaldehyde IRIS Assessment

III. The NAS review of the Draft IRIS Assessment was flawed

IV. The EPA HSRB peer review highlights that major revisions are needed to EPA's Draft IRIS Assessment
    a. The HSRB deep dive into the methods of the studies led to findings of significant concern
    b. A case study shows the differences between the HSRB and NAS review approaches, but both reviews find flaws in a critical study
    c. HSRB and NAS reviews show that significant revisions to both the systematic review and the scientific conclusions reached in the Draft IRIS Assessment are needed

V. The Draft Formaldehyde IRIS Assessment is not consistent with the IRIS Handbook

VI. The Draft Formaldehyde IRIS Assessment does not consider available information

VII. The Draft Formaldehyde IRIS Assessment does not address previous NAS recommendations

VIII. The 2022 Draft IRIS Formaldehyde Assessment is not best available science and presents a flawed interpretation of non-cancer inhalation hazards
    a. Observational studies are not best available science
    b. Observational studies relied upon by IRIS for chronic non-cancer hazards should be replaced by controlled human exposure studies - Understanding formaldehyde, sensory irritation, sensitive populations, and Haber's Law
    c. The observational studies used for chronic non-cancer hazards are highly flawed and unreliable for identifying a point of departure
    d. Understanding the strengths of the controlled human exposure studies
    e. Findings from other authoritative bodies

IX. The IUR for NPCs in the 2022 Draft IRIS Formaldehyde Assessment is flawed and overestimates risk
    a. Associations between formaldehyde and myeloid leukemia are not supported by the weight of the scientific evidence
    b. The IUR for NPC should not be framed as an underestimate of cancer risks

I. Interagency science consultation process for EPA's 2022 Draft Assessment undermines transparency and did not elicit information from potentially impacted agencies

At step three of its IRIS six-step process, EPA solicits input from other federal agencies. In this case, EPA, at the end of 2021, provided other federal agencies only four weeks to respond to its voluminous materials. While this time would be short under normal circumstances, EPA's 30 days included the period from Christmas through New Year's, a period when many in the federal government are out of the office, further reducing the actual time available for other agencies to review. Perhaps as a result of this, several federal agencies from whom responses should have been expected, did not respond. Given the lack of a clear record on the review, however, we are unable to discern why these agencies did not respond. For this reason, and others discussed below, EPA should reengage with other federal agencies in the current critical step six of final agency review/interagency discussion to ensure it has obtained their considered opinions.

Interagency consultation is extremely important. Federal agencies are the repositories of significant substantive expertise and experience. Interagency coordination ensures that actions taken by one agency do not conflict with the policies or actions of another agency, which could lead to inconsistent, incompatible, or duplicative policies. The interagency review process provides for identification and then aggregation of views and perspectives from numerous federal agencies. Additionally, it allows an agency to receive the specialized knowledge held by other agencies with related or overlapping jurisdiction.

The EPA process for the 2022 Draft Assessment was not designed to result in this type of interagency involvement. Indeed, based in large part on those agencies which failed to respond, the process was deficient. For example, neither the Food and Drug Administration nor the United States Department of Agriculture – the two key federal agencies whose input would have been most relevant to the assessment – appear to have provided comment. Additionally, neither the U.S. Department of Transportation nor the White House Council on Environmental Quality provided any comments on the 2022 Draft Assessment.

Given the unprecedented and truncated review period at the end of 2021, the fact that any federal agency was able to provide comments is noteworthy. Interagency commenters raised fundamental issues that are central to the underlying 2022 Draft Assessment:

- White House Office of Management and Budget: "[W]e are concerned with EPA's judgement of 'evidence demonstrates' for myeloid leukemia. Given the inconsistencies in the epidemiologic data and the lack of proposed MOA, it is not clear …. Claiming 'evidence demonstrates' while the confidence in the unit risk estimate is low and the data are limited may result in an overly conservative appreciation of the degree of hazard for myeloid leukemia, particularly considering no MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia, a disease that results from systemic exposure. The mechanistic information considered by EPA may support associations with

local, route-of-exposure, tumors associated with epithelial cells, but does not support the tumorigenesis or carcinogenesis of disease related to systemic exposures." [6]

- The Small Business Administration raised concerns about EPA "…making conclusions without being able to establish a MOA or without knowledge of mechanism(s) leading to cancer formation." They identified nearly a dozen key studies that had been excluded by EPA and flagged unanswered questions about the "mechanism by which exogenous formaldehyde create[s] 'extra' risks by adding to the endogenous formaldehyde."[7]
- The Agency for Toxic Substances and Disease Registry (ATSDR) argued that the lack of mechanistic data "needs to be a reason to down-grade the evidence findings. It is significant." ATSDR also stated that EPA's understanding of toxicokinetics of formaldehyde exposure to develop systemic reference concentrations "…doesn't make any sense" and examining confounding toxicities should happen "before making any evidence conclusion for formaldehyde." Furthermore, experts from ATSDR "disagree completely" with EPA's conclusions on female reproductive toxicity.[8]
- The Department of Defense: "The decision to go forward with a reference concentration that is not simply the lowest one calculated but is based on data in which Agency has higher confidence is appropriate."[9]

And on an earlier version of the draft assessment a senior environmental health scientist in EPA's Office of Research and Development stated, with respect to a flaw that still exists:

> I really, really think that you cannot argue for a direct effect of exogenous [formaldehyde] on bone marrow in humans at typical exposure levels, or those occurring in the [epidemiological] study which reports the association with leukemia. The total mass inhaled is just not large enough and the idea that the body somehow keeps exogenous [formaldehyde] separate from endogenous anyplace but at the [point of exposure] cannot be supported…. [i]t appears that there is a base assumption that the leukemia association is 'fact', and there has been a grasping at explanations or mechanisms by which it might be true. That is not good science and (going beyond what I've said before) I think it's fairly plain that the current storm of criticism, congressional hearings, etc., is the fallout of trying to maintain that position/assumption in this assessment (and similar overly-precautionary approaches in others).[10]

Given the deficiencies thus far in the interagency consultation process, it is imperative that federal agencies are given a meaningful opportunity to provide needed information on the

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[6] *See* Office of Management and Budget (OMB) comments on the Interagency Science Consultation on the Draft 2022 Assessment, available at: https://www.regulations.gov/document/EPA-HQ-ORD-2010-0396-0046

[7] *See* Small Business Administration (SBA) Office of Advocacy comments on the Interagency Science Consultation on the Draft 2022 Assessment, available at: https://www.regulations.gov/document/EPA-HQ-ORD-2010-0396-0048

[8] *See* Agency for Toxic Substances and Disease Registry (ATSDR) comments on the Interagency Science Consultation on the Draft 2022 Assessment, available at: https://www.regulations.gov/document/EPA-HQ-ORD-2010-0396-0045

[9] *See* Department of Defense comments on the Interagency Science Consultation on the Draft 2022 Assessment, available at: https://www.regulations.gov/document/EPA-HQ-ORD-2010-0396-0044

[10] *See*: https://www.americanchemistry.com/chemistry-in-america/chemistries/formaldehyde/formaldehyde-the-real-story

different uses of formaldehyde that impact their sectors before EPA moves into finalization of the assessment.

II. Diverse group of stakeholders, experts and peer reviewers identify major issues with EPA's reliance on the Draft Formaldehyde IRIS Assessment

EPA held a four-day, virtual public meeting of its Scientific Advisory Committee on Chemicals (SACC) from May 20-23, 2024, to discuss the Draft TSCA Risk Evaluation and related documents and for EPA to use feedback from the SACC to inform both the TSCA and FIFRA evaluations.[11] During that meeting comments from peer reviewers made clear that EPA has imposed upon them a timeline that does not allow adequate and independent peer review. In addition, SACC reviewers noted significant concerns with EPA's approach, and the need for substantial additional work. For example, reviewers expressed concern with EPA's reliance on a Draft IRIS Assessment and the need for EPA to provide adequate time to resolve inconsistencies between peer reviews.[12]

Peer reviewers also directly raised issues with EPA's overall approach for unreasonable risk determinations, and the need to integrate TSCA scientific standards around best available science and the weight of the scientific evidence. A few of the key SACC peer reviewer comments[13] are excerpted below from the transcript of the May 20-23 SACC meetings. [14]

- When commenting on EPA's reliance on the draft IRIS assessment, SACC panelists put forth a recommendation that "EPA needs to review the literature for best available science and calculate an IUR outside the inadequate IRIS Assessment."
- When evaluating the adequacy of the NAS peer review, the SACC indicated "since the so-called 'peer review' by NASEM was limited to the charge question supplied and was not a full review of the full body of literature relevant to the hazards and risks of formaldehyde, nor was NAS charged with reviewing alternative scientific opinions, we do not believe that this is a good peer review" and "many of the NASEM comments are not addressed, leaving open questions."
- When commenting on consideration of Haber's Law, the SACC stated that "EPA concludes justifiably that Haber's Law does not apply for formaldehyde."

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[11] The video recordings of the May 20-23, 2024 virtual SACC meetings are available at: Peer Review of 2024 Draft Risk Evaluation for Formaldehyde | US EPA. The transcript is available at: https://www.regulations.gov/document/EPA-HQ-OPPT-2023-0613-0297

[12] *See* comment from Dr. Apte noting that while the IRIS assessment was peer reviewed by NASEM in 2023, EPA has yet to issue a final version showing any changes based on NAS's recommendations. "The IRIS document doesn't seem to be a final document, it's a draft and many of the NASEM comments are not addressed, leaving open questions." May 21, 2024 at 5:57:35, available at: https://youtu.be/jId4MytcFaM?t=21455; See follow-up question from Dr. Apte on May 22, 2024 at 19:42 questioning the status of the IRIS assessment, available at: https://youtu.be/MqYas169e9U?t=1182

[13] In some instances the panelist may have been expressing their own views while in others it was clear that they were reflecting the broader views of the SACC.

[14] *See* transcript of SACC May 20-23, 2024 virtual meeting, available at: https://www.regulations.gov/document/EPA-HQ-OPPT-2023-0613-0297

- When considering study selection, the SACC panelists favored the controlled chamber studies over observational epidemiological studies noting that the Kryzanowski 1990 study was "poor quality" compared to the controlled chamber studies like the Lang et al. and Kulle et al. studies and that use of these studies would result in a much higher RfC.
- SACC panelists also noted that "… the three observational studies relied upon by IRIS for a chronic non-cancer hazard are not appropriate to determine a dose-response and a POD. Therefore, the POD that was selected is also not suitable to use in this or any instance in this risk assessment" due to several limitations such as "the ability to determine causality specific to formaldehyde, cofounders that were not addressed, and including the use of self-completed questionnaire instead of a major health effect, which decreases the reliability of the result."
- When discussing mode of action, SACC panelists indicated that a non-linear threshold mode of action is the best approach stating "…the mode of action for formaldehyde-induced carcinogenesis, being based on a cytotoxicity-regenerative mechanism, the consideration of formaldehyde as a threshold carcinogen, along with development of a cancer risk POD, as opposed to using linear no- threshold model, is recommended under all scenarios, including indoor air" and "it's again important to emphasize that the IUR from the IRIS Assessment shouldn't be used and a better one used. It's not sufficient just to go to the myeloid leukemia where there's no rational, biological, plausible mechanism where that could occur. And so, basing it on the key events associated with the well-constructed mode of action is the best approach for the IUR for this risk."
- When discussing development of the IUR, SACC panelists pointed to the approach taken by the WHO, stating "given that cancer from formaldehyde is likely a threshold effect, only evident at the site of contact when formaldehyde concentrations are at or above 2 ppm, it may be worthwhile taking a unified approach to both cancer and non-cancer effects. This is the type of approach taken by WHO for formaldehyde in their indoor air guideline document from 2010. Protecting against formaldehyde concentrations at or above 2 parts per million would prevent both non- cancer and cancer impacts in people in all instances. The recommendation is that EPA needs to review the literature for best available science and calculate an IUR outside the inadequate IRIS Assessment."
- When commenting on the most sensitive endpoint which protects from other health effects, SACC panelists stated that "given the preference for high quality human data, EPA should consider using sensory irritation as a key effect for concerns pertinent to chronic exposure of adults and children."
- When discussing consideration of acute and chronic effects, a recommendation was made to "explore a unified approach for the chronic and cancer assessments based on using the NOEL POD, for irritancy effect via the relevant route of exposure, since the acute irritating effects of formaldehyde makes it unlikely for these long-term exposures over many hours, days, weeks, and months to actually occur."

In addition, nearly 40 public commenters from a variety of different sectors and backgrounds presented oral comments to the SACC, highlighting the legal, scientific, and economic issues with EPA's Draft TSCA Risk Evaluation. Key themes emphasized the exclusion of important issues from the peer review process, including the underlying draft IRIS assessment, occupational exposure value, and approach for unreasonable risk determinations, and the need to integrate TSCA scientific standards around best available science and the weight of scientific

evidence. More than 200 public comments have been submitted to the EPA docket [15] on the Draft TSCA Risk Evaluation and nearly 50 public comments on the Draft FIFRA Risk Assessment [16] from agencies, elected officials, trade associations, companies, and scientific experts echoing these concerns and highlighting additional ones.[17]

Commenters including federal agencies, state or tribal organizations, and elected officials raised fundamental concerns on both the TSCA and FIFRA risk evaluations for formaldehyde that relied on the Draft 2022 IRIS assessment:

- The National Association of State Departments of Agriculture stated that "EPA's reliance on the draft IRIS assessment is a fatal flaw and violates statutory requirements for best available science."
- The California Department of Food and Agriculture stated "Notwithstanding EPA's exclusion of the aquaculture from the TSCA risk evaluation, CDFA AUS respectfully urges the EPA to proceed cautiously and in consultation with the best available science. The formaldehyde risk analysis findings may result in unintended consequences that inadvertently, negatively affect aquaculture and animal feed producers' legitimate access to formaldehyde for FDA-approved uses…. aquaculture producers may face prohibitive costs and undue delays or barriers in accessing this critical therapeutic, which could ultimately increase the need to use antibiotics and threaten food security for our great state and nation."
- The Northwest Indian Fisheries Commission explained that "EPA must consider how the TSCA process will impact the use of this drug in programs that sustain treaty fisheries and support the recovery of [Endangered Species Act]-listed stocks, and the ecological balance of our marine and freshwater ecosystems."
- The Association of Fish and Wildlife Agencies expressed concerns that an unreasonable risk determination for formaldehyde that is based on the IRIS assessment would "lead to reductions in threatened and endangered species husbandry programs, delaying the recovery and delisting of threatened and endangered fish species…We trust that any restrictions on the manufacturing and usage of formaldehyde-based products will be based on the best available science and will take into consideration the availability of alternatives and the negative impacts on end users, including State fish and wildlife agencies. They also expressed concern that "formalin produced overseas may not meet the strict quality controls of the FDA for use as a drug and so may not solve any shortage of the drug in the event of increased regulation."
- The U.S. Department of Homeland Security commented on their support for the continued laboratory use of formaldehyde for decontamination at their Plum Island Animal Disease Center which has "served as the nation's premier defense against accidental or international introductory of transboundary animal diseases —highly

[15] *See* EPA Docket for Draft TSCA Formaldehyde Risk Evaluation Public Comments, available at: https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613

[16] *See* EPA Docket for Draft FIFRA Risk Assessment for Formaldehyde and Paraformaldehyde, available at: https://www.regulations.gov/docket/EPA-HQ-OPP-2015-0739

[17] *See* Diverse Group of Stakeholders, Experts, and Peer Reviewers Identify Major Issues with EPA's Draft Formaldehyde Risk Evaluation Under TSCA - American Chemistry Council, May 31, 2024.

transmissible diseases of livestock and other animals, including foot-and-mouth disease (FMD) and African swine fever (ASF)—that can significantly affect food security, trade, and the economy." [18]

- The U.S. Department of Agriculture provided EPA with information on the benefits of agricultural uses of formaldehyde and paraformaldehyde and its "importance to animal health and food safety." [19]
- The Washington State Department of Agriculture provided comments related to a Special Local Need registration that allows use of formaldehyde as a dip-tank treatment for control of nematodes, insects, mites and certain plant pathogenic fungi on bulbs of daffodil in Washington State. The agency stated that it was "submitting this letter to help reframe uncertainties EPA identified regarding this SLN use pattern" and "to help provide realistic use estimates." [20]
- Building on numerous Congressional letters to EPA raising concerns with EPA's formaldehyde activities under TSCA and IRIS since 2021,[21] a bipartisan group of Members of Congress commented that EPA's risk evaluation which relies on the IRIS assessment could disrupt supply chains for the automotive, aerospace, building and construction, agriculture, defense, health care, and semiconductors industries. They also called on EPA to "undertake a comprehensive interagency review process." [22] State Attorneys General, led by Brenna Bird of Iowa, argued that EPA's action could "in effect, ban formaldehyde and place billions of dollars of livestock at risk of disease, jeopardize the food supply, and threaten the entire agricultural industry." These officials urged "EPA to look at the best available science, reconsider its draft evaluation, and maintain the current regulatory levels."

III. The NAS review of the Draft IRIS Assessment was flawed

The charge that EPA provided to NAS for its review of the 2022 Draft IRIS Formaldehyde Assessment was significantly flawed and not fit for purpose.[23] EPA unduly narrowed the charge, and this prevented the NAS from conducting a robust review of the scientific analyses in the assessment. Instead of conducting an independent assessment of the formaldehyde science, the committee only evaluated whether the 2022 Draft IRIS Formaldehyde Assessment "adequately and transparently" evaluated the scientific literature provided by EPA and used appropriate

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[18] *See* comments from the U.S. Department of Homeland Security on the Draft FIFRA Formaldehyde and Paraformaldehyde Risk Assessment, available at: https://www.regulations.gov/comment/EPA-HQ-OPP-2015-0739-0021

[19] *See* comments from the U.S. Department of Agriculture on the Draft FIFRA Formaldehyde and Paraformaldehyde Risk Assessment, available at: https://www.regulations.gov/comment/EPA-HQ-OPP-2015-0739-0031

[20] https://www.regulations.gov/comment/EPA-HQ-OPP-2015-0739-0029

[21] See letter from Representative Don Davis et al. to EPA Administrator Michael Regan, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0150

[22] *See* letter from 20 State Attorneys General, available at: https://www.iowaattorneygeneral.gov/media/cms/0514__FinalEPA_Formaldehyde_Letter_7723B60AD3139.pdf

[23] For additional details on this topic, see the ACC letter submitted to EPA and NASEM on Apr. 13, 2022, which details the requirements for peer review as described in EPA's Peer Review Handbook, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0127/attachment_3.pdf and the ACC blog https://www.americanchemistry.com/chemistry-in-america/news-trends/blog-post/2023/epa-human-studies-review-board-peer-review-shows-that-not-all-peer-reviews-are-equal-a-tale-of-two-peer-reviews-on-formaldehyde.

methods to synthesize the state of the science.[24] The NAS committee was not charged with commenting on the full body of literature relevant to the hazards and risks of formaldehyde, nor was it charged with reviewing alternative scientific opinions.[25] The NAS committee repeatedly referred to evaluating whether EPA's approach was consistent with "its state of practice" methods. While this term was not defined, the NAS committee focused on whether EPA's approaches were consistent with EPA guidance documents. And, because the NAS report states that the committee "was not charged with … reviewing alternative opinions of EPA's assessment," it is doubtful that public comments were considered relevant to the NAS committee. The narrow charge provided to NAS for its review is not consistent with EPA's Peer Review Handbook and the requirements for highly influential scientific assessments.[26]

Peer reviewers were not asked to evaluate EPA's analyses and literature choices, including feedback on over 100 peer-reviewed scientific studies that EPA excluded from the Draft IRIS Assessment. [27] The superficial review that was conducted was predominantly to determine if EPA had followed its own IRIS guidelines. The Formaldehyde Panel has provided constructive and actionable written and oral comments to EPA and the NAS to ensure that EPA is aware of and relying on information consistent with the best available science and based on the weight of the scientific evidence. [28]

The NAS review also did not resolve many important scientific issues that are relevant to formaldehyde. For example, NAS did not address validity of the toxicity values in EPA's 2022 Draft Assessment, stating "the committee did not conduct an independent hazard evaluation or dose-response assessment, and therefore does not recommend alternative hazard identification conclusions or toxicity values."

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[24] NAS, Review of EPA's 2022 Draft Formaldehyde Assessment (2023), available at: https://nap.nationalacademies.org/catalog/27153/review-of-epas-2022-draft-formaldehyde-assessment.

[25] ACC has provided information to NASEM and EPA noting that over 100 peer-reviewed scientific studies were excluded from the Draft IRIS Assessment. Because NASEM was not asked to comment on excluded information and was not asked to comment on alternative scientific information, none of this information was considered by NASEM during its peer review. Those letters are available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0067 and https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103 (see Appendix A). The list of excluded studies was also provided to the SACC and EPA on May 3, 2024, available at pages 23-33: ACC Formaldehyde Panel Comments for May 3, 2024 SACC Meeting - American Chemistry Council.

[26] ACC Letter to EPA and NASEM Regarding Comment on the Charge Questions and Committee Task for Peer Review of Draft Formaldehyde Assessment, Apr. 13. 2022, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0127/attachment_3.pdf.

[27] The Formaldehyde Panel repeatedly provided documentation to NAS and EPA regarding important studies that were not considered, integrated and assessed. Those letters are available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0067 and https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103 (see Appendix A). The list of excluded studies was also provided to the SACC and EPA on May 3, 2024, available at pages 23-33 at ACC Formaldehyde Panel Comments for May 3, 2024 SACC Meeting - American Chemistry Council.

[28] *See* NAS public access file materials available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0113; https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0114; https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0115; https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0116; and https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0117.

The NAS review was additionally compromised due to procedural shortcomings and FACA violations including and a lack of fair balance on the committee.[29] ACC raised serious concerns related to fair balance including the overall process by which the provisional committee was established, the Study Director assigned to oversee and manage the committee, the overall composition and balance of the committee, and several of the provisional appointees who should have been disqualified because of appearance of a lack of impartiality or independence.[30] Yet NAS did not address the concerns with the committee in violation of NAS's policies and guidelines and in conflict with OMB and EPA Guidelines for Peer Review.

IV. The EPA HSRB peer review highlights that major revisions are needed to EPA's Draft IRIS Assessment

On August 23, 2023, the EPA Human Studies Review Board (HSRB) approved a report which recommended major revisions to EPA's approach for assessing formaldehyde risks.[31] The HSRB was provided a detailed charge to inform EPA's assessment of formaldehyde under both the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

The charge to the HSRB focused on assessing the acute endpoints related to sensory irritation, with two distinct sets of charge questions. One set of charge questions focused on ethics, asking the HSRB to evaluate whether the studies were conducted ethically and whether they met prevailing ethical standards at the time studies were conducted. The HSRB found that all the studies evaluated were conducted ethically. A second set of questions asked the HSRB to evaluate four specific studies and determine whether they were each "scientifically sound, providing reliable data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposures to formaldehyde." In addition to reviewing four studies individually, the HSRB was asked to comment on the use of the four studies in EPA's weight of evidence evaluation for acute inhalation endpoints, as well as on the proposed points of departure (PODs) presented by EPA as the basis for calculating safe exposure limits.

These charge questions required the HSRB to do a deep dive into the scientific issues and conduct its own evaluation of the studies. This is in stark contrast to the recent NAS review, where EPA explicitly told the NAS committee that it "shall not conduct an independent assessment separately from the IRIS document."[32] Unlike the constraints that EPA put on the NAS, the HSRB review "considered materials presented at both meetings, both from the EPA

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[29] *See* for example, ACC Comments to NASEM on Committee Composition, Aug. 25, 2022; ACC Letter to NASEM on Information Requests, Sept. 9, 2022; and NASEM Response to ACC on Information Gathering Session Request Mar. 6, 2023, all available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0126.

[30] ACC, Comments to NASEM on Committee Composition, Aug. 25, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0126.

[31] HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf.

[32] *See* the September 2021 contract between EPA and NASEM established, prior to public comment or solicitation of panel members, that the committee "shall not conduct an independent assessment separately from the IRIS document nor shall the NAS comment on the broader aspects of the of the IRIS program" and the constraint that the committee "shall be limited to responding to the materials provided by the EPA" with a directive that other background information provided to the Committee by others "shall not be reviewed by the NAS." Available at: https://www.americanchemistry.com/media/files/acc/industry-groups/formaldehyde/files/formaldehyde-task-order

and from the public comments, research articles, and related materials, the Agency's review, the Agency's statistical analysis of the research data, and oral comments from Agency staff during the HSRB meeting discussions."[33] In fact, the HSRB review was sufficiently broad that the HSRB took it upon itself to review not just the four studies it was asked about, but also two additional studies that were part of EPA's weight of evidence evaluation for the sensory irritation endpoint.

a. The HSRB deep dive into the methods of the studies led to findings of significant concern

The HSRB review provided many important recommendations to EPA that have a broad impact not just on the TSCA and FIFRA risk evaluations of formaldehyde, but also on EPA's Draft IRIS assessment for formaldehyde, which the agency is seeking to finalize. A few of these important recommendations are described below.

- When commenting on study designs and which studies should be used to develop a point of departure (POD) for effects, the HSRB favored the use of controlled chamber studies (like Kulle et al. (1987) and Lang et al. (2008)) over the use of observational studies (like Hanrahan et al. (1984) and Liu et al. (1991)). HSRB found that the controlled chamber studies had a "preferred study design and greater scientific rigor" than the observational epidemiology studies and recommended that EPA rely on the controlled chamber studies rather than observational epidemiology studies.
- When reviewing EPA's finding that Haber's Rule applies to formaldehyde, the HSRB, after considering the scientific evidence (including responses from EPA staff, consideration of previous EPA applications of Haber's Rule, and public comments), determined that formaldehyde does not follow Haber's Rule, and no exposure adjustment is necessary when calculating a POD.[34]
- When evaluating the sensory irritation endpoint, the HSRB questioned whether it met EPA's definition of an "adverse" health effect and instead suggested that these endpoints could be used as a lower bound for potential adverse effects, rather than a POD for adversity. Consistent with the determination that sensory irritation is not an adverse health effect, the HSRB recommended that uncertainty factors do not need to be applied to the POD.
- When evaluating which populations are most sensitive to sensory irritation, the HSRB concluded that younger individuals are more sensitive to sensory irritation than older individuals. Consistent with this finding, the HSRB recommended that an uncertainty factor need not be applied when the study population included younger individuals. The HSRB stated that this approach is consistent with the approach EPA used in its assessment of chloropicrin.

[33] See the HSRB report discussion of its review process available at: HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf

[34] Haber's Rule states that the severity of a toxic effect is a function of the time of exposure and the concentration of exposure, and that as these increase, the toxic effect increases. The impact of not applying Haber's Rule to formaldehyde means that PODs from short-term studies are not adjusted downward when calculating a POD for a longer-term exposure.

- The HSRB recommended that EPA have a "more coordinated approach" as its different offices conduct their evaluations for formaldehyde. In particular, the HSRB cited NASEM and the TSCA Science Advisory Committee on Chemicals (SACC), as well as other state and federal agencies, as groups which EPA should bring together, rather than isolating them, when establishing PODs.

b. A case study shows the differences between the HSRB and NAS review approaches, but both reviews find flaws in a critical study

The NAS did not conduct an in-depth review but did however provide a case study to determine if the committee could replicate the steps described in the Draft IRIS Assessment to translate findings from Hanrahan et al. (1984) to develop a sensory irritation POD, as replicability is a critical indicator of regulatory transparency. HSRB also evaluated Hanrahan et al. (1984), but as noted above, the HSRB review did look closely at EPA's methods.

Neither the HSRB nor the NAS supported the use of the Hanrahan et al. (1984) study. NAS determined that "[t]he committee's review of the Hanrahan et al. (1984) study generated concerns not captured by EPA's review." [35] The committee noted, among other findings, that the data collection instrument was not well described in the study and that this was not consistent with rating of "medium" quality that EPA gave to the study. It also noted deficiencies in the analysis domain of the study that EPA did not recognize. Additionally, the committee stated that "[i]nconsistencies are also apparent in how study quality deficiencies are represented in the four-domain summary confidence figure for human sensory irritation studies." The case study review found inconsistencies between EPA's evaluation criteria for sensory irritation and how they were applied to the Hanrahan et al. (1984) study, as well as how study limitations were presented for other sensory irritation studies. The case study findings support the NASEM committee's overall conclusion that it could not replicate the EPA process with "complete fidelity."

The HSRB found that observational studies, like Hanrahan, cannot and should not be used to support a quantitative POD. The HSRB in-depth review of the methods also determined that the study did not meet its original intent of being representative of Wisconsin mobile homes, as noted by the authors. The HSRB justifiably asked EPA to provide a rationale for the value of the study as the HSRB did not find it representative or generalizable.

c. HSRB and NAS reviews show that significant revisions to both the systematic review and the scientific conclusions reached in the Draft IRIS Assessment are needed

A review of general methods and approaches by the NAS found EPA's methods, as described above in the case study, to be lacking in transparency and consistency. This was reflected in NAS's most important Tier 1 recommendation to EPA. Not surprisingly, when HSRB dove deeply into the individual studies and conducted an independent evaluation of EPA's conclusions, it disagreed with EPA's choice of preferred studies and dose-response conclusions,

[35] See page 142 of the NAS Report, Aug 2023, available at: Review of EPA's 2022 Draft Formaldehyde Assessment | The National Academies Press

including the application of uncertainty factors for sensory irritation endpoints, as is summarized above.

While the EPA's HSRB evaluated only acute sensory irritation endpoints, the same studies it evaluated were relied upon by EPA for chronic endpoints (e.g., Hanrahan et al. (1984)) in the Draft IRIS assessment. Thus, the HSRB findings regarding the strengths and weaknesses of these studies are relevant to the Draft IRIS assessment. Importantly, the HSRB review shows that an in-depth science review, according to EPA's own guidelines, is necessary for all non-cancer and cancer endpoints in the IRIS assessment. While the NAS conducted a review for transparency and clarity, their review did not include an independent evaluation of the science; nevertheless, as is shown by the case study evaluated by the NAS, and the NAS Tier 1 recommendation to EPA, significant process concerns were identified in the 2022 Draft Formaldehyde Assessment. The HSRB and NAS reviews support the need for an independent in-depth review of all science underlying the critical endpoints and conclusory revisions to the 2022 Draft IRIS Formaldehyde Assessment.

V. The Draft Formaldehyde IRIS Assessment is not consistent with the IRIS Handbook

After years of work, the IRIS program finalized and released in 2022 the *ORD Handbook for Developing IRIS Assessments* (IRIS Handbook).[36] The IRIS Handbook implements some of the recommendations and input from the National Academy of Sciences (NAS), EPA agency reviewers, other federal agencies, EPA's Science Advisory Board (SAB), and experts in systematic review and provides the operating procedures to the scientists in the IRIS program. While still needing significant improvement, these procedures are necessary steps to help ensure a consistent and transparent science-based approach to the development of hazard assessments. The IRIS Handbook articulates the importance of a structured seven-step process. Unfortunately, the Draft Formaldehyde IRIS Assessment is not consistent with this process.[37]

EPA's failure to be consistent with the IRIS Handbook starts with step one of the process, where EPA simply failed to implement step one and never released an IRIS assessment plan, which would have included scoping and problem formulation materials. Inexplicably, formaldehyde is the only one of the 17 chemicals under review by the IRIS Program for which EPA has not developed an IRIS Assessment Plan or Systematic Review Protocol.[38] These work products – the IRIS assessment plan, the systematic review protocol, and the identification of key science issues – are not trivial or inconsequential. For instance, the systematic review protocol is a central component of the systematic review which should guide the entire IRIS assessment. EPA has used post hoc rationalizations to describe why its failure to meet these requirements is not problematic, but these arguments are not convincing and do not correct EPA's failure to provide

[36] EPA, *ORD Handbook for Developing IRIS Assessments* (IRIS Handbook), Dec. 22, 2022, available at: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=356370.

[37] *See* detailed ACC comments provided to EPA and NAS on this topic including: Letter to Kathryn Guyton regarding Procedural Deficiencies in Developing the 2022 Draft IRIS Formaldehyde Assessment, Oct. 25, 2022 available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0114/attachment_9.pdf, and Letter to Jonathan Samet regarding Summary of Insufficient EPA Responses to the Recommendations From the NAS 2011 Review of EPA's 2010 Draft IRIS Assessment of Formaldehyde, Mar. 31, 2023, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf.

[38] *See* IRIS Program Outlook, June 2024, available at: IRIS Program Outlook | US EPA

a clear systematic review framework for public comment and input before the assessment was developed.[39]

The IRIS Handbook also requires that study evaluation be conducted independently by at least two reviewers.[40] However, when explaining its approach to the NAS, EPA described a process whereby the secondary reviewer was not blinded to the primary reviewer's analysis.[41] This failure to have independent review of individual studies jeopardizes the integrity of the entire systematic review underpinning the Draft IRIS Assessment. And, notably, EPA's process for the inclusion and exclusion of studies deviated from the IRIS Handbook requirements; therefore, the Draft IRIS Assessment failed to consider key studies.[42]

Finally, the Draft IRIS Assessment is also inconsistent with the IRIS Handbook's requirement that EPA integrate separate evidence streams to identify health hazards that are plausibly associated with the chemical.[43] When it came to evaluating formaldehyde and leukemia, EPA relied on only epidemiological studies and did not consider the biological plausibility based on MOA information. EPA acknowledged the lack of plausibility but did not incorporate this information into its hazard determination.

VI. The Draft Formaldehyde IRIS Assessment does not consider available information

As described further below, the Draft Formaldehyde IRIS Assessment did not consistently apply inclusion and exclusion criteria during the systematic review step. Instead of seeking to include all available information in the Draft Formaldehyde IRIS Assessment, EPA chose to rely on only what it considered to be "primary" studies. EPA also overlooked some studies that it would consider to be "primary." Thus, the assessment did not consider peer-reviewed re-analyses of data or critically important mode of action information. The Formaldehyde Panel has identified over 100 publications relating to important scientific issues including sensory irritation, formaldehyde modeling, weight of evidence, dermal exposure, and systematic review methods that have all been excluded from the Draft IRIS Assessment.[44] The Draft IRIS Assessment also does not integrate conclusions and methods from other authoritative bodies like the EU, World Health Organization, or other offices at EPA.

VII. The Draft Formaldehyde IRIS Assessment does not address previous NAS recommendations

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[39] *See* ACC Letter to Jonathan Samet regarding Summary of Insufficient EPA Responses to the Recommendations From the NAS 2011 Review of EPA's 2010 Draft IRIS Assessment of Formaldehyde, Mar. 31, 2023, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf.

[40] EPA, *IRIS Handbook*, at page 4-4.

[41] *See* EPA responses to NAS, Jan. 17. 2023, at page 16, available at: https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D68387109D2AC09286D94B621C4C6E83410005858BE3?noSaveAs=1.

[42] *See* ACC Letter to Jonathan Samet regarding Summary of Insufficient EPA Responses to the Recommendations From the NAS 2011 Review of EPA's 2010 Draft IRIS Assessment of Formaldehyde, Mar. 31, 2023, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf.

[43] EPA, *IRIS Handbook*, at page xvi.

[44] See List of Excluded Science, available at: https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613 and at pages 23-33 at ACC Formaldehyde Panel Comments for May 3, 2024 SACC Meeting - American Chemistry Council.

The Draft Formaldehyde IRIS Assessment was informed by a 2011 NAS review of an earlier 2010 Draft Formaldehyde IRIS Assessment. In the 2022 Draft IRIS Formaldehyde Assessment, EPA provides a cursory summary of responses to the NAS 2011 recommendations in Appendix D. However, as we described in the March 31, 2023 comments to the NAS, there are many important scientific areas where EPA has not addressed important comments from 2011.[45] These important areas include: responding to NAS comments related to understanding the MOA of formaldehyde; recognizing that formaldehyde is present in exhaled breath; following recommendations related to evaluating NPC; appropriately characterizing portal-of-entry effects, including the appropriate application of uncertainty factors and quantification of effects; and ensuring that LHP cancers were appropriately grouped.

VIII. The 2022 Draft IRIS Formaldehyde Assessment is not best available science and presents a flawed interpretation of non-cancer inhalation hazards

EPA's selection of studies for the point of departure for non-cancer inhalation effects is fundamentally flawed. Below we describe why the Draft IRIS Formaldehyde Assessment inappropriately relies on flawed epidemiological studies instead of existing controlled human exposure studies, which are the "gold standard" for toxicological evaluations of human risks. Formaldehyde's unique chemistry, including the fact that it does not follow Haber's Law, must be appropriately weighed and considered. The IRIS Assessment is not consistent with the best available science, given the available information regarding formaldehyde, including what we know about health effects at background levels.

a. Observational studies are not best available science

Observational epidemiological studies seek to evaluate the association between the occurrence of a disease and an exposure. Conflicting results from observational epidemiological studies that look at the risks to daily life, such as coffee, alcohol, chocolate, hormones, or carbohydrates have provided a constant source of stress and angst for the general public. We often find that, when further evaluated in randomized control trials, the results are contradicted. This is because confounding due to the presence of other factors in the exposure environment is hard to control for, and the poor design of many observational studies does not allow for a full accounting of these external influences. It is well accepted that a randomized control study will always be preferred, and, although often difficult and expensive, controlled human exposure studies (also known as chamber studies) are the most reliable "gold standard" for evaluating cause and effect.

In a controlled human exposure study, subjects are known, exposures are known, and confounders are known and controlled. Because of the challenges, and potential ethical concerns associated with controlled human exposure studies, we often do not have data from them, and thus lesser quality epidemiological studies are used. In the case of formaldehyde, multiple high quality controlled human exposure studies exist and should be used.

[45] *See* ACC Letter to Jonathan Samet regarding Summary of Insufficient EPA Responses to the Recommendations From the NAS 2011 Review of EPA's 2010 Draft IRIS Assessment of Formaldehyde, Mar 31, 2023, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf.

b. Observational studies relied upon by IRIS for chronic non-cancer hazards should be replaced by controlled human exposure studies - Understanding formaldehyde, sensory irritation, sensitive populations, and Haber's Law

Numerous studies evaluating formaldehyde have shown that the threshold for odor detection is generally lower than the ocular or nasal irritation threshold (also known as chemesthesis).[46] To date, no chemical has been identified as having an irritation threshold that is lower than its odor threshold, and formaldehyde is no exception.[47] Formaldehyde can be sensed at 100-500 ppb, and existing studies do not show sensory irritation occurring until 500-1000 ppb.[48] EPA's draft IRIS Assessment reliance solely on the data from the Hanrahan study has resulted in the identification of an irritation threshold that is orders of magnitude below the acknowledged odor threshold. The number of well conducted controlled exposure trials with no evidence of ocular irritation at 300-500 ppb provide ample evidence that maintaining exposures at or below these concentrations will provide sufficient protection from sensory irritation, including eye irritation. While we are pleased to see that EPA, in the Draft TSCA Risk Evaluation, has pivoted away from using the Hanrahan study, as is described below, the other observational studies are similarly flawed and should not be relied upon. Sensory irritation provides the appropriate lower bound on potential risk from adverse effects because any tissue irritation and other adverse effects will occur at concentrations higher than those where sensory irritation is observed.[49] The EPA HSRB, which questioned whether sensory irritation meets the EPA IRIS definition of adverse, not only agreed that using this endpoint as a lower bound is appropriate, but also recommended that no uncertainty factor need be applied when sensory irritation is used as the point of departure.[50] Other inhalation experts have also questioned the adversity of the sensory irritation endpoint, noting that the "chemesthesis response to formaldehyde is a normal physiological response and does not reflect adverse health effects unless the sensory organs are overwhelmed to the point of being functionally impaired or objectively incapacitating."[51]

It is also important to recognize that the well-established declines in olfactory and trigeminal (chemesthetic) sensitivity with age and age-related diseases means a younger, healthier population (which is typically the demographic of participants in controlled exposure studies) will be most sensitive to the odor and irritancy of formaldehyde.[52] Other authoritative bodies have this same conclusion. The NAS found that, at exposure concentrations at or below 3 ppm,

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[46] Doty, R. L., J. E. Cometto-Muñiz, A. A. Jalowayski, P. Dalton, M. KendalReed and M. Hodgson (2004). *Assessment of upper respiratory tract and ocular irritative effects of volatile chemicals in humans*, Critical Review in Toxicology 34(1): 85-142.

[47] Dalton, P., comments to NAS 2022, PAF-20, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0114 and also comments at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0086 and https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613/comments.

[48] *Id*.

[49] See Celanese comments to EPA, Oct. 13, 2023, in particular the summary discussion of the SCOEL opinion regarding the mechanistic support for threshold effects, at page 8, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0128.

[50] HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf.

[51] Kaden, D., comments to NAS 2022, PAF-43, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0115/attachment_10.pdf.

[52] See Dalton, P., comments to NAS 2022, PAF-20, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0107.

asthmatic individuals do not appear to be at greater risk of suffering airway dysfunction than non-asthmatic individuals.[53] WHO, in its 2010 evaluation, concluded that there is no evidence indicating an increased sensitivity to sensory irritation to formaldehyde among people often regarded as susceptible.[54] In addition, chemosensory expert Dr. Pamela Dalton has reviewed numerous studies, controlled and observational, that included asthmatics and other sensitive individuals, and these studies do not show that asthma and other health conditions predispose individuals to be more sensitive to formaldehyde.[55] Thus, when it comes to formaldehyde, consistent with the findings of the HSRB,[56] it is important to remember that a younger and generally healthier population will be the most sensitive. Thus, there is no disproportional effect on populations that are typically considered to be potentially exposed or susceptible subpopulations.

Finally, and perhaps most important, the observation that neither formaldehyde sensory nor tissue irritation adhere to Haber's Law has been noted in several publications in the peer-reviewed literature, including in evaluations conducted by NAS.[57] NAS, which considered sensory irritation the primary health effect of concern, agreed with the literature that found that exposure to concentrations that do not produce short-term sensory irritation also do not result in sensory irritation after repeated exposure.[58] Tissue irritation only occurs at concentrations higher than those that elicit sensory irritation. Recognizing the sequence of effects at increasing air concentrations, NAS also stated that at air concentrations that did not produce chronic tissue irritation, risk of cancer and other health effects (including asthma) appeared negligible.[59]

On May 18, 2023, in response to the HSRB questions asking why EPA disregarded information about the inapplicability of Haber's Law, EPA responded with two arguments. The first argument cited limited low concentration data from the Andersen and Mølhave (1983) study which indicated symptoms may increase over time at low concentration and higher concentration data that indicated symptoms may decrease over time. However, the HSRB review of the Andersen and Mølhave (1983) study, among other concerns, raised questions about the reliability of the study due to the lack of details presented and expressed concerns with the small sample size, highly variable responses, lack of dose response, and inclusion of potential confounders in the data. Based on these concerns, the HSRB final report recommends that EPA only use this

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[53] NAS, *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants Volume 1*, 2007, at page 108, available at: https://nap.nationalacademies.org/download/11170#.
[54] World Health Organization (WHO) (2010): Regional Office for Europe. *WHO Guidelines for Indoor Air Quality: Selected Pollutants*. Copenhagen, Denmark: World Health Organization.
[55] Dalton, P, Comments to EPA on the Draft IRIS Formaldehyde Assessment, June 13, 2023, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0086 and https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613/comments.
[56] HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf.
[57] See comments submitted to the HSRB, May 16, 2023, by Dr. Holm on behalf of the American Forest & Paper Association and the American Wood Council, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0106/attachment_8.pdf. See also NAS 2007, Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants Volume 1, 2007, available at: https://nap.nationalacademies.org/download/11170#.
[58] NAS, *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants Volume 1*, 2007, at page 105, available at: https://nap.nationalacademies.org/download/11170#.
[59] *Id*.

study qualitatively.[60] The study was determined to not provide reliable evidence to inform the inapplicability of Haber's Law. And the final HSRB report supports the finding that formaldehyde effects do not adhere to Haber's Law.[61] As seen with formaldehyde exposures, accommodation to low concentrations that cause short-term irritation has been reported, and in such cases irritation subsides with exposure duration. This was also an important consideration of the NAS during its review of emergency exposure levels.[62] Because Haber's Law does not apply, short term exposure studies can indeed be used to inform chronic exposures, and there is no basis for the application of adjustment or uncertainty factors. After reviewing all the evidence, the HSRB disagreed "with EPA's assumption of Haber's Law for formaldehyde and recommends that EPA not make duration adjustments to develop the PODs."[63]

In summary, with formaldehyde, when evaluating the best available science and conducting a weight of the evidence evaluation, EPA must be mindful that sensory irritation is the most sensitive endpoint which protects against other health effects, and that a younger population will be more sensitive than an older or asthmatic population, and that concentration, not duration, is the driver of whether effects will be seen.

c. The observational studies used for chronic non-cancer hazards are highly flawed and unreliable for identifying a point of departure

The 1990 study by Krzyzanowski et al. was inexplicably assigned high confidence by the IRIS program for its findings of decreased pulmonary function in children. However, there are significant transparency concerns with this study, which were also noted by the NAS in both its 2011 and 2023 reviews of the Draft Formaldehyde IRIS Assessments. Study characteristics are not fully reported, there is no information provided on NO_2 levels (even though the study says measurements were taken), readers cannot discern how the authors picked the preferred best model, the study design is unclear, and, although information on symptoms was collected, no information on the relationship between these symptoms and pulmonary function are presented. This was a cross-sectional study conducted over two weeks, where only two measurements of formaldehyde levels were taken for each participant, and four pulmonary function measurements were taken each day. However, the observations presented in the data tables represent, on average, only two measurements per day per person, not four measurements per day. Day-to-day and morning-to-night fluctuations in formaldehyde levels in indoor air were not accounted for. And, although EPA reports that confounding was addressed, in the final model used there was no adjustment for smoking status, NO_2, or episodes of acute respiratory illness. Finally, while the study also evaluated respiratory effects in adults, no effects in adults were associated with formaldehyde exposures.

Putting aside the weaknesses above, and other weaknesses that are not mentioned here, Krzyzanowski et al. is simply not reliable for conducting dose-response analysis to identify a point of departure. The study's ability to determine causality specific to formaldehyde is weak at

[60] HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf.
[61] *Id*.
[62] NAS, *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants Volume 1*, 2007, at page 105, available at: https://nap.nationalacademies.org/download/11170#.
[63] *Id*.

best. Dr. Paustenbach in his review refers to the point of departure derived from the study as "scientifically unsound" due to the plethora of confounders that were not addressed, and Linda Dell in her review considers the study to be simply "uninformative."

The Draft Formaldehyde IRIS Assessment also relies on other observational epidemiological studies and endpoints to support the point of departure determined from the Krzyzanowski study. Annesi-Maesano et al. was assigned high confidence for its finding of increased prevalence of rhinoconjunctivitis (as a marker of allergy-related conditions) in children and medium confidence for the outcome of current asthma in children. Matsunaga et al. was assigned high confidence for its finding of allergic rhinitis and atopic eczema in pregnant women and Venn et al. was assigned medium confidence for its finding of reduced symptom control among children with asthma. Matsunaga et al. notes that its results cannot be generalized to an adult population, and the other two studies were in populations of children, which are not relevant for an occupational hazard value. Independent reviews of each of these studies do not support EPA's confidence ratings and do not support confidence in the conclusions of these studies.[64]

For instance, in Annesi-Maesano et al., a temporal relationship between formaldehyde exposure and prevalence of rhinoconjunctivitis was not established. Complicating the study is the admission from the authors that, while formaldehyde was measured in school classrooms, the five-day measurements may not be representative of the students' usual school exposure. Prevalence of rhinoconjunctivitis and asthma symptoms in this study was based on a parental report for the previous 12 months, but concentrations of formaldehyde were only measured over a five-day period. There was no statistically significant exposure-response trend, and there was an unexplained inconsistency between results for rhinoconjunctivitis and allergic asthma. There was also no statistically significant exposure-response trend for current asthma; therefore, there is simply no basis for setting a toxicity value to protect against an adverse effect that is not identified in the study.

The Matsunaga et al. study is also not reliable for dose-response characterization. The study investigators reported that there was no increased prevalence of allergic rhinitis related to formaldehyde exposure. Although formaldehyde and nitrogen dioxide were measured, study investigators did not report concentrations of nitrogen dioxide or otherwise evaluate nitrogen dioxide as a potential confounder. Additionally, the study explained that rhinitis symptoms during pregnancy may be due to hormonal changes during pregnancy and cannot be distinguished from allergic rhinitis, and the association between formaldehyde exposure and atopic eczema was only seen in pregnant women with a negative family history of allergies and not in pregnant women with a positive family history of allergies.

Finally, the Venn et al. study is also not reliable for dose-response characterization. In this cross-sectional study, Venn et al. found no significant effect of formaldehyde on asthma risk but did report that formaldehyde exposure increased "disease severity" among cases (i.e., those with asthma). Disease severity was measured by "peak flow variability, frequent symptomatic days, and frequent symptomatic nights (symptoms were recorded in a diary on 10% or more of days/nights)." 10% of days (or nights) is approximately 3 days (or 3 nights) over a 4-week

[64] *See*, in particular, Comments from Linda Dell (Ramboll) submitted to the SACC, May 2024, available at https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613.

period; however, EPA mistakenly reports these data as symptoms reported on ≥10 consecutive days. There is significant uncertainty about the window of exposure relative to the effect findings in this study, and, while the study reports that control for potential confounding had little impact on the results seen, these results are simply not presented. Interestingly, this study also evaluated pulmonary function, similar to Krzyzanowski et al., and, while EPA does not report on this endpoint in the Venn et al. evaluation, the findings are not consistent with Krzyzanowski et al.

With regard to the reported associations between formaldehyde exposures and childhood or adult asthma risk, there remain a number of unanswered questions. In exploring possible mechanisms for formaldehyde-induced bronchoconstriction, Thompson and Grafstrom (2008) noted that "The potential for formaldehyde to provoke asthma, hypersensitivity, and airway constriction in adults and children has received extensive attention over the years, yet data regarding these effects remain equivocal."[65] Although the hypothetical mechanism proposed by those authors may or may not lead to a better understanding of whether formaldehyde plays a causative role in asthma-related bronchoconstriction, at present the evidence suggests that asthma is neither caused nor exacerbated by low-level exposure (i.e., less than 1-2 ppm).[66]

Additional mechanistic support, as reported in multiple publications, explaining why asthmatics are not more sensitive to formaldehyde at environmentally relevant levels is the well documented effective scrubbing of low levels of formaldehyde in the upper airways below 3 ppm.[67] As a result, little formaldehyde at these concentrations reaches the mid- to lower airways where an asthmatic reaction may be triggered. The lack of sensitivity of asthmatics at these lower air levels in controlled human studies is consistent with expected patterns of absorption in the upper airways. While formaldehyde is clearly a sensory irritant at sufficient concentrations, its potential to cause or exacerbate asthma is far less certain, particularly at low exposure levels (<1-2 ppm). OSHA regulations state that "[c]oncentrations of above 5 ppm readily cause lower airway irritation characterized by cough, chest tightness, and wheezing."[68] It is also worth noting that there are no studies in which exposure to formaldehyde alone has been shown to cause or exacerbate asthma. Instead, studies that have reported this effect are all observational studies

[65] Thompson, C. M. and R. C. Grafstrom (2008). *Mechanistic Considerations for Formaldehyde-Induced Bronchoconstriction Involving S-Nitroglutathione Reductase*. Journal of Toxicology and Environmental Health Part A [US CPSC] US Consumer Product Safety Commission 1982. Release # 82-005. Available from: 71: 244-248, available at: https://doi.org/10.1016/j.taap.2008.09.011.

[66] Noisel N, le Bouchard M, Carrier G. *Evaluation of the health impact of lowering the formaldehyde occupational exposure limit for Quebec workers*. Regul Toxicol Pharmacol. 2007;48:118–127.

[67] *See* for example, Schlosser PM, Lilly PD, Conolly RB, Janszen DB, Kimbell JS. *Benchmark dose risk assessment for formaldehyde using airflow modeling and a single-compartment DNA-protein cross-link dosimetry model to estimate human equivalent doses*. Risk Anal. 2003;23:473–487; Kimbell JS, Gross EA, Joyner DR, Godo MN, Morgan KT. *Application of computational fluid dynamics to regional dosimetry of inhaled chemicals in the upper respiratory tract of the rat*. Toxicol Appl Pharmacol. 1993;121:253–263; Kimbell JS, Overton JH, Subramaniam RP, Schlosser PM, Morgan KT, Conolly RB, Miller FJ. *Dosimetry modeling of inhaled formaldehyde: Binning nasal flux predictions for quantitative risk assessment*. Toxicol Sci. 2001;64:111–121; Overton JH, Kimbell JS, Miller FJ. *Dosimetry modeling of inhaled formaldehyde: The human respiratory tract.* Toxicol Sci. 2001;64:122–134; and, Garcia GJ, Schroeter JD, Segal RA, Stanek J, Foureman GL, Kimbell JS. *Dosimetry of nasal uptake of water-soluble and reactive gases: A first study of interhuman variability*. Inhal Toxicol. 2009;21:607–618.

[68] 29 C.F.R. § 1910.1048. Formaldehyde Appendix C.

which have been confounded, to an unknown extent, by simultaneous co-exposures to other chemicals, many of which have been associated with exacerbating asthmatic symptoms.[69]

d. Understanding the strengths of the controlled human exposure studies

EPA asked the HSRB to evaluate the controlled human exposure studies to inform acute exposures. The HSRB did not find any ethical issues with the key studies identified by EPA (Mueller et al. 2013, Lang et al. 2008, Kulle et al. 1987, and Andersen and Mølhave, 1983), and the HSRB also noted that the controlled chamber studies have "a preferred study design and greater scientific rigor than the observational studies."[70] As noted above, controlled human exposure studies provide great advantages over observational studies, and in each of the studies evaluated by the HSRB, the subjects, exposures, and confounders are known and controlled.

In particular, the HSRB recommended relying on Mueller et al. and Lang et al., and particularly Lang et al.. for deriving a point of departure consistent with the best available science and based on a weight of the evidence approach. The OPP Data Evaluation Records (DERs) for Mueller and Lang also concluded that both of these studies provide data for quantitative use for deriving a point of departure.[71] While OPP was focused on points of departure for acute inhalation, based on what we know regarding formaldehyde's properties as an exception to Haber's Law, these findings should apply equally to chronic durations. Commenting on the applicability of these findings for the weight of evidence for the chronic point of departure was not part of the charge to the HSRB because EPA only sought its input on acute findings.

e. Findings from other authoritative bodies

When evaluating formaldehyde for the determination of occupational limits, other authoritative bodies have chosen to rely on controlled human exposure studies over observational epidemiological studies and in doing so relied upon sensory irritation effects as protective of all other non-cancer and cancer effects.[72] In 2017, ACGIH relied upon Lang et al., and in 2016, SCOEL relied on Mueller et al. and Lang et al. In 2010, for general population exposures, WHO also relied on controlled human exposure studies (Lang et al.), and in 2007, the NAS also recommended controlled human exposure studies when evaluating formaldehyde exposures in submarines.

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[69] *See* comments submitted to the SACC from AF&PA, May 2024, available at https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613.

[70] HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf.

[71] *See* DERs for Lang et al. 2008 and Mueller et al. 2013, available at 42. DER Lang 2008 Draft Risk Evaluation for Formaldehyde and 43. DER Mueller 2013 Draft Risk Evaluation for Formaldehyde, and Debra Kaden presentation to the HSRB on Lang et al. and Mueller et al., available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0106/attachment_3.pdf and https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0106/attachment_2.pdf.

[72] *See* Goyak and Holm (2024). *Sensory irritation and use of the best available science in setting exposure limits: Issues raised by a scientific panel review of formaldehyde human research studies.* Reg Tox Pharm., available at: https://doi.org/10.1016/j.yrtph.2024.105587; and Celanese comments, to EPA, Oct. 13, 2023, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0128.

These organizations evaluated the weight of the evidence and determined that the best science came from relying on studies where the populations, exposures, and confounders were controlled. EPA should similarly use the controlled human exposure studies for points of departure for evaluating the occupational, consumer, indoor air, and ambient air scenarios.

IX. The IUR for NPCs in the 2022 Draft IRIS Formaldehyde Assessment is flawed and overestimates risk

The IUR analysis for NPC in the 2022 Draft IRIS Formaldehyde Assessment has been criticized for over a decade, and EPA has still not addressed these concerns. In 2011, after reviewing EPA's 2010 Draft IRIS Formaldehyde Assessment, NAS recommended that EPA conduct an independent analysis of the National Cancer Institute (NCI) cohort that EPA relied upon and also recommended that EPA consider alternative models, consistent with EPA's 2005 Cancer Guidelines.[73] Despite these recommendations, EPA did not conduct an independent analysis, and instead based the IUR on undocumented personal communications with Dr. Beane-Freeman, who is a lead author on the NCI cohort publications. Furthermore, EPA has given no consideration to the application of alternative models. For instance, while NAS 2011 recommended a Cox proportional hazards model, EPA continued to rely on external publications as well as communications with Dr. Hauptmann and Dr. Beane Freeman (as described by EPA on pages 2-49 and D-37 of the 2022 Draft IRIS Formaldehyde Assessment), rather than conduct an independent analysis.

Consideration of alternative models, including non-linear models, is necessary because, over the past 30 years, a mode of action (MOA) of cytotoxicity with regenerative hyperplasia for NPC has become globally accepted. A former director of the IRIS program (Dr. James Cogliano) is one of four authors of the first peer-reviewed publication detailing the cytotoxicity with regenerative hyperplasia MOA for nasal tumors (McGregor et al. 2006), which was recently updated and published by Thompson et al. (2020).[74] McGregor et al. (2006) was cited incorrectly in one paragraph of the 2022 Draft IRIS Formaldehyde Assessment as evidence against the cytotoxic MOA. The exclusion of the Thompson et al. (2020) study of cytotoxicity with regenerative hyperplasia (following the IPCS MOA framework) from the 2022 Draft IRIS Formaldehyde Assessment is noteworthy. This MOA, as described by Thompson et al., for nasal tumors was recently adopted by the European Chemicals Agency (ECHA) and approved by the 32 countries in the European Union. While the 2022 Draft IRIS Formaldehyde Assessment says that nasal tumors/NPC is presumed to have a mutagenic MOA, there is no formal determination as described in and required by in the EPA Cancer Guidelines. Nor was an assessment performed according to a data-driven, recognized framework (i.e., cytotoxicity with regenerative

[73] NAS, *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde,* 2011, at page 134, available at: https://nap.nationalacademies.org/catalog/13142/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-formaldehyde.

[74] Thompson et al. (2020). An updated mode of action and human relevance framework evaluation for formaldehyde related nasal tumors. Critical Reviews in Toxicology. 50(10): 919-952.

hyperplasia assessed according to the IPCS MOA framework), as is also described and required by the EPA (2005) Cancer Risk Assessment Guidelines.[75]

A detailed discussion of how EPA's 2022 Draft IRIS Formaldehyde Assessment fails to consider MOA, misinterprets critical scientific information from peer-reviewed publications that inform the mode of action, and is inconsistent with EPA's Cancer Guidelines was provided to NAS in 2023 to inform its review.[76] In addition, the ACC Formaldehyde Panel provided significant technical comments to EPA, which were also shared with NAS.[77] Nonetheless, consistent with its charge, NAS did not consider alternative information. As such, public comments, which presented voluminous amounts of scientific analyses, were not considered in the limited peer-review that was conducted.[78] The concerns with the NAS process are discussed above in more detail.

A more recent analysis, provided to the SACC by Drs. Thompson and Gentry, also describes the detailed scientific flaws in EPA's IUR analysis for NPC and describes some of the scientific publications that EPA must also consider.[79] This new analysis shows how EPA's treatment of formaldehyde is inconsistent with the approach taken in the TSCA risk evaluation for 1,4-dioxane, where EPA acknowledged that there are nonlinearities in response to exposure to genotoxic agents.

As described above, robust scientific information that has been provided to EPA, but not considered in the 2022 Draft IRIS Formaldehyde Assessment, supports a non-genotoxic mode of action where protecting against sensory irritation would also be protective of cancer.[80] In addition, the CIIT Formaldehyde Biologically Based Dose Response (BBDR) model has been updated to address uncertainties associated with modeling DNA adducts and nasal tumors due to formaldehyde exposure. This model predicts that the probability of tumors from chronic

[75] The EPA Cancer Guidelines, when discussing procedures for cancer modeling, state that, if the information "is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager." at page 1-9, available at: https://www.epa.gov/sites/default/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

[76] ACC, *Summary of Insufficient U.S. Environmental Protection Agency (EPA) Responses to the Recommendations From the National Academy of Sciences (NAS) 2011 Review of EPA's 2010 Draft IRIS Assessment of Formaldehyde*, Mar. 31, 2023, at pages 4-7, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf.

[77] ACC, Formaldehyde Panel Comments on the 2022 Draft IRIS Assessment for Formaldehyde, these comments provide additional information about scientific studies which EPA misinterpreted when evaluating the epidemiological data and mode of action information relating to NPC, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0127/attachment_7.pdf.

[78] While the NAS thanked public commenters for their input, there is no indication in the NAS report that NAS considered any public comments in their review.

[79] See Comments submitted to the SACC, May 2024, from Dr. Chad Thompson and Dr. Robinan Gentry, available at: https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613.

[80] MacGregor 2006, and Panel 2010 comments at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0029, document 5 etc.

exposure of rats to 1 ppm formaldehyde would be indistinguishable from controls.[81] Despite recommendations from NAS, EPA has not relied upon this model.

An analysis which sought to ground-truth EPA's NPC IUR projects that, using the draft IUR, background exposures of formaldehyde at levels of 5 and 20 ppb will cause 20 or 51 percent of the annual incidence of NPC in the U.S. population.[82] These values do not match the available literature, which shows that minimal, if any, NPC are due to background levels of formaldehyde. And this finding is also inconsistent with molecular dosimetry data that indicates that little to no exogenous formaldehyde is entering human cells at average indoor air concentrations.[83] EPA's approach, which uses linear modeling for NPC, has led to an unrealistic and overestimated IUR.

In addition to longstanding concerns with EPA's analysis, and the implausibility of the draft IUR as noted above, significant scientific information available in the peer-reviewed literature was not considered in the 2022 Draft IRIS Formaldehyde Assessment.[84] EPA used systematic review criteria which allowed the agency to ignore important studies (such as Thompson et al.) because they were not considered to be primary literature. EPA sought to include only studies that provided new data sets, not re-analysis of existing information. EPA's refusal to consider studies that provide a reanalysis means that no matter how flawed the initial study may be, EPA is precluding analyses that point out fundamental flaws in the study. EPA must consider how this additional information would lead to significant scientific changes in the IUR for NPC.

a. Associations between formaldehyde and myeloid leukemia are not supported by the weight of the scientific evidence

Despite a 2011 NAS recommendation that EPA provide a clear causality framework for determinations regarding LHP cancers, the Draft Formaldehyde IRIS Assessment simply lacks such a framework.[85] NAS 2011 noted inconsistencies in the epidemiologic data, weak animal data, and the lack of mechanistic data leading to a conclusion that "there is a noticeable lack of

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[81] Conolly RB, Schroeter J, Kimbell JS, Clewell H, Andersen ME, Gentry PR. 2023. *Updating the biologically based dose-response model for the nasal carcinogenicity of inhaled formaldehyde in the F344 rat*. Toxicol Sci. 193(1):1-17. https://doi.org/10.1093/toxsci/kfad028. PMID: 36912747; PMCID: PMC10176246.

[82] ACC Formaldehyde TSCA Risk Evaluation Consortium comments on the 2022 Draft Formaldehyde IRIS Assessment, pages 46-54, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0127/attachment_8.pdf.

[83] *Id*.

[84] See multiple data submissions on the missing studies submitted to the IRIS docket from study authors, including Dr. Robinan Gentry, June 9, 2022, available at https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0074, Dr. Chad Thompson, June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0087, and Dr. Rory Conolly, June 9, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0075, and the ACC Formaldehyde Panel comments on the 2022 Draft Formaldehyde Assessment, June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103, and the ACC Formaldehyde TSCA Risk Evaluation Consortium comments on the 2022 Draft Formaldehyde Assessment, June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0100, ACC comments submitted to NAS, March 31, 2023, *Summary of Insufficient U.S. Environmental Protection Agency (EPA) Responses to the Recommendations From the National Academy of Sciences (NAS) 2011 Review*, available at: PAF-76, https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf. These comments are also available in this docket: https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613.

[85] ACC, *Summary of Insufficient U.S. Environmental Protection Agency (EPA) Responses to the Recommendations From the National Academy of Sciences (NAS) 2011 Review* at page 15 for a detailed discussion, available at: PAF-76, https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf.

evidence of a causal relationship of formaldehyde exposure and Hodgkin lymphoma or leukemia."[86] In response to these comments, the 2022 Draft Formaldehyde IRIS Assessment did two important things:

1) EPA acknowledged that "the lack of systemic distribution of formaldehyde is sufficiently supported" (at page D-6) and admits that "no MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution" (at pages liv, 2-43); and,

2) EPA put in place a causality framework that allows it to ignore the strong mechanistic evidence against the systematic effects they acknowledge above and relies upon the inconsistent epidemiological data, questionable biomarker data to characterize mutagenic or genotoxic potential, evidence against lymphohematopoietic malignancies of any kind in animal models (e.g., "Increased LHP cancers have not been observed in well-reported chronic rodent bioassays…. Further, positive associations with leukemia have not been reported in rodent studies" (page 1-435)), and an assumption about hypothetical key events with a lack of defined mode of mechanisms of action to find that the "evidence demonstrates" that formaldehyde inhalation causes myeloid leukemia.

This cannot be what NAS 2011 intended when recommending that EPA develop a clear, non-subjective framework that uses the weight of the evidence to assess causality. Yet EPA has developed a flawed causality framework that allows it to ignore robust mechanistic information (e.g., molecular dosimetry documenting no systemic distribution of inhaled formaldehyde) and no evidence of leukemia in multiple cancer bioassays in multiple species, while continuing to evaluate epidemiological information in an inconsistent manner (despite NAS 2011 recommendations for clear criteria) outside of any recognized framework for data integration. Each of these points is addressed, in detail, in a comment letter the Formaldehyde Panel provided to NAS on March 31, 2023.[87] The Formaldehyde Panel and external scientific experts have also provided significant comments to EPA discussing the lack of scientific rigor in EPA's analyses related to myeloid leukemia.[88]

EPA simply did not consider existing MOA information in an integrative framework. Using the well-established international, consensus-based World Health Organization (WHO)/ International Programme on Chemical Safety (IPCS) MOA framework, Gentry et al., 2020, evaluated postulated MOAs for leukemia following formaldehyde inhalation.[89] Using the IPCS

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[86] NAS, *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde,* 2011, at page 135, available at: https://nap.nationalacademies.org/catalog/13142/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-formaldehyde.

[87] ACC, *Summary of Insufficient U.S. Environmental Protection Agency (EPA) Responses to the Recommendations From the National Academy of Sciences (NAS) 2011 Review* at page 15 for a detailed discussion, available at: PAF-76, https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf.

[88] *See*, for example references in ACC Formaldehyde Panel comments on Draft 2022 Formaldehyde Assessment to Gentry/Checkoway/Mundt/Rhomberg papers, June 13, 2022, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0127/attachment_7.pdf, and comments submitted to the SACC from Dr. Harvey Checkoway, May 1, 2024, where he states "Based on my review of the draft EPA report, I do not find that its conclusions are grounded in the best available science and also fails to fully incorporate key recommendations from previous peer reviews, " available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0140.

[89] Gentry, R., Thompson, C.M., Franzen, A., Salley, J., Albertini, R., Lu, K. and Greene, T., 2020. *Using*

framework, the authors showed that a significant amount of research supports the null hypothesis that there is no causal association between formaldehyde inhalation exposure and leukemia. The analysis showed a lack of confidence in any of the postulated leukemia MOAs currently in the published literature and a lack of dose-response or concordance with many of the key events postulated in the EPA 2022 Draft Assessment, most of which require systemic delivery. This increases confidence in the conclusion that there is a lack of biological plausibility for a causal association between formaldehyde inhalation exposure and leukemia. EPA did not consider the findings of this publication.

More recently, Vincent et al., 2024, conducted a systematic review focusing on the relationship between formaldehyde and LHP cancers, including myeloid leukemia.[90] This systematic review found "no credible explanation linking inhaled formaldehyde to LHP cancers, and no evidence of formaldehyde entering the bone marrow or blood when inhaled" and determined that causation is unlikely.[91]

As summarized above, because the Draft Formaldehyde IRIS Assessment does not properly weigh the available information, it does not represent the best available science. Nor does the Draft Formaldehyde IRIS Assessment integrate available information into a weight of the scientific evidence framework. EPA must properly integrate new publicly available information, as well as existing information that the Formaldehyde Panel has already provided, including the Gentry et al., 2020 publication and other information that informs MOA.[92]

b. The IUR for NPC should not be framed as an underestimate of cancer risks

As described above, the NPC IUR discounts important information about the MOA of formaldehyde and overpredicts NPC cancer risks by using linear modeling. While EPA recognizes that that the myeloid leukemia findings are not sufficient to develop quantitative estimates of cancer risk, it also suggests that the cancer risks presented are an underestimate and that, if myeloid leukemia were considered, the IUR could increase by as much as four-fold.[93] It is inconsistent and scientifically unsound for EPA to suggest that the risks cannot be quantified and at the same time provide an estimate for those uncertain risks. As described above and discussed in previous comments,[94] due to the biological implausibility of formaldehyde causing myeloid

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mechanistic information to support evidence integration and synthesis: a case study with inhaled formaldehyde and leukemia. Critical reviews in toxicology, 50(10), pp. 885-918.

[90] M J Vincent, S Fitch, L Bylsma, C Thompson, S Rogers, J Britt, D Wikoff, *Assessment of associations between inhaled formaldehyde and lymphohematopoietic cancer through integration of epidemiological and toxicological evidence with biological plausibility*, Toxicological Sciences, 2024, kfae039, https://doi.org/10.1093/toxsci/kfae039.

[91] Truth in Science, *Why Robust Methods in Systematic Review Matter: The Case of Formaldehyde and Myeloid Leukemia*, available at: https://truthinscience.org/why-robust-methods-in-systematic-review-matter-the-case-of-formaldehyde-and-myeloid-leukemia%ef%bf%bc/.

[92] *See*, Examples of Excluded Science, including Key Studies, Recent Publications, and Authoritative Reviews, available at: https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613 and Attachment B, at pages 23-33 of ACC Formaldehyde Panel Comments for May 3, 2024 SACC Meeting - American Chemistry Council.

[93] EPA, *Toxicological Review of Formaldehyde-Inhalation*, Apr. 2022, at page 2-104, available at: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544587

[94] See multiple data submissions on the missing studies submitted to the IRIS docket from study authors, including Dr. Robinan Gentry, June 9, 2022, available at https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0074, Dr. Chad Thompson, June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0087, and Dr. Rory Conolly, June 9, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-

leukemia, as well as the weaknesses in the epidemiological literature upon which EPA relies, there is no sound scientific reason for EPA to suggest that using the NPC IUR underestimates cancer risks due to a hypothetical potential for myeloid leukemia. Publicly available publications which considered all available information, including MOA and mechanistic data, in robust integrative frameworks found that causality is improbable and not supported by the evidence. It is false and misleading for EPA to suggest that there is an underestimate of cancer risk, especially when EPA's linear modeling of NPC cancers leads to an overestimate of cancer risk.

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Taken together, these critiques make clear that there is a substantial amount of additional work that EPA will likely need to do to ensure the 2022 Draft Assessment adheres to EPA policy and procedural requirements and relies on the best available science, incorporates a weight-of-evidence approach and properly integrates evidence streams in assessing noncancer and cancer endpoints. Should you have any questions, please reach out to Sahar Osman-Sypher at sahar_osman-sypher@americanchemistry.com or 202-249-6721.

Sincerely,

Sahar Osman-Sypher
Senior Director
Chemical Products & Technology Division
American Chemistry Council
On Behalf of the ACC Formaldehyde Panel

Attachment: ACC Formaldehyde Panel comments on the Draft TSCA Risk Evaluation for Formaldehyde, May 14, 2024, available at: Regulations.gov

Cc: Richard Revesz, OIRA Administrator
Christine Kymn, Chief of the Natural Resources and Environment Branch, OIRA
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ORD-2010-0396-0075, and the ACC Formaldehyde Panel comments on the 2022 Draft Formaldehyde Assessment, June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103, and the ACC Formaldehyde TSCA Risk Evaluation Consortium comments on the 2022 Draft Formaldehyde Assessment, June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0100, ACC comments submitted to NAS, March 31, 2023, *Summary of Insufficient U.S. Environmental Protection Agency (EPA) Responses to the Recommendations From the National Academy of Sciences (NAS) 2011 Review*, available at: PAF-76, https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0117/attachment_7.pdf, and M J Vincent, S Fitch, L Bylsma, C Thompson, S Rogers, J Britt, D Wikoff, *Assessment of associations between inhaled formaldehyde and lymphohematopoietic cancer through integration of epidemiological and toxicological evidence with biological plausibility*, Toxicological Sciences, 2024; kfae039, https://doi.org/10.1093/toxsci/kfae039. These comments are also available in this docket: https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613.