Submitted Via Email

March 31, 2023

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Board on Environmental Studies and Toxicology
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RE: 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

Dear Dr. Samet,

On behalf of the American Chemistry Council's (ACC) Formaldehyde Panel (the Panel), I am submitting to you a review document that provides a summary of the insufficient responses EPA has provided to the specific recommendations from the NAS 2011 report entitled *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (NAS 2011). The NAS 2011 report provided comments and recommendations on 1) general issues associated with the 2010 Draft IRIS Assessment, 2) specific aspects of the draft IRIS assessment including derivation of the reference concentration and the unit risk estimates, 3) improving the IRIS assessment for formaldehyde, and 4) improving the IRIS development process. These recommendations were intended to inform a revised IRIS assessment of formaldehyde.

Ahead of the release of the 2022 Draft Assessment, the Panel has previously catalogued detailed reasons why EPA's failure to fully address relevant findings and recommendations of the 2011 report renders the 2022 Assessment and its peer review inconsistent with requirements of the Toxic Substances Control Act, Clean Air Act, Federal Advisory Committee Act, and EPA guidance.[1]

As you will see in the enclosed review, there are many important recommendations that EPA has not satisfactorily addressed. EPA, in the 2022 Draft IRIS Assessment, provides a cursory summary of responses to the NAS 2011 recommendations in Appendix D. The enclosed review does not reiterate the responses that EPA has provided; however, where applicable, it discusses where EPA's responses overstate resolution of, or do not respond to, NAS 2011

[1] https://www.americanchemistry.com/content/download/10668/file/Formaldehyde-Panel-Follow-Up-Letter-to-EPA-031022.pdf.

recommendations. In addition, EPA provided responses to NAS committee questions which were posted during the public comment period of the January 30, 2023 public meeting[2] and subsequently updated them with clarifications on February 8.[3] Both of these responses make incorrect and confusing claims about the responsiveness of the 2022 Draft IRIS Assessment to the 2011 recommendations, claiming that the 2011 report recommendations were "[t]he primary guidance used to develop" the assessment and that 2011 report helped fulfill "the functional role" of a systematic review protocol. The focus of this document is on the effect the EPA omissions and inaccurate characterizations have on the scientific foundation of the 2022 Draft IRIS Assessment.

The NAS 2011 recommendations are essential not just to EPA, but also to stakeholders including the U.S. Congress, the scientific community, the public, regulators at U.S. EPA, other federal agencies, and state and local governments, and industry. As evidence of the significance of the recommendations, ACC's Formaldehyde Panel spent significant resources on developing original research over the last decade, including new data and analyses, with the intent of addressing NAS 2011 recommendations. Similarly, multiple acts of Congress in the last 12 years have directed EPA to follow the NAS 2011 recommendations and they have been featured prominently in congressional hearings as well as Federal Government oversight and authorization activities. As the Panel has documented previously, EPA's failure to fully address all recommendations of the 2011 NAS report has serious legal, scientific, policy, and procedural implications for the use of the 2022 Draft IRIS Assessment.[4] Similarly, efforts to narrow or limit the scope of the Committee's activities to exclude whether broader recommendations have been satisfactorily addressed runs contrary to the law and EPA guidance.[5] In addition, by focusing on the NAS 2011 recommendations, and by having independent experts take the lead on developing peer reviewed publications, the Panel and its members fully expected that the scientific information developed could and would then be used to better inform EPA's next revision of the 2022 Draft IRIS Assessment.

As is discussed in the enclosed review, and in other comments previously provided to EPA and NAS, there are many cases where EPA chose methods and approaches that inappropriately discounted or dismissed this new scientific information. The disconnect between the 2011 NAS recommendations and EPA's continuing dismissal of, or failure to incorporate, information developed specifically to address these recommendations is striking.

Should you have any questions, I would welcome the opportunity to speak with you and the NAS committee regarding the attached review. I can be contacted at sahar_osman-sypher@americanchemistry.com.

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[2] https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D68387109D2AC09286D94B621C4C6E83410005858BE3?noSaveAs=1

[3] https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D3A22C29743668E583CD8759F633481333EE3E7ECF54?noSaveAs=1

[4] https://www.americanchemistry.com/content/download/10668/file/Formaldehyde-Panel-Follow-Up-Letter-to-EPA-031022.pdf

[5] https://www.americanchemistry.com/content/download/10864/file/ACC-EPA-NASEM-Charge-Questions.pdf.

Sincerely,

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Senior Director
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American Chemistry Council
On Behalf of the ACC Formaldehyde Panel

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

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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

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I. Overview

In 2011, the National Academies of Sciences, Engineering, and Medicine (NAS) released a report entitled *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (hereinafter referred to as NAS 2011). That report was the culmination of an independent scientific review of the 2010 EPA Draft IRIS Assessment for Formaldehyde (2010 Draft IRIS Assessment or 2010 Draft Assessment). The NAS 2011 report provided comments and recommendations on 1) general issues associated with the 2010 Draft IRIS Assessment, 2) specific aspects of the draft IRIS assessment including derivation of the reference concentration and the unit risk estimates, 3) improving the scientific basis of the IRIS assessment for formaldehyde, and 4) improving the IRIS development process. All these recommendations were intended to inform a revised IRIS assessment of formaldehyde. In 2022, EPA released a Draft IRIS Assessment for Formaldehyde (2022 Draft IRIS Assessment or 2022 Draft Assessment). This document describes how the 2022 Draft IRIS Assessment addresses the NAS 2011 recommendations.

In these comments, the focus is on formaldehyde. As such, they provide a discussion, predominantly, of the recommendations made by the NAS to address the first three areas noted above. In particular, we focus on the key scientific recommendations made by the NAS that EPA has not satisfactorily addressed in the 2022 Draft IRIS Assessment and that also have important impacts on the outcome of the 2022 Draft IRIS Assessment. EPA, in the 2022 Draft IRIS Assessment, provides a cursory summary of responses to the NAS 2011 recommendations in Appendix D. Our comments do not reiterate the responses that EPA has provided; however, where applicable, they discuss where EPA's responses inaccurately characterize or do not respond to NAS 2011 recommendations that have been made. The focus of this document is on the scientific implications of those inaccurate characterizations.

It is important to recognize the NAS 2011 recommendations were important not just to EPA, but also to stakeholders that manufacture and use formaldehyde. While we do not speak for all stakeholders, those that are members of the American Chemistry Council (ACC), spent significant resources on developing scientific information, including new data and analyses, with the intent of addressing NAS 2011 recommendations. By focusing on the NAS 2011 recommendations, and by having independent experts take the lead on developing peer reviewed publications, ACC and its members fully expected that the scientific information developed could and would then be used to inform EPA's next draft IRIS assessment. As is discussed in the comments below, and in other comments previously provided to EPA and NAS, there are many cases where EPA chose methods and approaches that inappropriately discounted or dismissed this new scientific information.

The discussions that follow are organized to mimic the flow of the NAS 2011 report; however, we include the discussion of the failures to address recommendations related to the identification and quantification of potential health risks as we discuss the specific endpoints. Because Chapter 7 of NAS 2011 provides comments on some of the fundamental aspects of the approach used in the 2010 Draft Assessment we present the discussion of these comments, when relevant, in the review of the methods section and when discussing endpoint specific determinations. These examples help to demonstrate the inadequacy of the EPA's Appendix D for the 2022 Draft IRIS Assessment as well as the EPA's responses to the Committee on January 30 and February 8,

2023 (in which EPA suggested that the 2011 NAS report was "[t]he primary guidance used to develop the current draft IRIS assessment" and that their faithful implementation of these recommendations supplanted the need to follow the IRIS process regarding systematic review protocols).

Unless otherwise provided, bibliographic citations for publications are all available in the EPA 2022 Draft Assessment and not repeated herein.

II. Review of Methods

A. EPA Does Not Address NAS 2011 Recommendations to Use the Best Available Science and Understanding of Mode of Action.

NAS 2011 recommended that EPA "[s]elect outcomes on the basis of available evidence and understanding of mode of action." (page 164). This recommendation, while not necessarily specific to the formaldehyde assessment (it was in Chapter 7 of NAS 2011), was something that EPA should have easily addressed when EPA began to develop a new formaldehyde assessment in 2011. As is discussed further below, the weight of evidence approach used to determine causality did not appropriately consider mode of action (MOA) when evaluating leukemia and other systemic effects, as well as point-of-contact toxicological effects, including nasopharyngeal cancer. In addition, likely because EPA skipped the problem formulation and scoping step for this assessment, EPA's inclusion criteria for literature did not include important peer reviewed publications that had unique MOA analyses that are important to informing EPA's conclusions on biological plausibility.[1] Studies that conducted weight of the evidence and MOA analysis were inappropriately treated as secondary literature (or "reviews") by EPA, not as primary evaluations. Thus, many studies and important analyses were excluded from EPA's evidence evaluation and synthesis. Some of these studies are discussed below and a full listing of "missed" studies is provided in comments sent to EPA in June 2022.[2]

NAS 2011 made many recommendations that sought to add "transparency and validity" to EPA's process. Yet the 2022 Draft Assessment falls short in meeting these recommendations. In attempting to improve many of the methodological flaws in the 2010 Draft Assessment, the 2022 Draft Assessment was in development for over an 11-year period. EPA referred to the approach as being an "incremental incorporation of methods."[3] During this period, EPA was developing and improving systematic review practices while older practices were used to develop the 2022 Draft Assessment. For instance, in addition to not releasing a protocol, when EPA screened studies and conducted study evaluations, EPA did not use an approach that included using blind reviewers to resolve conflicts.[4] As noted in previous ACC comments, criteria for study selection were not clearly documented and evolved over time, and many other systematic review best

[1] We note that EPA states that the 2022 Draft Assessment was "de novo" and started "from scratch". However, EPA does not explain why they did not follow the 7-step IRIS process and include a problem formulation step.
[2] Comments from ACC have been shared with the NAS committee and are also available in EPA's docket at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103.
[3] See EPA responses to NAS Panel Questions for the January 30, 2023, public meeting.
[4] Comments from EPA's Dr. Andrew Kraft at the January 30, 2022, NAS public meeting on the formaldehyde review.

practices were not followed.[5] Instead of clear criteria, EPA used subjective and variable definitions throughout the assessment. This is well documented in comments provided by the ACC Formaldehyde TSCA Risk Evaluation Consortium.[6] EPA also did not provide clear and transparent rationales for selecting the modeling approaches for non-cancer endpoints.[7] EPA began the assessment using older methods and models and did not consistently incorporate the tools and approaches that have become available since then. For instance, as noted by Dr. Thompson, EPA's benchmark dose modelling analysis cannot be replicated as the model outputs were run nearly a decade ago and using an outdated version of EPA's software.[8] EPA's approach in itself leads to significant confusion regarding what approaches were followed for individual studies and different streams of evidence. The net result is an assessment that is nearly 2000 pages, confusingly bifurcates individual study evaluations, is difficult to follow, and is not transparently presented.

The Cochrane Handbook, speaking to the issue of updating a review and whether the review was conducted well and used appropriate methods, states that "it may be more appropriate to conduct a new review from scratch meeting current standards."[9] Considering the importance of the use of formaldehyde to so many diverse sectors, as was recommended by NAS 2011, EPA's review must represent the best available science. While NAS 2011 did not recommend delaying the assessment, when recommendations were made, it was highly unlikely that anyone on the committee expected that it would be 11 years before EPA released a revised draft assessment. Considering how EPA's approach does not meet today's systematic review standards, exemplified by the exclusion of dozens of key studies, it is hard to see how this draft is consistent with the NAS 2011 recommendation.

NAS 2011 also recommended to EPA (at page 80), in the context of the "state of knowledge" of asthma pathogenesis, "[a]bundant research and review articles are available and should have been cited." EPA has inconsistently applied this recommendation, noting its compilation of public comments on the draft assessment provided to the Committee that "Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO."[10] As ACC detailed in its comments on the draft assessment, EPA excluded or dismissed over 70 key publications with high relevance to revising the 2010 Draft IRIS Assessment.[11] Further, labeling

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[5] Comments from ACC have been shared with the NAS committee and are also available in EPA's docket at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103.

[6] See issue #3 in comments from the ACC Formaldehyde TSCA Risk Evaluation Consortium were shared with the NAS committee and are also available in EPA's docket at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0100.

[7] *Id*. at issue #8.

[8] See comments submitted to EPA by Dr. Thompson on June 13, 2022. EPA used BMDS v1.9 whereas the current version BMDS v3.2. Comments are available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0087.

[9]Cumpston, M and Chandler, J. "Chapter IV: Updating a review." (2022). In Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available at: https://training.cochrane.org/handbook/current/chapter-iv.

[10] See EPA's Summary of Public Comments Received on the 2022 Draft IRIS Toxicological Review of Formaldehyde (Inhalation), available at: https://www.regulations.gov/document/EPA-HQ-ORD-2010-0396-0105.

[11] Comments from ACC have been shared with the NAS committee and are also available in EPA's docket at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103.

studies as supplemental materials should not have excluded them from consideration or from informing the weight of the evidence.

In light of the shortcomings, some of which are also described below, NAS should not refer to the 2022 Draft Assessment as one which follows best available scientific practices, including those recommended by NAS 2011 and those that are part of the EPA (2005) Cancer Risk Assessment Guidelines. It also does not reflect the best practices for systematic review. Because EPA's assessment appears to have been developed intermittently over an extended period of time, the NAS 2011 recommendations to provide a more transparent assessment that reflects best available science have not been adequately addressed.

III. Toxicokinetics and Modes of Action

A. EPA Fails to Address the NAS 2011 Recognition That Formaldehyde is in Exhaled Breath.

NAS 2011 acknowledged that formaldehyde was present in exhaled breath at an average concentration of a few parts per billion and that endogenous production complicates the assessment of exogenous formaldehyde exposures (at page 4). Instead of revising their modeling approach and taking relative dosimetry into account throughout the assessment, EPA has stated that the toxicity value is meant to represent extra risk imposed by inhalation of formaldehyde in the air. This means that EPA has developed acceptable levels for both cancer and noncancer endpoints in the part per billion range without considering the potential contribution of endogenous production of formaldehyde. However, their approach of dismissing relative risk relationships and homeostasis leads to untenable conclusions which imply that if a person sitting in a seat next to you breathes on you, you are exposed to concentrations of formaldehyde that cause unacceptable cancer and non-cancer health effects. The flaws of EPA's approach are provided in detail in comments that have been provided to you from Dr. Sherman and Ms. Osman-Sypher.[12] In addition, detailed comments on EPA's flawed treatment of endogenous and exogenous formaldehyde have been provided to you by the ACC Formaldehyde TSCA Risk Evaluation Consortium.[13]

B. EPA Does Not Follow NAS 2011 Recommendations for Evaluating Nasopharyngeal Cancer (NPC).

NAS 2011, citing EPA's Cancer Guidelines (2005) suggested that EPA conduct an independent analysis of the NCI cohort and also recommended that EPA consider alternative models. NAS 2011 (at page 134) states:

[12] See Comments from Dr. Sherman submitted to NAS after the October 2022 public meeting, available at https://downloads.regulations.gov/EPA-HQ-OPPT-2018-0438-0108/attachment_7.pdf and https://downloads.regulations.gov/EPA-HQ-OPPT-2018-0438-0107/attachment_12.pdf; and also comments from Ms. Osman Sypher submitted November 28, 2022 available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2018-0438-0108/attachment_17.pdf

[13] See issue #6 in comments from the ACC Formaldehyde TSCA Risk Evaluation Consortium were shared with the NAS committee and are also available in EPA's docket at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0100.

> "The committee agrees that the NCI studies are a reasonable choice because they are the only ones with sufficient exposure and dose-response data for risk estimation. However, the NCI studies have limitations. The committee is concerned about the clustering of seven of nine NPC deaths in a single plant (Hauptman et al. 2004) and missing death reports (Beane-Freeman et al. 2009). The committee strongly encourages EPA to state its inclusion and exclusion criteria clearly for its systematic review, analysis, and selection of studies. Systematic use of such criteria enhances the transparency of risk assessment." Yet EPA did not have such clear criteria, and instead had only "considerations."

EPA also did not consider peer reviewed literature that critically evaluated and identified potential errors or issues with the NCI studies. A study by Marsh et. al. 2014, found that the errors in the NCI analysis were so grave that they required retraction. [14] Similarly, an updated reanalysis by the same authors found that there was "little or no evidence" to support the NCI's suggestion of an association between formaldehyde exposure and NPC mortality.[15]

Additionally, despite the NAS 2011 advice, EPA did not conduct an independent analysis, as exemplified by basing IURs on undocumented personal communications with Dr. Beane-Freeman. 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 Assessment), rather than conduct an independent analysis.

In response to significant comments from NAS 2011 on EPA's characterization and use of the BBDR modelling, EPA still concluded that while the BBDR model could be used to derive multiple PODs and HECs for comparison to other modeling approaches, they ultimately indicated that the BBDR model cannot be used for extrapolation to human exposure scenarios (at page 2-80). NAS 2011 stated (at page 6) "Given that the BBDR model for formaldehyde is one of the best-developed BBDR models to date, the positive attributes of BBDR models generally, and the limitations of the human data, the committee recommends that EPA use the BBDR model for formaldehyde in its cancer assessment, compare the results with those described in the draft assessment, and discuss the strengths and weaknesses of each approach." Additionally,

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[14] Marsh, G.M., Morfeld, P., Collins, J.J. *et al.* Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. *J Occup Med Toxicol* 9, 22 (2014). https://doi.org/10.1186/1745-6673-9-22 which states: "In 2013, the National Cancer Institute reported results from their follow-up through 2004 of the formaldehyde cohort and concluded that the results continue to suggest a link between FA exposure and NPC. We discuss in this commentary why we believe that this interpretation is neither consistent with the available data from the most recent update of the National Cancer Institute cohort study nor with other research findings from that cohort, other large cohort studies and the series of publications by some of the current authors, including an independent study of one of the National Cancer Institute's study plants. Another serious concern relates to the incorrectness of the data from the follow-up through 1994 of the National Cancer Institute study stemming from incomplete mortality ascertainment…. We conclude that the NCI publications that contain incorrect data from the incomplete 1994 mortality follow-up should be retracted entirely or corrected via published errata in the corresponding journals, and efforts should be made to re-analyze data from the 2004 follow-up of the NCI cohort study."

[15] Marsh, G.M., Morfeld, P., Zimmerman, S.D. *et al.* An updated re-analysis of the mortality risk from nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study. *J Occup Med Toxicol* 11, 8 (2016). https://doi.org/10.1186/s12995-016-0097-6

NAS 2011(at page 6) called EPA's manipulations of the model in the 2010 Draft Assessment "extreme" and suggested that they "may not be scientifically justified" and "should not have been used as a basis of rejection of the use of the BBDR model". Dr. Rory Connolly, a lead developer of the model, has provided comments explaining why EPA's limited understanding of the model has kept EPA from relying on it as it should have.[16] Dr. Conolly concludes that EPA should consider the uncertainties of the BBDR model relative to the hidden uncertainties embedded in the empirical dose-response functions that EPA prefers, since the lack of explicit description of mechanism does not avoid accountability for the mechanism, especially when so much relevant Mode-of-Action (MOA) data are available.

In a separate submission, Dr. Thomas Starr also provided comments related to a novel "bottom up" approach to bounding human cancer risks from chronic inhalation exposure to formaldehyde he developed with Dr. James Swenberg.[17] Results from this evaluation are important in bounding the potential risks for cancer in consideration of the endogenous production of formaldehyde. Dr. Starr describes EPA's concerns with the "bottom up" approach identified in the 2022 Draft Assessment and discusses several publications related to this approach that EPA failed to include.

Over the past 30 years, the 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 on the first peer-reviewed publication detailing the cytotoxic with regenerative hyperplasia MOA for nasal tumors (McGregor et al. 2006), which was recently updated and published by Thompson et al. (2020).[18] McGregor et al. (2006) was inexplicably cited in one paragraph of the Draft Assessment as evidence against the cytotoxicity MOA. The exclusion of the Thompson et al. (2020) study of the cytotoxicity with regenerative hyperplasia (following the IPCS MOA framework) from the 2022 Draft 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 Assessment says that nasal tumors/NPC is presumed to have a mutagenic MOA, there is neither a formal determination as described in the EPA Cancer Guidelines nor is there an assessment performed according to a data-driven, recognized framework (i.e., cytotoxicity with regenerative hyperplasia assessed according to the IPCS MOA framework), as described and required by the EPA (2005) Cancer Risk Assessment Guidelines.

In the EPA decision to avoid accepting alternative non-linear approaches, despite the NAS 2011 recommendation, EPA also unjustifiably reinterpreted and misused a 1992 peer reviewed publication on changes in the p53 tumor suppressor gene to incorrectly conclude that the paper supported a mutagenic mode of action. These errors are addressed in detail by Dr. Recio's comments that he submitted to the EPA docket in June 2022[19] and presented orally to during the

[16] See comments from Dr. Connolly submitted to EPA June 9, 2022, available at https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0075.
[17] See comments from Dr. Starr submitted to EPA June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0084.
[18] 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.
[19] See comments submitted by Dr. Leslie Recio, June 15, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0077.

NAS Public Comment session on January 30, 2023. EPA also ignored important data streams in their MOA analysis. In his comments, Dr. Thompson describes research on the alcohol dehydrogenase-5 (ADH5) pathway and the role it plays in detoxifying endogenous and exogenous formaldehyde.[20] This research, including results from studies with ADH5 mice, inform the levels at which adducts are needed to cause genotoxicity. Had EPA conducted a robust MOA analysis, and followed a well-accepted framework (which could include the IPCS framework or the EPA Cancer Guidelines) that included integration of toxicokinetics and toxicodynamics, this would have allowed EPA to recognize the widely accepted sequence of key events in the development of nasal tumors, and EPA would have appropriately determined that a linear dose-response (i.e., LNT modeling) cannot be supported when the exposure to the molecular target in the target tissue is highly non-linear and there is a homeostatic level necessary to sustain life. Thus, the non-linear approach, conducted according to the IPCS MOA Framework, is justified.[21]

In further violation of the Cancer Guidelines, EPA should have objectively presented this alternative analysis that supports quantifications of NPC using a threshold model; an analysis that demonstrates both time and dose concordance with the tumor response, in contrast to the LNT modeling that fails to demonstrate time and dose concordance with the observed tumor response. These elements are critical considerations for acceptance of any model.

IV. Portal-Of-Entry Health Effects and Quantification

A. EPA Did Not Provide an Appropriate Comparison as NAS 2011 Recommended for the RfC for Noncancer Pathology.

NAS 2011 recommended that EPA calculate a candidate RfC from the animal data for noncancer pathology (page 78). NAS 2011 recognized that the effects in animals showed a concentration, time, and site dependent gradient. NAS 2011 stated that the animal studies offer one of the most extensive datasets for any inhaled chemical. NAS 2011 also recommended that in using the animal data, computational fluid dynamics (CFD) models could be used to predict the dose to humans and decrease the need for an animal to human extrapolation factor (page 77). However, EPA did not use these dosimetry models. Instead, EPA developed RfCs from the Kerns 1983 and Woustersen et al. 1989 studies to develop an RfC that is approximately 300x lower than the NOAEL for tissue irritation in rats and a hundred-fold lower than the sentinel effect concentrations that can be sensorily detected by TRP receptors and perceived as odor by humans. In addition, for Kerns, despite the data being available after 24-months of exposure, the 2022 assessment relied upon results from the 18-month sacrifice. Then, EPA unnecessarily applied an additional 3x uncertainty factor for what they considered to be a subchronic exposure. This is particularly problematic, since the EPA explicitly recognizes any rat study ≥12 months is

[20] See comments submitted to EPA by Dr. Thompson on June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0087.

[21] In his comments, Dr. Thompson states that "Unlike existing MOA and AOP frameworks that describe MOA as a series of key events linked by dose-response relationships, EPA simply lists events with no obvious relationships beginning from exposure to tumor development. For example, the table lists "oxidative stress, immune disease and dysfunction in the URT" as a hypothesized mechanistic event. Notwithstanding that these are not an obvious single mechanistic event, it is unclear how and where these events fall within a sequence of key events leading from exposure to nasal tumors."

considered a chronic study (OPPTS 870.4100 test guideline for chronic toxicity). Compounding the interpretative issues identified above, EPA's use of the BMD modeling and application of uncertainty factors has led to an illogical outcome where you have irritation and metaplasia preceding sensory detection. This is likely due to conservatisms in EPA's general modeling approach that do not take into consideration the chemical-specific properties of formaldehyde. Consistent with EPA's BMD guidance, EPA should have also calculated an RfC using a NOAEL approach. During evidence integration EPA would then have had more information to consider when selecting the best method to derive a RfC that best reflects consideration of all data streams.

B. EPA Did Not Correctly Characterize the Asthma Phenotype and the Approach Taken Remains Contrary to NAS 2011 Recommendations.

NAS 2011 recommended that EPA provide clear criteria for identifying asthmatic responses. However, EPA has not done this and continues to provide insufficient support for identifying asthmatic responses in epidemiology studies and advancing those studies for the classification of formaldehyde as an asthmatogen. In the 2022 Draft Assessment, EPA integrated evidence for the prevalence of current asthma for children and adults and concluded that the evidence was moderate for asthma based on elevated risks in eight medium confidence studies of current asthma in adults and children. The EPA concluded that "inconsistencies in study results appear to be explained by exposure levels" as evidenced by:

- No elevated risk of current asthma in six high and medium confidence studies with relative low exposures (<0.05 mg/m^3) but associations with adequacy of asthma control were observed in one study at this lower exposure levels.

- Strongly elevated risks in three medium confidence studies in occupational settings with exposures from 0.1 to >0.5 mg/m^3.

EPA's integration of evidence is overly simplistic. Asthma is widely recognized as a heterogeneous group of diseases based on clinical features, physiological characteristics, and varying outcomes ranging from mild to severe.[22] Variation in response to different asthma treatments also suggests that there are multiple mechanisms and pathways that are relevant to the development and exacerbation of asthma. It is not a single disease entity. EPA does not adequately address potential differences in asthma phenotypes that likely represent different underlying biological mechanisms for asthma development.

EPA does not describe how the postulated mechanistic pathways are potentially related to different asthma phenotypes.[23] As a result of differences in phenotypes and endotypes, there are likely different mechanisms (and different modes of action) by which chemicals can potentially increase risk. At the very least, the evidence related to potential mode of action for formaldehyde should be synthesized separately for occupational asthma (a phenotype that is generally not related to atopic or allergic asthma). Differences in potential mechanisms and the pathogenesis

[22] Carr T. and Bleecker E. (2016) Asthma Heterogeneity and Severity. World Allergy Organ J, 9(1): 41-49.
[23] For additional details, see comments submitted by the ACC Formaldehyde Panel to EPA on June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103.

for early onset/atopic asthma versus early onset/non-atopic asthma could also be described (even if these groups cannot be distinguished in the existing epidemiologic studies). Collectively, these differences, which are not related to differences in exposure concentrations, potentially explain inconsistencies in results.

Three studies were selected to derive a point of departure (POD) for current asthma (Annesi-Maesano et al. 2012; Krzyzanowski et al. 1990; Venn et al. 2003). However, none of the studies carried forward showed clear associations between current asthma and formaldehyde exposure.

- Annesi-Maesano et al. (2012) was selected to derive a POD for current asthma; however, there is no clear temporal relationship reported between formaldehyde exposure and atopic asthma or non-atopic asthma (see Annesi-Maesano et al. 2012, Figures 5 and 6). In fact, the study showed an inverse correlation of asthma and increasing formaldehyde concentrations, with an odds ratio of 0.9, suggesting increasing formaldehyde concentrations reduce the incidence of asthma.

- Krzyzanowski et al. (1990) reported an association between formaldehyde exposure and current asthma; however, after stratifying by exposure to secondhand smoke, there was no association between formaldehyde exposure and current asthma among children who were not exposed to tobacco smoke; the association between formaldehyde exposure and asthma was only observed among children exposed to tobacco smoke. Lastly, there are numerous critical deficiencies in the study that render the results interpretable, as presented in an evaluation presented to NAS.[24]

- Venn et al. (2003) measured persistent wheezing illness in a case-control study of 9-11 year old children and specifically stated that they did not equate wheezing as representing an asthmatic response. This study also had numerous critical deficiencies that render the results interpretable, as presented in an evaluation presented to NAS.[25]

EPA's misrepresentation of the three studies (Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012; Venn et al. 2003) it relied on to derive a POD cannot be ignored. EPA's use of a negative study in support of an association does not represent the best available science and is not consistent with the NAS 2011 recommendation that EPA strengthen its discussion of asthma and its pathogenesis.

There are numerous environmental exposures that were identified by the NAS (2011) as triggers for asthma including secondhand smoke, dust mites, molds, cockroaches and pests, pets, nitrogen dioxide, outdoor air pollution, and wood smoke (see discussion below). The overwhelming majority of epidemiologic studies were cross-sectional designs that did not consider or adjust for these potential asthma triggers in indoor air.

More importantly, NAS 2011 was clear that EPA needed to better describe and consider the current understanding of asthma. Not only did EPA ignore the two relevant publications by Drs.

[24] See oral comments from Dr. Sherman and associated submission to NAS on January 30, 2023, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2018-0438-0110/attachment_9.pdf
[25] *Id.*

Golden and Holm,[26] the 2022 Draft Assessment also ignored potential confounding factors that are considered causally related to asthma (e.g., acrolein). In doing so, the 2022 Draft Assessment presents conclusions that are at odds with NAS 2000 (an authoritative review for the endpoint of asthma)[27] and Kanchongkittiphon et al. (2015)[28] (a comprehensive update involving 69 additional studies focused on indoor environmental exposures and exacerbation of asthma), both of which demonstrated a practical weight of evidence approach.

In assessing potential exposures that might exacerbate asthma in children, NAS 2000 identified potential causal relationships between asthma and the allergens produced by cats, cockroaches, house-dust mites, environmental tobacco smoke (ETS) exposure, dog allergen exposure, fungal exposure, and damp conditions or indicators of dampness (e.g., dust mite and fungal allergens). It is well documented (i.e., Garrett et al., 1998, 1999; Rumchev et al., 2002, 2004) that other substances in indoor air (e.g., VOCs and fungal spores) can cause and/ or exacerbate respiratory symptoms quite apart from formaldehyde. For instance, acrolein, an aldehyde that is 200 times more potent as a sensory irritant than formaldehyde (Fowles and Dybing 2003)[29] and ubiquitous in indoor air, was significantly associated with asthma, whereas formaldehyde was not (Annesi-Maesano et al. 2012). The implications of acrolein as a previously unrecognized confounder are that indoor air studies, which report associations between formaldehyde and childhood asthma, should be interpreted with caution unless/until potential contributions and/or associations with acrolein are also considered. In addition, due to ever-increasing acrolein emissions into the environment, acrolein as a direct irritant may increasingly become a health hazard in individuals with respiratory diseases such as asthma.[30] A recent paper (Golden and Holm 2017)[31] that was not cited or integrated into the 2022 Draft Assessment supplies a roadmap of why unrecognized exposure to acrolein is an important confounding factor in many indoor air-related studies focused on formaldehyde.

The discovery that acrolein is virtually certain to have been present in the indoor air of all studies in which formaldehyde has been implicated as associated with asthma raises a red flag with respect to EPA's conclusions. Other than a single study Annesi-Maesano et al. 2012, none of the other studies currently relied upon with respect to the formaldehyde/asthma issue in childhood considered co-exposures to acrolein. Consequently, conclusions with respect to formaldehyde alone can only be considered as suspect. This is particularly the case since acrolein is a

[26] Golden R. (2011) Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards. Crit Rev Toxicol. 41(8):672-721; Golden R, and Holm S. (2017). Indoor Air Quality and Asthma: Has Unrecognized Exposure to Acrolein Confounded Results of Previous Studies? Dose Response. Feb 15;15(1).
[27] NAS, Clearing the Air: Asthma and Indoor Air Exposures, National Academies Press 2000.
[28] Kanchongkittiphon W, Mendell MJ, Gaffin JM, Wang G, Phipatanakul W. (2015) Indoor environmental exposures and exacerbation of asthma: an update to the 2000 review by the Institute of Medicine]. Environ Health Perspect 123 (1): 6-20
[29] Fowles J and Dybing E. (2003) Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tob Control. 2003;12(4):424-430.
[30] Leikauf GD. (2002) Hazardous air pollutants and asthma. Environ Health Perspect 110(suppl.4):505-526.
[31] Golden R, and Holm S. (2017). Indoor Air Quality and Asthma: Has Unrecognized Exposure to Acrolein Confounded Results of Previous Studies? Dose Response. Feb 15;15(1).

demonstrably more potent respiratory tract irritant than formaldehyde, with the clear ability to exacerbate asthma symptoms.[32]

Therefore, there is inadequate or insufficient evidence to determine an association between indoor residential VOC exposures and the development or the exacerbation of asthma. These results highlight the need to investigate and focus on factors known to be causally associated with asthma exacerbations, rather than formaldehyde for which the evidence does not rise to this level of confidence. However, rather than conducting a full weight of the evidence evaluation on asthma and allergies, EPA reviews only a subset of the relevant literature to conclude that the "evidence indicates" that formaldehyde plays a role in "allergic conditions and current asthma symptoms or degree of asthma control." In doing so, EPA overlooks the significant influence of confounding factors in low formaldehyde air concentration studies.

Additionally, if one were to assume that the studies chosen by EPA were appropriate, which they are not, EPA was overly conservative in the application of the human variability uncertainty factor. Annesi-Maesano et al. (2012) was a school-based study with over 6000 children. It is not consistent with EPA guidance for EPA to consider this not sufficiently representative of variability in children.[33] For this large child-base cohort, EPA should have used a human variability uncertainty factor of 1x not 3x. Similarly, Venn et al. (2003) was a study evaluating only asthmatic children and Krzyzanowski et al. (1990) was a study of almost 300 children, including children that have asthma. Yet EPA applied inter-human variability uncertainty factors of 3x and 10x, respectively, to these studies. This effectively double counted uncertainties related to inter-human variability/sensitivity.

C. When Evaluating Irritation EPA Did Not Consider the Chamber Study Data as Recommended in NAS 2011.

NAS 2011 strongly recommended that EPA consider the concentration-response data from the human chamber studies (page 68). This is consistent with the approach taken in the World Health Organization Indoor Air Quality Guidelines.[34] The Mueller et al. (2013) chamber study and the Lang et al. (2008) chamber study were considered by WHO to be the best available science for deriving a safe exposure concentration for humans. Both support the indoor air guideline value of 0.1 mg/m^3. Yet EPA discounted use of these high-quality studies, in favor of a population-based study where exposure was not controlled (Hanrahan et al. 1984), which EPA states was supported by older controlled human exposure studies (Kulle et al. 1993; Andersen and Molhave, 1983). However, EPA does note that these older studies (Kulle et al. 1993; Andersen and Molhave 1983) are limited by reporting deficiencies regarding blinding (Figure 1-2). The rationale provided by EPA was that the more recent chamber studies did not find a dose-response

[32] Fowles J and Dybing E. (2003) Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tob Control. 2003;12(4):424-430.

[33] We note that EPA's IRIS Handbook has provided new recommendations for applying uncertainty factors based on a 2002 technical panel report (U.S. EPA. 2002. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F). However, this technical panel report, which contains dozens of recommendations to EPA has not gone through a formal process at EPA by which it could be considered EPA guidance. As such, it is inappropriate for EPA to treat this a guidance and suggest that an EPA guidance document recommends this new overly conservative approach.

[34] World Health Organization, WHO guidelines for indoor air quality: selected pollutants, 2010, available at: https://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf.

relationship. However, only one of these studies did not find any effect, even at the highest exposure, and the other study only found mild chemosensory effects. EPA discounts better conducted studies simply because no effects were observed, which seems to be biased towards finding an effect where none exists. EPA also has a tendency to describe chosen studies in a more positive light than is warranted, as previously pointed out by NAS.[35] Experts from the WHO panel (Drs. Kaden and Wolkoff) have provided comments to EPA stating that properly controlled human exposure studies are the "gold standard" for setting safe exposure limits, as they offer the major advantage of having reliable controls, defined exposure conditions, carefully characterizing volunteers, and altering experimental methods to consider potential confounding factors.[36] These comments are bolstered by comments submitted to EPA by Dr. Holm. [37] Dr. Holm points out that EPA's reliance on studies conducted in residential settings rather than those conducted under controlled conditions was criticized by NAS (2007)[38] and runs contrary to approaches of other authoritative bodies.[39] The significant limitations in basing conclusions on studies in residential settings is also discussed in the comment by Dr. Holm.

NAS 2011 recognized both the strengths and weaknesses of the chamber studies when they recommended that EPA present the concentration response data on the same graph as the residential and occupational studies. In response to this, EPA commented that the doses were higher in the chamber studies, a fact NAS 2011 was aware of, and did not present the data in the graphical manner as NAS 2011 recommended. In rejecting the recommendations of NAS 2011, EPA chose to rely on much less reliable residential data that has greater uncertainty than the controlled chamber studies. This is not consistent with an approach that relies on the best available scientific information.

D. When Evaluating Pulmonary Function EPA Did Not Consider the Chamber Study Data as Recommended in NAS 2011.

While the 2022 Draft Assessment supported the use of Krzyzanowski et al. (1990), NAS 2011 also recommended that EPA recognize the value of the chamber studies and display the data in a manner that would inform the agency (page 72). Unfortunately, despite NAS 2011 recognizing uncertainties in these studies when they made their recommendation, EPA has continued to disregard the chamber studies due to those uncertainties. The chamber studies are arguably much less uncertain in comparison to subjective retrospective epidemiology studies. EPA again relied upon the retrospective epidemiology studies, without an objective comparison of the strengths and weaknesses of each approach. EPA is nonresponsive to this NAS 2011 recommendation.

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[35] See for example comments submitted to NAS on January 30, 2023 where Dr. Sherman describes how EPA depicts Kryzanowski et.al. as "well-designed and executed" while overlooking the weaknesses of its cross-sectional design, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2018-0438-0110/attachment_9.pdf

[36] See comments from Drs. Kaden and Wolkoff submitted to EPA June 9, 2022, and available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0080.

[37] See comments from Dr. Holm submitted to EPA on June 8, 2022, and available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0073.

[38] National Academy of Sciences (NAS) (2007) Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants. Washington, DC: Subcommittee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Committee on Toxicology, National Research Council.

[39] See 2016 EU Scientific Committee on Occupational Exposure Limits (SCOEL) Report on Formaldehyde, available at: https://op.europa.eu/en/publication-detail/-/publication/7a7ae0c9-c03d-11e6-a6db-01aa75ed71a1/language-en.

Considering the additional weaknesses, recently identified during public comments by Dr. Sherman (including the cross-sectional study design and the lack of dose response), an objective comparison of the chamber studies to the Krzyzanowski et al. (1990) is warranted.

In addition, NAS 2011 also recommended that EPA consider other studies, including Kriebel et al. (1993, 2001). Despite these studies being classified as medium confidence, EPA did not derive PODs for them and only briefly discusses the possibility of using these studies.

EPA has added an additional 3x human variability uncertainty factor.

E. EPA's Causality Approach and Quantitation of Reproductive/Developmental Effects Does Not Follow NAS 2011 Recommendations.

NAS 2011 expressed concerns about deriving an RfC on a single human study and a minimal data base (page 107), yet in quantifying the Taskinen et. al. (1999) study, and relying upon it, EPA has not taken the NAS 2011 concerns into account. In fact, while the 2022 Draft Assessment appropriately classifies the POD confidence, and confidence in the RfC for the Taskinen et. al. study as low, EPA inexplicably declares the study to be of medium confidence.[40] EPA must be consistent with NAS 2011 in recognizing the critical deficiencies in this study and consistent throughout the IRIS assessment in its conclusions regarding this study.

In addition, EPA's finding that the "evidence indicates" that formaldehyde causes increased reproductive toxicity is misleading and inappropriate. EPA states that the occupational data provide moderate evidence, yet there is no relevant study, with clearly quantified exposures, that EPA can rely upon. Animal evidence is indeterminate, a plausible mode of action does not exist, and there is low confidence in the overall database. A determination of "evidence suggests (but is not sufficient to infer)" is more appropriate. Similarly, for male reproductive toxicity, EPA states that the evidence is 'robust' in animals, however EPA has no studies that can be used at realistic exposure levels. It is not appropriate for EPA to say that the data are robust when they are not representative of human exposures. Coupled with the lack of a plausible mode of action, and only slight evidence in low confidence human studies, and low confidence in the database, a determination of "evidence suggests (but is not sufficient to infer)" is more appropriate.

For both these endpoints, EPA provides no discussion or references to the toxicokinetic discussion which indicates that inhaled formaldehyde is not distributed to an appreciable extent beyond the respiratory tract to distal tissues (page xxi; Appendix A-2). This EPA conclusion regarding the toxicokinetics of formaldehyde is seemingly not considered when EPA makes an evidence judgment regarding hazard. This is another example of the flaws in EPA's evidence integration framework. Toxicokinetic information, and mechanistic data, or lack thereof, are not considered in the framework as EPA only uses mechanistic information to increase confidence in a judgment, but not to decrease confidence in a judgment. NAS 2011 describes how systemic responses, including neurotoxicity, reproductive toxicity, and leukemia—are unlikely to arise from the direct delivery of formaldehyde (or methanediol) to a distant site in the body, such as the brain, the reproductive tract, and the bone marrow. NAS 2011 disagreed with EPA findings in the 2010 Draft Assessment that epidemiology evidence supported a convincing relationship

[40] See ACC comments submitted to NAS on Nov. 9, 2022, where a peer review of the Taskinen study is provided in the appendix, available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2018-0438-0108/attachment_16.pdf

between exposure to formaldehyde and reproductive outcomes in women. NAS 2011 stated that this relationship was only suggestive of an association. However, contradictory to NAS 2011, EPA seems to come to the conclusion that the evidence is much stronger than suggestive, finding that that the "evidence indicates (likely)". The best available science does not support EPA's conclusions.

F. Human Variability Uncertainty Factor Application Ignored the NAS 2011 Recommendations.

NAS 2011 provided a robust analysis of the study populations that were considered for sensory irritation, including Hanrahan et al. (1984) (page 127-129) that is fraught with methodological and reporting errors. As a result of this evaluation, NAS 2011 unequivocally recommended a human variability uncertainty factor of 3x. In contrast, in the 2022 Draft Assessment EPA applies a human variability uncertainty factor of 10x.

In fact, if EPA had followed the NAS 2011 evaluation of the studies, and EPA guidelines, the overall RfC would have been quite different. EPA chose an overall RfC (0.007 mg/m^3) that falls within the range of respiratory system effects from four non cancer endpoints (osRfC values of 0.006-0.009 mg/m^3, see discussion in section 2.1.4 of the 2022 Draft Assessment). If EPA were to have applied the human variability uncertainty factor as the NAS supported in 2011, and consistent with previous standardized approaches, the osRfC range would likely have been 3-10 fold higher.[41] By disregarding EPA guidance[42] and NAS 2011 recommendations, EPA has developed osRfC values which are not only overly conservative in nature.

V. Systemic Health Effects and Quantification

A. EPA Inappropriately Grouped LHP Cancer Types Despite NAS Recommendations.

NAS 2011 recommended (pages 11 and 113) that EPA not group "all LHP" cancers. NAS 2011 recognized the if cancers are not closely related in cells or origin and other characteristics, they should not be grouped due the biological heterogeneity.[43] Instead, NAS 2011 recommended that EPA focus on the most specific diagnoses available. EPA stated in Appendix D of the 2022 Draft Assessment that they agreed with the NAS recommendation; however, in direct conflict to this, the 2022 Draft Assessment (p. 1-423) states: "For the purposes of this evaluation, cancer cases reported as monocytic leukemia or nonlymphocytic leukemia were included as myeloid leukemia." EPA provides no explanation for this grouping. While EPA no longer has an "all LHP category", EPA grouped AML and CML under "myeloid leukemia" and then summarized the few results available for AML and CML separately. It is not clear why EPA grouped them,

[41] It is important to note that while we do not necessarily support the studies chosen or the PODs derived for the different osRfCs, the impact of the choice of the human variability uncertainty factor on the final RfC should be considered.
[42] See footnote 26 for further discussion.
[43] NAS 2011 at page 11 states: "The committee does not support the grouping of "all LHP cancers" because it combines many diverse cancers that are not closely related in etiology and cells of origin."

considering the recommendations of NAS 2011 that indicate that their etiologic bases may be distinct.

EPA also appears to combine various leukemias when assessing myeloid leukemia background incidences, as confusingly evidenced by the statement (page 2-87): "However, the inclusion of any leukemia subtypes not related to formaldehyde exposure should theoretically dampen the exposure-response relationship (lowering the regression coefficient) relative to that for all the myeloid leukemias alone; thus, this should mitigate at least some of the effect of using the all leukemia background rates." EPA's approach is in contradiction to the NAS 2011 recommendations and the best scientific understanding of leukemia today.

B. EPA Avoids NAS 2011 Recommendations on Leukemia by Ignoring and Mischaracterizing the Evidence.

NAS 2011 recommended that EPA provide a clear causal framework for determinations regarding LHP cancers and revisit arguments that support determinations of causality (page 11). In particular, NAS 2011 noted inconsistencies in the epidemiologic data, weak animal data, and the lack of mechanistic data. NAS 2011 also noted that "there is a noticeable lack of evidence of a causal relationship of formaldehyde exposure and Hodgkin lymphoma or leukemia."[44] In response to this recommendation EPA 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 below.

[44] NAS 2011 at page 135.

EPA's causality framework and approach is not consistent with the well-established, international, consensus based World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) MOA framework (Meek et al. 2014).[45] This framework, established by the IPCS to aid in the evaluation of MOA and human relevance for both cancer and noncancer provides guidance for considering the weight of evidence available for each hypothesized MOA. During the October 12, 2022, public meeting, EPA acknowledged that they had no formal framework for evaluating biological plausibility, despite the IPCS framework being available since 2007. Earlier versions of the IPCS framework and its application (IPCS 1999; Sonich-Mullin et al. 2001; Meek et al. 2003) are cited in the EPA's 2005 Guidelines for Carcinogen Risk Assessment. In the Guidelines, the EPA notes that the framework outlined is similar to the IPCS frameworks; however, rather than being a stand-alone document addressing mode of action issues, the MOA framework in the EPA cancer guidelines are incorporated into the context of all of the data regarding weight of evidence for carcinogenicity. In fact, Gentry et al 2020, used the IPCS framework to evaluate the postulated MOAs for leukemia following formaldehyde inhalation.[46] Using this framework, which integrates of all the available evidence, similar to that outlined in the Cancer Guidelines, 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. Their analysis showed a lack of confidence in any of the postulated 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. Not only did EPA not use a similar framework, but EPA also did not consider the findings of this publication.

In addition to lacking a framework for evaluating MOA information, EPA's framework for integrating evidence is flawed. When the NAS conducted a review of the IRIS handbook, the tool through which EPA has developed a causality and evidence integration framework, EPA, in 2018, presented a framework which stated "Lack of mechanistic understanding does not weaken evidence outright, but it can if well-conducted experiments exist and demonstrate that effects are unlikely."[47] In the context of the EPA 2018 presentation, this can be interpreted to mean that well-conducted mechanistic information on biological plausibility can be used to weaken human or animal evidence. However, in the formaldehyde assessment, and in the finalized 2022 IRIS handbook, EPA has pivoted, and this sentence is no longer in the framework; well conducted studies can no longer be used to demonstrate that effects are unlikely. While EPA states in the 2022 Draft Assessment (at page xxxvii) that "mechanistic evidence could add to or detract from the strength of evidence", in describing the overall evidence integration judgments for characterizing hazards (2022 Draft Assessment at Table VIII), there is no consideration of mechanistic evidence downgrading the strength of evidence. It is simply not an option in EPA's

[45] Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C. (2014) New developmental in the evaluation and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol. 34(1):1-18.

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

[47] See NAS report 2018. *Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: 2018 Evaluation*, Appendix C, page 61.

causality framework for formaldehyde. EPA acknowledges that no MOA exists, but this does not impact EPA's finding. A robust database of well conducted studies supports the fact that there is no mechanism by which formaldehyde could reach systemic tissues to cause leukemia, yet EPA discusses but disregards this information and does not appropriately integrate evidence in a weight-of-evidence causality framework.

EPA does however rely on misinterpreted biomarker data to suggest that mechanistic information supports mutagenicity and genotoxicity. Dr. Albertini, a renowned expert with over 203 publications on mutagenicity, presented information to NAS on October 12, 2022, explaining how EPA misinterpreted genetic changes in circulating blood cells to suggest that formaldehyde exposure caused genotoxic changes in hematopoietic tissues.[48] However, the Draft Assessment still considers indirect biomarkers of systemic genotoxicity as evidence supporting a genotoxic MOA. The Draft Assessment uses questionable indirect evidence to support the hypothesis of cytogenetic effects in circulating blood cells and based on conclusions that effects in circulating cells may indicate effects on cells in the bone marrow, calculates a linear inhalation unit risk for leukemia in the absence of any dose-response observations for leukemia or direct evidence of in vivo genotoxicity. In contrast, the 2022 Draft Assessment fails to integrate molecular dosimetry that demonstrates a lack of exposure to blood forming units. Detailed comments describing how EPA misinterpreted mutagenicity and genotoxicity data have been provided to EPA and are available to the NAS committee.[49]

The third evidence stream that EPA relies upon for myeloid leukemia is epidemiologic data. NAS 2011 noted concerns with the leukemia data stating (at page 135) "The exposure-response trend of leukemia mortality (123 deaths) was only marginally significant for peak and cumulative exposure and was not significant for average intensity (Beane-Freeman et al. 2009). The lack of consistency in exposure-response relationships between various exposure metrics and the three types of cancer is of concern. The inconsistency may simply be a result of applying multiple metrics, some of which are not highly valid or precise or are perhaps less relevant to the underlying mechanisms. It could also reflect the absence of causal mechanisms associating, for example, leukemia with formaldehyde exposure." As described by Dr. Checkoway, Dr. Mundt and Ms. Dell, there are significant concerns with EPA's analysis.[50] Many of these concerns stem from EPA's lack of clear criteria. EPA instead used only "considerations" to guide the study evaluation process. These "considerations" allowed for significant expert judgment which in turn led to inconsistencies in the evaluations. In his presentation to NAS on Oct 12, 2022, Dr. Mundt describes an example which shows how EPA's lack of clear criteria for evaluating epidemiologic data led to inconsistencies in EPA's evaluation of two studies, even though both studies used exactly the same data. One study was classified as "low confidence" (Checkoway et al. 2015) while the other was classified as "medium confidence" (Beane-Freeman et al. 2009, 2013).

[48] See slides and remarks presented to NAS on October 12, 2022, available at https://downloads.regulations.gov/EPA-HQ-OPPT-2018-0438-0107/attachment_16.pdf and https://downloads.regulations.gov/EPA-HQ-OPPT-2018-0438-0107/attachment_17.pdf

[49] This includes comments submitted by Dr. Thompson, Dr. Albertini, Dr. Recio, and by ACC. All these comments are available in the EPA docket and have been shared with the NAS committee.

[50] See comments submitted by Dr. Checkoway, Dr. Mundt, and Ms. Dell, June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0096.

EPA's epidemiologic review, which began in 2011, does not provide the clear and concise statements of criteria nor the standardized approach that NAS 2011 recommended.

EPA also ignored or summarily dismissed multiple additional attempts to reanalyze and replicate the results of the epidemiological data relied upon by EPA for quantitative analysis.[51] These re-analyses do not support the hypothesis that formaldehyde is a cause of myeloid leukemia. One study found that the documentation of the methods in the 2010 Draft IRIS Assessment lacked sufficient detail to allow for replication of the unit risk estimates.[52] Additionally, EPA's reliance on the peak exposure metric from Beane Freeman et al. (2009) for myeloid leukemia inappropriately relied on exposures estimates from Stewart et al. (1986), without taking into account more recent analysis (Checkoway et al. 2015) that correct the misclassifications in the Stewart et al. (1986).[53] This impacts EPA's dose-response analysis. Considering the NAS 2011 recommendation to consider alternative analyses, it is unclear why EPA did not use the updated exposure information.

In summary, EPA did not address the NAS recommendations as the causal framework that was used discounted high quality mechanistic information that informed the MOA for myeloid leukemia. In doing so, EPA's weight of the evidence approach ignored the NAS 2011 recommendation to integrate the information from all the individual lines of evidence. EPA's approach was also inconsistent with the EPA Cancer Guidelines which requires integration of all individual lines of evidence.[54]

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[51] See for example Checkoway H, Boffetta P, Mundt DJ, Mundt KA. *Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies*. Cancer Causes Control. 2012 Nov;23(11):1747-66; and Checkoway H, Dell LD, Boffetta P, Gallagher AE, Crawford L, Lees PS, Mundt KA. *Formaldehyde Exposure and Mortality Risks From Acute Myeloid Leukemia and Other Lymphohematopoietic Malignancies in the US National Cancer Institute Cohort Study of Workers in Formaldehyde Industries.* J Occup Environ Med. 2015 Jul;57(7):785-94.

[52] Van Landingham, C., Mundt, K.A., Allen, B.C. and Gentry, P.R., 2016. The need for transparency and reproducibility in documenting values for regulatory decision making and evaluating causality: The example of formaldehyde. *Regulatory Toxicology and Pharmacology*, *81*, pp.512-521.

[53] See comments from ACC have been shared with the NAS committee and are also available in EPA's docket at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103.

[54] Additional details regarding the inconsistencies between the 2022 Draft Assessment and the EPA Cancer Guidelines are provided in ACC comments that have been shared with the NAS committee and are also available in EPA's docket at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103.