April 13, 2022

The Honorable Michael Regan
Administrator
U.S. Environmental Protection Agency
William Jefferson Clinton Building
1200 Pennsylvania, N.W.
Washington, D.C. 20460

Dr. Clifford Duke
Director
Board on Environmental Studies and Toxicology
National Academies of Science, Engineering, and Medicine
500 Fifth Street, NW
Washington, DC 20001

Submitted via email and mail

RE: Comment on the Charge Questions and Committee Task for Peer Review of Draft Formaldehyde Assessment

Dear Administrator Regan and Dr. Duke:

As the U.S. Environmental Protection Agency ("EPA" or "the Agency") prepares to release an updated draft assessment of formaldehyde under the Integrated Risk Information System (IRIS) for public comment and independent peer review by the National Academies of Science, Engineering, and Medicine ("NAS"), the American Chemistry Council ("ACC")[1] Formaldehyde Panel ("the Panel") asks you to take steps to ensure transparency and public participation in the development of "charge" questions and the committee task. The Agency notes in its *Peer Review Handbook* that the "success and usefulness of any peer review depends on… the care given to the statement of the issues or 'charge.'"[2] There are troubling signs that EPA may be seeking to unduly narrow the scope of this review, threatening the independence of the peer review process.

The 1997 amendments to the Federal Advisory Committee Act require that "[a]n agency may not use any advice or recommendation provided by the National Academy of Sciences… that

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry.
[2] https://www.epa.gov/sites/default/files/2016-03/documents/epa_peer_review_handbook_4th_edition.pdf (pg. 12).

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was developed by that academy under an agreement with an agency" unless the report of the Academy "will be the result of the Academy's independent judgment" and "the committee was not subject to any actual management or control by an agency or an officer of the Federal Government."[3]

Under the amended Toxic Substances Control Act, the EPA Administrator must consider "the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models" used in undertaking rulemakings and risk evaluations of substances.[4] As outlined above, prior NAS committee panelists and stakeholders have articulated how unduly narrow charge questions limit the statutorily required independent role of a panel and may subject it to Agency control or management. In addition, failure to take public and interagency comment on the committee task and draft charge and meaningfully respond to those comments is contrary to EPA's own policies as well as past practice.

Consistent with the prior NAS review of this assessment and the valuable NAS feedback to improve the IRIS process as well as EPA's legal and scientific requirements, ACC and the Panel recommend the following steps:

- Request the Office of Management and Budget to conduct a **formal** interagency review for the draft formaldehyde IRIS assessment and charge questions prior to their release for public comment.
- Publish and respond to interagency comments on draft charge questions prior to commencing the public comment period or peer review process.
- Consistent with EPA[5] and White House policies,[6] take public comment on draft charge questions before initiating the peer review. In light of these clear directives on sequencing, EPA and NAS should evaluate those comments prior to selection of the panel "so that appropriate expertise is included to address all charge questions," and, if appropriate, re-open the nomination process.
- EPA should incorporate the recommended charge questions (Appendix 1) and those received during the public comment period and update the committee task.
- EPA should not restrict the committee's task to "responding only to the materials provided by the EPA".

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[3] 5a U.S. Code § 15.
[4] 15 U.S. Code § 2625(h).
[5] "Accepting public comments before peer review has two benefits: (1) the Agency can consider public comments on the scope of the charge before the selection of peer reviewers so that appropriate expertise is included to address all charge questions; and (2) the Agency's public comment process is kept distinct from the peer review panel's comment process." Ibid., pg. 86.
[6] "The charge to the reviewers should be determined in advance of the selection of the reviewers." 70 Fed. Reg. 2664, 2668 (Jan. 14, 2005).

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These steps are critical to the transparency, credibility, and quality of the peer review process. It is worrisome that the contract between EPA's Office of Research and Development (ORD) and NAS, signed September 7, 2021, suggests an unduly narrow committee task and subsequent charge questions, and limits the opportunity for NAS, stakeholders, or the public to provide feedback on this scope. The contract task states:[7]

> The NAS expert peer review committee shall evaluate the assessment's conclusions **using the charge questions set forth by EPA** and **shall not conduct an independent assessment** separately from the IRIS document **nor shall the NAS comment on the broader aspects of the IRIS program. Comments provided by the NAS committee shall be limited to responding to the materials provided by the EPA**.... Additional background information may be provided to the committee. **These materials shall not be reviewed by the NAS**, but may be informative as the committee deliberates. [emphasis added]

Recently released records by U.S. EPA also suggest an effort to constrain the scope of any internal or public response to past peer review comments, while making minimal changes to the underlying assessment. For example, an official with U.S. EPA's National Center for Environmental Assessment, which housed IRIS, and now the NAS responsible staff officer for this review of the draft formaldehyde assessment, sent emails in mid-2011 in suggesting "deleting reference to potential additional peer review..." and endorsing "a strong team opinion that additional peer review will not be needed, given that the major conclusions will not change... whether this is politically viable, however, I don't know."[8]

This sentiment was also echoed in a widely circulated internal email from the then-head of EPA's IRIS program the week after NAS issued their April 2011 report on the 2010 draft formaldehyde assessment. Noting that "it is painful to read the NAS's criticisms," he stated "I remain a pragmatist and do not wish to restructure documents already drafted.... We cannot leave ourselves open to further criticism on these points." He directed EPA chemical managers to give attention to only two of the voluminous and fundamental NAS recommendations for the formaldehyde assessment as well as other subsequent IRIS assessments.[9] In addition, both of these individuals directed an internal EPA review of an updated draft assessment for formaldehyde in 2013, limiting comments to four yes/no questions over a few weeks of review and further directing Agency experts to "... not review the original literature."[10]

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[7] https://foiaonline.gov/foiaonline/api/request/downloadFile/Contract%2068HERC19D0011%20Task%20Orders%2068HERC21F0115%20through%2068HERC21F0401%2C%20including%20modifications%20(Releasable).pdf/8f954e96-5c84-4e4d-ad52-15250063f855 (pg. 70-76)

[8] https://foiaonline.gov/foiaonline/api/request/downloadFile/Kate%20Guyton%20-%20All%20Documents%20Archive%20Notes%20Mail.pdf/f21cdc9b-b1e9-41ed-9b6a-659da21e6c90 (pg. 6).

[9] Ibid., pg. 47-48.

[10] https://foiaonline.gov/foiaonline/api/request/downloadFile/ED_006323_00014241.pdf/69ad0c72-b678-4754-852e-920af7feda83; https://foiaonline.gov/foiaonline/api/request/downloadFile/ED_006491_00000193.pdf/29d09d43-1fc6-49c4-9e61-05ac73b95760.

Narrow and Rigid Charge Ignores History of Independent Peer Review and this Assessment

2011 Congressional testimony from the Chair of NAS's Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, Dr. Jonathan Samet, summarized the need for a broader charge and committee task for review of this assessment:[11]

> Our charge focused primarily on specific questions related to the Agency's approach to the IRIS assessment. **But beyond these charge questions, the committee assesses the processes underlying the development of the draft and made suggestions about the process generally followed by EPA in developing the IRIS assessments**.... Much of our report is directed at providing constructive comments and recommendations on improving this draft specifically following our charge. That said, **we felt that we could not address our charge without considering the methods and structure of the document as a whole and in responding to its charge questions, the committee found some recurring methodological problems that are cut across components of its charge**. Consequently, we commented on the general methodology of the assessment in our second chapter and offered general suggestions in chapter seven with regard to processes used by EPA**. The general problems that we identified were not unique and have been reported by other committees.... We found relatively little documentation of methods and insufficient clarity and transparency in how the evidence reviewed in the report was related back to the weight of evidence guidelines.** [emphasis added]

As ACC testified at the same hearing[12]:

> There is little independence in the IRIS program's standard peer review process: the IRIS office controls the development of the assessment, the design of the peer review charge questions, and the evaluation of the peer review findings. Ultimately, the IRIS program itself decides which recommendations from peer review groups to act upon and which to ignore. As we have seen in the case of dioxin, the IRIS office has exhibited steadfast reluctance to upgrade the assessments in response to the demands of independent peer reviewers.

Unfortunately, this pattern appears to be repeating for the Agency's response to NAS recommendations for the 2010 draft IRIS assessment for formaldehyde. Despite an abundance of evidence that EPA has continued work on the draft assessment since 2011, the EPA-NAS contract from September 2021 makes the perplexing claim that: "While the 2010 draft is of similar length, the current assessment represents an entirely new draft developed de novo using systematic review methods and in a manner responsive to NAS comments on the prior draft." This claim is contradicted by the Agency's own timeline[13] as well as the absence of a

[11] https://www.govinfo.gov/content/pkg/CHRG-112hhrg67255/pdf/CHRG-112hhrg67255.pdf.
[12] Ibid
[13] https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=223614#tab-2.

chemical-specific systematic review protocol or IRIS assessment plan.[14] As a recent letter from ACC's Formaldehyde Panel documented, [15] EPA's failure to document implementation of critical and fundamental comments raised by peer reviewers in the 2011 NAS review of the 2010 draft IRIS assessment for formaldehyde raises legal, science, procedural, and policy issues for the Agency's use of this determination in regulatory settings.

In addition, Dr. Samet articulated that: "Our review of the draft assessment was written by a 15-member committee that had a wide range of scientific expertise, appropriate to the task." By comparison, the EPA-NAS contract from September 2021 only provides for "an expert panel of up to 12 experts," thus limiting opportunities to ensure balance and diversity, and recommends only five areas of expertise.

EPA's Approach is at Odds with Interagency Comments

Other federal agencies have also repeated concerns about the scope of the Agency's peer review charge questions related to IRIS. The Small Business Administration's Office of Advocacy, regarding the Inorganic Arsenic assessment, stated: "Instead of allowing review of all the critical scientific assumptions, inputs and methodologies, EPA narrowly crafted the charge questions, thus avoiding review of some very key questions."[16]

In 2010, EPA sought public comment on the draft charge questions[17] and made public interagency comments, including feedback on the draft charge questions, available upon release of the draft assessment.[18] EPA received comments from other federal agencies like the U.S. Department of Defense[19] on the draft charge to the NAS panel.[20] At that time, EPA emphasized this more transparent approach, stating:

> On June 2, 2010, the Toxicological Review of Formaldehyde and the charge to external peer reviewers were released for external peer review and public comment. The Toxicological Review and charge were reviewed internally by EPA and by other federal agencies and White House Offices before public release. In the new IRIS process, introduced by the EPA Administrator, all written comments on IRIS assessments submitted by other federal agencies and White House Offices will be made publicly available.[21]

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[14] https://www.epa.gov/system/files/documents/2022-02/iris-program-outlook_feb-2022.pdf; https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process.
[15] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/formaldehyde-panel-follow-up-letter-to-epa.
[16] https://www.sba.gov/content/written-comments-060910-environmental-protection-agency-1.
[17] 75 FR 30825.
[18] https://www.regulations.gov/document/EPA-HQ-ORD-2010-0396-0002.
[19] https://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=496580.
[20] https://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=496572.
[21] https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=223603.

Narrow and Rigid Charge Contradicts Congressional Direction

An EPA decision to sever this peer review from the 2011 NAS recommendations, including a committee task that suggests a narrow review excluding consideration of whether the Agency has fully implemented and documented prior recommendations is contrary to Congressional direction. For example, in the U.S. House of Representatives report 112-151[22] accompanying the 2012 Consolidated Appropriations Act,[23] the Committee on Appropriations directed that "EPA shall incorporate... the recommendations of Chapter 7 of the National Research Council's [NAS's] Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde, into the IRIS process" as well as that the Agency specifically document and address recommendations for future assessments. Furthermore, the Committee prohibited funds to be "used to take any administrative action based on any draft or final assessment that does not incorporate the recommendations... as part of the assessment process."[24] Similarly, the final conference report accompanying H.R. 244, the Consolidated Appropriations Act of 2017 points out that "[NAS] identified specific recommendations and considerations when evaluating the hazards of formaldehyde," directing EPA to "contract with the [NAS] to conduct the peer review of the revised draft IRIS assessment of formaldehyde... to verify the recommendations from the previous [NAS] report of 2011 have been fully resolved scientifically."[25]

In addition, the suggested charge questions, in Appendix 1 of this letter, connect EPA and NAS's scientific review with the statutory requirements that the Agency must follow in using a final assessment for regulatory purposes under TSCA, the Federal Advisory Committee Act, and the Clean Air Act. Grounding these broader scientific charge questions in the appropriate legal context is consistent with the 2012 recommendations from the Research Integrity Roundtable of the Keystone Center that "[p]anelists should be periodically reminded of the statutory requirements that govern the questions the panel is addressing."[26]

Narrow and Rigid Charge Violates EPA's Own Policies

EPA recently confirmed that its external "fit-for-purpose peer review[s]" are "conducted in accordance with the EPA Peer Review Handbook."[27] The *Handbook* contains significant

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[22] https://www.congress.gov/112/crpt/hrpt151/CRPT-112hrpt151.pdf.

[23] Pub. L. 112-74, December 23, 2011.

[24] The Committee also stated: "Furthermore, no funds shall be used for action on any proposed rule, regulation, guidance, goal or permit, issued after May 21, 2009, that would result in the lowering or further lowering of any exposure level that would be within or below background concentration levels in ambient air, public drinking water sources, soil, or sediment."

[25] https://www.govinfo.gov/content/pkg/CREC-2017-05-03/html/CREC-2017-05-03-pt2-PgH3327.htm.

[26] The Keystone Center, Research Integrity Roundtable, *IMPROVING THE USE OF SCIENCE IN REGULATORY DECISION-MAKING: Dealing with Conflict of Interest and Bias in Scientific Advisory Panels, and Improving Systematic Scientific Reviews*, September 2012, https://www.keystone.org/wp-content/uploads/2015/08/ResearchIntegrityRountableReport.pdf (pg. 16).

[27] https://sab.epa.gov/ords/sab/sab_apex/r/files/static/v403/Science%20Supporting%20EPA%20Decisions.pdf.

direction for U.S. EPA and its external peer review administrators, much of which appear to be disregarded in the narrow and rigid committee task in the NAS-EPA contract for this review:

- "It should be noted that certain questions posed in charges can be responded to with a yes or no answer. Clearly, that is not the type of response the agency generally wants; therefore, it is important to phrase charge questions carefully to ensure a fully satisfactory and thoughtful response." (pg. h-1)
- "Preparing a good charge is time well-spent, as the charge is crucial for an effective peer review. A good charge will direct the reviewers to give advice on issues relevant to the Agency and will lead to a greater understanding of the reviewer's reasoning, which is pivotal to the Agency's ability to address the reviewers' concerns and to craft specific improvements to the work product... These focused charge questions should be explicit enough to encourage constructive comments, but not so narrow that they preclude or limit informative responses that the reviewers may consider important to provide. The second type of questions invites a broad evaluation of the overall work product." (pg. 82-82)
- "The 'charge' contains the instructions to the per reviewers regarding the objective of the peer review and the specific advice ought. The importance of the information, which shapes the goal of the peer review, influences the charge." (pg. B-15)
- "The charge to the reviewers should be determined in advance of the selection of reviewers.... Peer review is most powerful when the charge is specific and teers the reviewers to specific technical questions while also directing reviewers to offer a broad evaluation of the overall product." (pg. B-15)
- "The charge should ask that peer reviewers ensure that scientific uncertainties are clearly identified and characterized.... Reviewers should be asked to ensure that the potential implications of the uncertainties for the technical conclusions drawn are clear. In addition, peer reviewers might be asked to consider value-of-information analyses that identify whether more research is likely to decrease key uncertainties.... For some reviews, evaluation of biological plausibility is as important as statistical modeling." (pg. B-15 to B-16)

<u>These Suggestions are Consistent with Recent NAS Review of the IRIS Handbook</u>

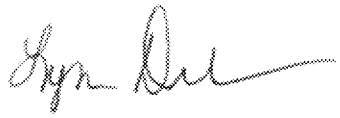
For review of the 2020 draft IRIS Handbook, "EPA released the draft IRIS Handbook and charge questions for public comment in advance of the NAS peer review. Following the public comment period, comments received were summarized and provided to the committee conducting the peer review."[28]

[28] https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086.

The appendix of this letter contains a series of overarching and detailed charge questions to inform NAS and the panelists. We appreciate EPA and NAS's consideration of these recommendations to improve the quality of the peer review process as well as the specific work product under review.

Thank you for your consideration of the ACC Formaldehyde Panel's request. Again, on behalf of the regulated community and the public, the Panel expects that EPA's 2022 draft formaldehyde IRIS assessment will reflect significant scientific revisions and improvements, prior to public dissemination and the subsequent peer review, as rigorously recommended by the 2011 NAS review.

Respectfully,



Lynn Dekleva Ph.D.

Senior Director, Chemical Products & Technology Division
On Behalf of the ACC Formaldehyde Panel

cc:
Maureen Gwinn, Acting Assistant Administrator, Office of Research and Development (ORD)
Chris Frey, Deputy Assistant Administrator for Science Policy, ORD
Wayne Cascio, Director, Center for Public Health and Environmental Assessment, ORD
Kris Thayer, Director, Chemical & Pollutant Assessment Division, ORD

Attachment: Appendix 1 Recommended Charge Questions for NAS Peer-Review Committee

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Appendix 1: Recommended Charge Questions for NAS Peer-Review Committee

I. Overarching questions

A. Does the systematic review protocol have sufficient information for the public to evaluate the formaldehyde assessment and EPA's approach to key issues? Were the following questions clearly evaluated in the protocol:

1. What was the rationale used in the systematic review protocol?
2. What PICO components were used?
3. What explicit inclusion/exclusion criteria were used?
4. Was the relevant, known, and current literature identified? What is the latest date for the literature used in the assessment?
5. What preliminary search terms and databases were used?
6. What data abstraction/data management tools were used? What were the quality assurance/quality control procedures?
7. How did the EPA assess and consider the risk of bias in the identification, selection and analysis of the studies to develop their conclusions?

B. EPA's *Peer Review Handbook* states that "[t]he credibility of [a] final influential work product is likely to be enhanced if the public understands how the Agency addresses the specific concerns raised by the peer reviewers."[29] Did EPA provide written documentation suitable for the public regarding how it has implemented all recommendations from the 2011 NAS Review?

C. How did EPA evaluate and characterize the extent to which variability and uncertainty affect the Assessment?

D. Does this assessment employ scientific information, technical procedures, measures, methods, protocols, methodologies, or models in a manner consistent with the best available science?

E. Consistent with EPA's Peer Review Handbook, were the scientific uncertainties clearly identified and characterized?[30]

F. Did EPA specifically reference any pertinent findings, recommendations, and comments from past peer reviews of this assessment or the IRIS process, including pertinent findings, recommendations, and comments from NAS? Did EPA provide an explanation for the

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[29] Draft_PeerReviewHandbook_07_2014_From_Agency_Review (epa.gov)

[30] "The charge should ask that the peer reviewers ensure that scientific uncertainties are clearly identified and characterized. Since not all uncertainties have an equal effect on the conclusions drawn, reviewers should be asked to ensure that the potential implications of the uncertainties for the technical conclusions drawn are clear. In addition, peer reviewers might be asked to consider value-of-information analyses that identify whether more research is likely to decrease key uncertainties."

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reason for any differences between this assessment and these findings, recommendations, and comments?

G. Does the Committee have appropriate standards for which to evaluate the draft Assessment?

II. Mode of action / mechanisms

A. Exposure, Dose and Systemic Delivery of Inhaled Formaldehyde: Role of Endogenous Formaldehyde Production

It is well known that endogenous formaldehyde is produced in all tissues through normal metabolic pathways. Inhaled exogenous formaldehyde is expected to be absorbed primarily at the site of contact. Further, endogenous tissue formaldehyde concentrations are similar to concentrations that have been shown to induce genotoxicity and cytotoxicity *in vitro*. However, there are multiple metabolic pathways in place to detoxify formaldehyde. These pathways are relevant for both exogenous and endogenous formaldehyde because they are chemically identical.

1. What are human-relevant levels of exposure to formaldehyde and what is the transport and fate of these exposures in the body? What evidence exists that exogenous formaldehyde moves beyond the point of initial contact (e.g., the nasal tissue or respiratory tissue)?

2. What is the current understanding of endogenous formaldehyde production (e.g., typical levels in blood and target tissues) and the potential contribution of endogenous formaldehyde to human health risks, if any?

3. Does EPA satisfactorily describe the current understanding of endogenous formaldehyde? Has EPA's evaluation of risks from exogenous formaldehyde adequately considered the relative contribution, if any, from endogenous formaldehyde?

B. Inflammatory response dynamics

1. Inflammatory mechanisms for portal-of-entry effects

Formaldehyde is an aldehyde that is highly irritating and highly reactive at the site of contact – when inhaled, the site of most local metabolism and detoxification is the nose. Thus, it has been postulated that formaldehyde point-of-contact toxicity may be the result of regenerative cellular proliferation resulting from cytotoxicity (Thompson et al., 2020). Because it is the site of first contact, EPA, and NAS note that the respiratory tract is considered a plausible location for formaldehyde-induced cancer. NAS indicated that

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the lung is less plausible simply because the delivered dose of formaldehyde in the lower respiratory tract is expected to be minimal[31].

i. What is the current evidence regarding the relative importance of this mode of action (MOA) in the context of carcinogenic effects at the site of contact from inhalation exposure to formaldehyde (i.e., nasal tumors)?
ii. What evidence was presented to support is that inhaled formaldehyde can penetrate further into the respiratory tract in quantities sufficient to produce effects? Does the evidence support those carcinogenic effects can occur at more distal portal-of-entry tissues, such as the lung?
iii. What evidence exists that irritation and inflammation are the operative MOA for non-cancer portal of entry of effects? Are there other MOAs that may be contributing to non-cancer effects and if so, what are these purported MOAs?

2. Mechanism for systemic non-cancer effects at locations beyond the portal of entry

In its 2011 review, NAS stated that, "the possibility remains that systemic delivery of formaldehyde is not a prerequisite for some of the reported systemic effects seen after formaldehyde exposure"[32] and that systemic non-cancer effects of formaldehyde, such as reproductive and developmental toxicity, local inflammation, irritation, and/or stress could lead to downstream, indirect toxicity.

i. How scientifically sound is this hypothesis that inflammatory cells could "migrate" beyond the site of contact to distant tissues and exert effects? Is there empirical evidence demonstrating that such a MOA is occurring in humans or animals? If available, does this evidence speak to early initiating events, or are there are multiple demonstrated effects that are part of a larger purported adverse outcome pathway (AOP)?

3. Mechanism for leukemogenicity via genotoxicity (including cytogenetic effects) at locations beyond the portal of entry

Formaldehyde is a DNA reactive chemical and thus, some potential for genotoxicity is plausible. NAS noted that "formaldehyde-induced DNA damage is postulated to lead to mutations and clastogenesis, critical cytogenetic events in the carcinogenic mode of action" [33].

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[31] Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde | The National Academies Press
[32] Ibid, Page 10
[33] Ibid, Page 38

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Regarding lymphohematopoietic malignancies specifically, "[t]here is some evidence that these diseases may originate from the same stem cell line (Gluzman et al. (2015); Goldstein (2010)) and could therefore arise from direct effects on these cells. There are no studies, however, that demonstrate an effect on these stem cells following exposure to formaldehyde. The largest population of these stem cells would be found in the bone marrow, and based on the available evidence, inhaled formaldehyde appears incapable of reaching the bone marrow). The affected cells would need to be circulating stem cells that encounter formaldehyde at the portal of entry (i.e., the nose or upper airways) and then return to the bone marrow.[34]"

i. What scientific evidence is provided in the draft assessment to support the hypothesis that circulating stem cells circulating past the nose at the time of a substantial exposure to formaldehyde sustain transformative non-lethal mutations and subsequently migrate into the bone marrow and propagate, leading to leukemia?

ii. Does this hypothesis necessarily contradict the evidence that exogenous formaldehyde cannot reach the bone marrow? What evidence might indicate that circulating stem cells present in the nasal tissues directly exposed to formaldehyde are genetically damaged in a way compatible with carcinogenicity would return to the bone marrow and propagate? Assuming that this chain of events might plausibly occur, what is the probability that it does, given a substantial exogenous exposure to formaldehyde?

iii. Regardless of the biological plausibility, what, if any, evidence has been generated since the previous IRIS Draft Formaldehyde Review that informs this hypothesis?

iv. Does the new evidence support or refute the hypothesis, and why? What is the evidence that genotoxicity is an early initiating key event in the development of formaldehyde-induced cancers?

III. Toxicological studies / models informing genotoxicity

A. Animal studies lack evidence of leukemogenicity

The NAS (2011) review indicates that the EPA (2010) conclusion that formaldehyde causes myeloid leukemia was based primarily on selected epidemiological studies, and other streams of evidence (animal, mode of action) were not considered beyond studies conducted by Zhang et al. (2009, 2010a).

[34] Mundt, et al. (2017) Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells?, Critical Reviews in Toxicology, 47:7, 598-608, DOI: 10.1080/10408444.2017.1301878 Link

1. What is the weight of evidence regarding lymphohematopoietic malignancies in animals exposed to formaldehyde? How should one interpret EPA's unpublished re-analysis of the Batelle chronic studies in rats and mice? Do these studies alter overall conclusions when weighed with the multiple null experimental animal studies?

2. Morgan et al. (2017) was published after the last IRIS review of formaldehyde. In this study, inhalation of formaldehyde did not cause leukemia in genetically predisposed animals. How can this study be used to inform the overall synthesis of the experimental animals?

B. Zhang et al. (2010) study of cytogenetic markers of hematopoietic function and chromosomal aneuploidy in formaldehyde-exposed workers. Gentry et al. (2013) and Mundt et al. (2017) rebuttal of Zhang et al. (2010)

"The [NAS] peer review further pointed out that the EPA (2010) conclusion that formaldehyde causes ML was based primarily on selected epidemiological studies, and other streams of evidence (animal, mode of action) were not considered beyond studies conducted by Zhang et al. (2009, 2010a)."

"One key study cited in multiple agency evaluations as providing evidence of cytogenetic events in the development of leukemias is by Zhang et al. (2010a, 2010b) compared the prevalence of markers of hematopoietic function and chromosomal aneuploidy among workers occupationally exposed to formaldehyde with those of a group of unexposed workers in China. Ninety-four workers were included, with 43 workers occupationally exposed to formaldehyde and 51 workers unexposed to formaldehyde as controls. The authors reported a higher prevalence of monosomy 7 (loss of a chromosome) and trisomy 8 (gain of a chromosome) in metaphase spreads prepared from cultures of CFUGM colony cells. The authors suggested that this demonstrated that formaldehyde exposure was associated with an increase in leukemia specific chromosomal aneuploidy in vivo in the hematopoietic progenitor cells of the exposed workers." (Mundt et al. 2017)

"However, no direct *in vivo* metaphases had been examined in workers blood. Furthermore, this was a cross-sectional comparison of blood and cytogenetic measures between two groups and observed differences could not be established as resulting from formaldehyde exposure or due to other overall differences between the two groups." (Mundt et al. 2017)

Gentry et al. (2013) and Mundt et al. (2017) rebuttal of Zhang et al. (2010) "individual data on blood cell counts in both formaldehyde exposed and unexposed individuals including any data on health status of these individuals; 2) individual data on the FISH results for monosomy 7 and trisomy 8 for cultures of samples obtained from 10 formaldehyde-exposed workers and 12 unexposed controls; 3) data on additional chromosomal abnormalities examined and/or observed; and 4) details of the methods sufficient for a

qualified scientist to replicate the results reported in the Zhang et al. (2010) study. The results of this reanalysis suggested that factors other than formaldehyde exposure likely contributed to the reported findings." (Mundt et al. 2017)

"In addition, although the authors stated in their paper that 'all scorable metaphase spreads on each slide were analyzed, and a minimum of 150 cells per subject was scored,' this protocol was not followed specifically for chromosome 7 or chromosome 8 (recent correspondence indicates a minimum of 150 total metaphases were scored for 24 chromosomes per subject). Far too few cells were counted to draw any meaningful conclusions, and far fewer than the approximately 400 per chromosome cited in previous analyses in which the protocol was described (Zhang et al., 2005, 2011). (Mundt et al. 2017)

"In addition, the assays used (CFU-GM) do not actually measure the proposed events in primitive cells involved in the development of AML. Evaluation of these data indicates that the aneuploidy measured could not have arisen in vivo, but rather arose during in vitro culture." (Mundt et al. 2017)

"In 2014, Mundt et al. requested the individual exposure measurement data for each of the participants in the Zhang et al. (2010a) study from NCI. In 2016, the request was in part granted and the mean formaldehyde estimate for each exposed worker (but not the individual exposure measurement values) was provided via a Technology Transfer Agreement (TTA) with NCI." (Mundt et al. 2017)

"Results of this second reanalysis showed that differences seen at the group comparison level, i.e., comparing the prevalence of white blood cell, granulocyte, platelet, and red blood cell counts at the group level in fact were independent of measured formaldehyde exposure level. Among exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of ML risk. Differences between the two groups of workers, other than formaldehyde exposure, were therefore likely to explain the results reported by Zhang et al. (2010a)." (Mundt et al. 2017)

1. What is the potential importance of Zhang et al. (2010) deviating from their own protocol in conducing the CFU-GM assays, i.e., counting a smaller fraction of fields than specified in their protocol? What is the value of a study protocol and what would be the proper approach to deviating from it (if necessary and scientifically justified)?

2. Given that Zhang et al. (2010) is a cross-sectional study, how (as the title indicates) can it validly demonstrate "changes" in any of the measures obtained?

3. What are the main reasons that a study that measures individual formaldehyde exposure level (three measurements for most participants) presents no results based on the actual exposures (but rather limits comparisons to the crude classification of "exposed" versus "unexposed")?

4. The reported "changes" exclusively were based on observed differences between the "exposed" and "unexposed" groups at large, but (only as reported in the fuller analyses reported by Mundt et al. 2017b) not by level of measured formaldehyde exposure (based on the average of three personal monitoring results). How can the differences reported between "exposed" and "unexposed" be explained in light of the evidence that the level of measured exposure was randomly distributed with respect to all outcome measures?

IV. Human (epidemiological) evidence

A. Quality of exposure ascertainment and quantification in epidemiological studies

1. Choice and quality of exposure metric (cumulative vs. 'peak') (Checkoway et al. 2019)

"[T]he reliance on the peak exposure metric to determine causality rather than the more conventional dose metric of cumulative exposure should be further justified particularly in the absence of established modes of action" (NAS, 2011, p.112).

"In the absence of evidence regarding exposure-disease mechanisms, as in the case of formaldehyde and LHP cancers, cumulative exposure is typically the default dose metric applied in epidemiologic analyses and risk assessment. But the most significant results were found for peak exposures, which have the greatest associated uncertainty. In view of the importance of this study, EPA should clarify the basis of its interpretations of the results regarding the various dose metrics and the various LHP cancers. Despite those concerns, the committee agrees that the NCI study is the most appropriate available to carry forward for calculation of the unit risk." (NAS, 2011, pp. 112–113)

"NCI investigators (Beane Freeman et al., 2009; Blair et al., 1986; Hauptmann et al., 2003) defined peak exposure as the maximum peak, and the NCI investigators substituted the time-weighted average (TWA) for jobs without assigned peak exposures (Stewart et al., 1986). The authors reported a significant test for trend between peak formaldehyde exposure and leukemia, but only when unexposed subjects were included. Increased risk was not seen for higher peak exposure categories (2.0 to<4.0 ppm, or ≥ 4.0 ppm) when compared to the lower peak category (> 0 to<2.0 ppm). No association was reported with frequency of peak exposure, average intensity of exposure or with cumulative exposure to formaldehyde ("There was little evidence among formaldehyde workers of association for any lymphohematopoietic malignancy (LHM) with average intensity or cumulative exposure at the end of follow-up in 2004." (Beane Freeman et al., 2009, p. 751). In fact, a 10% deficit of ML deaths (acute and chronic types combined) was reported when compared to US population mortality rates. In an internal analysis, Beane Freeman et al. (2009) reported that ML deaths were not associated with the number or frequency of peaks. If there were a

true association between peak exposure and leukemia, one would expect to see an association with number of peaks and not only ever having a (perhaps single) peak exposure. Hauptmann et al. (2003) acknowledged that "no measurements of peak exposure were available in this study. Peak exposures were therefore estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average" (Hauptmann et al., 2003, p. 1616; Stewart et al., 1986; Mundt et al. 2017)

"In extended analyses of the NCI cohort study, Checkoway et al. (2015) refined the classification of peak exposure. Workers who did not work in jobs identified as likely having peak exposures were classified as not exposed to peaks and became the referent group. A total of 3478 cohort members were classified as having worked in jobs with estimated peak exposure of 2-<4 ppm, and 2907 worked in jobs with estimated peak exposure of ≥4 ppm. Analysis by ML subtype (i.e., AML and CML deaths, separately) found no association between peak exposure and AML mortality (HR 1.71, 95% CI 0.72–4.07 and HR 1.43, 95% CI 0.56–3.63, respectively) (Checkoway et al., 2015). However, 13 of the 34 AML deaths were classified as having worked in jobs likely having peak exposure>2.0 ppm, only 4 of which worked in these jobs within the 20 years preceding their AML death (i.e., latest exposure), and only one occurred (similar to the number expected) within the typical AML latency window of 2–15 years." (Mundt et al. 2017)

"Ultimately, the Beane Freeman et al. (2009) study alone does not (and cannot) provide reliable support for a conclusion that peak formaldehyde exposure causes ML or AML, especially considering the absence of peak measurement data in the US study, the results of the reanalysis by Checkoway et al. (2015), and the updated results from the UK study (Coggon et al., 2014), which used a more conservative approach to exposure estimation." (Mundt et al. 2017)

i. What is the biological rationale for favoring or focusing on "peak" formaldehyde exposure and risk of AML (or any LHM)?

ii. What is the most appropriate peak exposure metric for formaldehyde and AML (or any LHM) and how might it be more valid than the traditional cumulative or average intensity exposure metrics?

iii. How does the extended analysis by Checkoway et al. (2015), demonstrating that very few cohort members with AML had been classified as having "peak" exposures (despite no actual direct individual monitoring results) and that most of these would have had their last "peak" exposure 20 or more years before their AML-related deaths, impact the broad conclusion that "peak" exposure is important?

B. Specificity of outcome (LHM vs individual malignancies)

"EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of LHP cancers: 'all LHP cancers,' 'all leukemias,' and 'myeloid leukemias.' 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. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas." (NAS 2011; p. 11)

"The NAS (2011) raised the issue that diverse types of leukemias, and lymphomas should not be grouped "because it combines many diverse cancers that are not closely related in etiology and cells of origin. Although the draft IRIS assessment explores specific diagnoses—such as AML and CML, as well as Hodgkin lymphoma and multiple myeloma (see, for example, EPA 2010, Tables 4–92)—the determinations of causality are made for the heterogeneous groupings of "all LHP cancers," "all leukemias," and "ML." (Mundt et al. 2017)

"When results for heterogeneous groupings are presented, there is no evidence of increased risk of all LHP cancers (Meyers et al., 2013; Beane Freeman et al., 2009) or all leukemias combined (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009) in industrial cohorts when compared to general mortality rates. In addition, there is no evidence of exposure-response associations between all LHPs combined (or all leukemias combined) and cumulative exposure or average exposure (Beane Freeman et al., 2009) or duration of exposure (Meyers et al., 2013; Coggon et al., 2014)." (Mundt et al. 2017)

"After the [NAS] peer review was published, Checkoway et al. (2012) critically reviewed the epidemiological evidence and reported inconsistent and sporadic associations between formaldehyde exposure and various specific LHM, including ML. Only a few epidemiology studies considered AML specifically. Since the critical review (Checkoway et al., 2012), several additional epidemiological studies have been published that provide insights on formaldehyde exposure and AML risk and address other specific issues raised by the 2011 NRC peer review." (Mundt et al. 2017)

1. Given the general appreciation that many of the individual malignancies that fall under the inclusive category of "LHM" are discrete disease with "evidence of etiological heterogeneity" (IARC 2018 – Monograph on Benzene), what (if any) is the validity and value of evaluating formaldehyde and LHM as a group?
2. The previous NAS Committee recommended that specific LHM be evaluated individually. What is the evidence that such individual evaluations of LHMs provide evidence of etiological heterogeneity?

i. Studies with results specific to AML

Mundt et al. (2017) found that only six epidemiological studies of workers substantially exposed to formaldehyde have reported AML-specific results (Blair et al., 2001; Checkoway et al., 2015; Hauptmann et al., 2009; Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014), four of which were not available at the time of the IARC review or the release of the Draft IRIS Assessment. Saberi Hosnijeh et al. (2013) found no association between "low" formaldehyde exposure and incidence of myeloid leukemia (HR 1.02, 95% CI 0.72–1.42 based on 49 cases exposed to formaldehyde and 130 unexposed cases). Saberi Hosnijeh et al. (2013) found no differences between subtypes: AML (HR 1.01, 95% CI 0.65–1.57) or CML (HR 0.92, 95% CI 0.46–1.84) and no myeloid cases (and therefore no AML cases or CML cases) occurred among those classified as having "high" formaldehyde exposure. Talibov et al. (2014) found no association between formaldehyde and incident AML, after adjusting for exposure to specific solvents and ionizing radiation (HR 1.17, 95% CI 0.91–1.51 for 136 workers and 628 controls exposed to > 1.6 ppm-yrs). Meyers et al. (2013) reported a SMR for AML of 1.22 (95% CI 0.67–2.05) based on 14 observed AML deaths. Checkoway et al. (2015) performed AML-specific analysis using the NCI cohort, which had provided results only for all ML combined (Beane Freeman et al., 2009), and found when compared to US referent rates, AML mortality risk was decreased among workers exposed to formaldehyde (SMR 0.80, 95 %CI 0.46–1.14) and did not observe a trend with increasing cumulative exposure or peak exposure categories. Checkoway et al. (2015) found that acute myeloid leukemia (AML) was unrelated to cumulative, average, or peak exposure, and few deaths occurred within 20 or more years of last peak exposure.

Coggon et al. (2014) in an extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941–2012, found no support for an increased hazard of myeloid leukemia from formaldehyde exposure. Meyers et al. (2013) in an extended follow-up of 11,098 employees of three garment manufacturing facilities found limited evidence for formaldehyde exposure and any LHM including AML, based on 14 observed cases.

1. Assuming that AML/ANLL are the most biologically plausibly chemical-induced LHM, what is the evidence (epidemiological or toxicological) that formaldehyde increases the risk of these malignancies?

2. Given the generally consistent lack of association reported between occupational formaldehyde exposure and risk of AML/ANLL, what is the strongest available contradictory evidence? How does this inform the overall conclusions regarding formaldehyde's possible leukemogenicity?

ii. Other LHM and combinations of LHM

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Checkoway et al. (2015) reported suggestive associations with peak exposure for chronic myeloid leukemia, based on very small numbers. Hodgkin lymphoma relative risk estimates suggested trends for both cumulative (ptrend = 0.05) and peak (ptrend = 0.003) exposures. However, no other lymphohematopoietic malignancy was associated with either cumulative or peak exposure. Meyers et al. (2013) and Saberi Hosnijeh et al. (2013) both found that associations reported by Beane Freeman et al. (2009) between formaldehyde exposure and Hodgkin lymphoma and CML have not been observed in other studies. Meyers et al. (2013) determined a SMR of 1.35 (95% CI 0.44–3.15), based on 5 CML cases and Saberi Hosnijeh et al. (2013) determined a RR of 0.92 (95% 0.46 to 1.84) based on 46 CML cases. Checkoway et al. (2015) concluded that the association between formaldehyde exposure and Hodgkin lymphoma and CML are less plausible, given the lack of known associations with Hodgkin lymphoma or CML and other chemicals or agents, such as benzene.

1. Assuming that AML/ANLL are the most biologically plausibly chemical-induced LHM, what is the rationale for considering associations between formaldehyde exposure and risk of other LHM?

2. The Beane Freeman (2010) study, at face value, presents the strongest evidence of an association and exposure-response relationship between formaldehyde exposure Hodgkin lymphoma, although other studies fail to corroborate this. What is the evidence demonstrating that such an observed association is biologically plausible? What is the significance of other comparable studies failing to find such a clear association?

3. Hodgkin lymphoma is one of several LHM. Given that associations between formaldehyde and LHM as a group were reported, to what extent might this association have been driven by the clear association (regardless of biological plausibility) with Hodgkin lymphoma?

V. Non-Cancer Effects

Does the evidence support -- and if so, how -- that respiratory tract pathology is a critical effect of chronic inhalation exposure to formaldehyde? What evidence exists that supports respiratory pathology as one of the most sensitive effects and thus, an effect that should be considered for toxicity value derivation?

VI. Evidence Integration

Lacking from the previous IRIS Draft was "an approach to weight of evidence that includes "a single integrative step after assessing all of the individual lines of evidence. . . Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version." (NAS, p. 113) (Mundt et al. 2017)

A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode-of-action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. Rhomberg et al. (2011)

The NAS Committee concluded that EPA's claims that formaldehyde causes leukemia, ML or related hematopoietic cancers were not supported in EPA's assessment:

> "As with the respiratory tract cancers, the draft IRIS assessment does not provide a clear framework for causal determinations. As a result, the conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data." (NAS 2011; p. 11)
>
> "Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality. That will add needed transparency and validity to its conclusions." (NAS, 2011; page 11)

A. What is the specific causal model for the evaluation of formaldehyde as leukemogenic?

B. How has the available evidence (epidemiological and toxicological) been evaluated to determine its validity, reliability, and value in informing the causal model?

C. If formaldehyde is determined to be leukemogenic, what is the epidemiological evidence (and of what scientific quality) that supports this conclusion, and what is the epidemiological evidence that undermines it?

D. Given that the prior NAS Committee found that "the conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data,

the weak animal data, and the lack of mechanistic data," what new evidence has become available in each of the key lines of inquiry that supports the earlier conclusion? What new evidence refutes the earlier conclusion? What conclusion does a balance of the totality of evidence today support?

VII. Dose-response and risk characterization

The documentation of the methods applied in the Draft IRIS Assessment (EPA, 2010) lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the NCI cohort study (Beane Freeman et al., 2009). This lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints (Van Landingham et al. (2016) (Mundt et al. 2017).

Further, NAS noted, "Although EPA followed its guidelines for assessing the risk of cancer associated with a mutagenic mode of action, it acknowledged that major uncertainties and controversy remain regarding application of linear models for low-dose extrapolations for a chemical that is formed endogenously and is too reactive to be measured in the body apart from portal-of-entry tissues. As discussed in the following section on BBDR modeling, the committee recommends that, for transparency and completeness, EPA consider providing alternative calculations that factor in nonlinearity associated with the cytotoxicity-compensatory cell proliferation mode of action and assess the strengths and weaknesses of each approach."

A. How can a unit risk for leukemia (and AML specifically) validly be estimated in the absence of 1) adequate evidence to establish causality; and 2) adequate evidence demonstrating exposure-response relationships for the most biologically plausible outcomes (notwithstanding the strong evidence indicating that exogenous formaldehyde cannot reach the bone marrow and therefore cannot plausibly cause myeloid leukemias)?

B. Regarding the derivation of a carcinogenic potency estimate, what are the most appropriate quantitative methods to account for the uncertainties regarding the use of linear models for endogenous chemicals?

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