June 21, 2023

Tom Tracy
Designated Federal Officer
Human Subjects Review Board
US Environmental Protection Agency
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Submitted via email to tracy.tom@epa.gov

Re: Comments for the Human Subjects Review Board

Dear Mr. Tracy and HSRB members,

The American Chemistry Council Formaldehyde Panel (ACC Panel) appreciates the important work being conducted by the Human Subjects Review Board (HSRB) members to review certain studies on formaldehyde science that will inform formaldehyde assessments being conducted within the Office of Chemical Safety and Pollution Prevention (OCSPP). The HSRB detailed evaluation of the studies is an important part of the peer review process and we applaud the attention that is being given to the details of each study evaluated.

The ACC Panel represents producers, suppliers and users of formaldehyde and formaldehyde products, as well as trade associations representing key formaldehyde applications. Formaldehyde is a critical chemical building block in the production of hundreds of items and plays an important role in everyday life, including in the automotive, agricultural, building and construction, aerospace and medical sectors. Not only is the generation of formaldehyde essential for human metabolism, but formaldehyde is also used as part of the process to create and form many materials that we depend upon regularly. The ability of formaldehyde, in combination with countless other molecules, to chemically react and subsequently build resilient structures makes it one of the most functionally important chemical building blocks in the manufacturing world today.

Scientific research and regulatory advocacy are important activities of the ACC Panel and the Panel has invested millions of dollars on scientific research to help inform the Federal government's toxicity assessments. Since 2010 over 50 peer reviewed publications on various key topics have been added to the literature to inform the formaldehyde hazard and dose-response assessment. All this information has been made available and discussed with EPA Office of Research and Development (ORD) staff over that time. These efforts have included scientific research evaluating causal associations between formaldehyde and cancers, quantifying exposure thresholds for formaldehyde health effects and understanding how inhalation of formaldehyde found in the environment relates to formaldehyde produced by normal body

processes. The ACC Panel and its members are committed to helping promote the safe use of formaldehyde and understanding on the science.

The studies you have been asked to evaluate are important to assessments being conducted by the Office of Pollution Prevention and Toxics (OPPT) under the Toxic Substances Control Act (TSCA) and by the Office of Pesticide Programs (OPP) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Once completed, these assessments have the potential to significantly impact how formaldehyde is used throughout commerce. It is critically important that the scientific evaluations are robust and consistent with the best available science.

We appreciated your attentiveness to public comments during the May HSRB meetings and below provide additional information that may be helpful to your ongoing review.

Consideration of Public Input is an Important Part of the FACA Process

The HSRB operates under the Federal Advisory Committee Act (FACA) at EPA. FACA governs the operation of federal advisory committees and emphasizes public involvement through open meetings and reporting.[1] As a cornerstone of FACA, public involvement is a critical requirement. For instance, the public must be notified of all meetings, meetings must all be open to the public, and meeting minutes and reports must be available to the public. Public comment and input is also a necessary element of all EPA FACA committees, including the HSRB.[2] As noted by EPA, "[p]ublic involvement also ensures confidence that the advisory committee decisions are objective and comprehensive."[3]

While the HSRB does not have a handbook for members, the EPA Science Advisory Board (SAB) does have such a handbook.[4] SAB is also a FACA committee and its requirements are consistent with those of the HSRB. The SAB handbook states that, "[p]ublic input, through written comments and oral statements at meetings, is an important part of the advisory process. Panel members are expected to consider public comments. If members find scientific information from the public helpful and informative, it is appropriate to acknowledge the information in the panel report."[5] Similarly, EPA's Peer Review Handbook strongly encourages that EPA make draft work products as well as draft peer review charge questions available for the public and emphasizes the benefits of seeking these comments in advance of a peer review proceeding.[6] It further outlines how public comments "inform the deliberations of the [federal advisory committee] as it reviews the draft EPA work product," noting that "[M]embers of the

[1] See details on FACA available at: https://www.epa.gov/laws-regulations/summary-federal-advisory-committee-act.
[2] See HSRB Charter available at: https://www.epa.gov/system/files/documents/2022-04/2022-hsrb-renewal-charter-final-.pdf.
[3] See SAB Staff Office Report "*Advisory Committee Meetings and Report Development: Process for Public Involvement*" available at: https://sab.epa.gov/ords/sab/r/sab_apex/files/static/v403/sabso_04_001.pdf.
[4] See the SAB Handbook available at: https://sab.epa.gov/ords/sab/r/sab_apex/files/static/v403/Serving%20on%20the%20EPA%20Science%20Advisory%20Board%20SABSO-12-001.pdf.
[5] *Id.*
[6] See EPA Peer Review Handbook, at page 86, available at: https://www.epa.gov/sites/default/files/2020-08/documents/epa_peer_review_handbook_4th_edition.pdf.

public can submit relevant comments pertaining to the group providing advice, the EPA's charge questions, EPA review of background documents, and draft advisory reports prepared by a [federal advisory committee] or its panels."

We note this information to remind HSRB members that, consistent with FACA principles, HSRB members should not be tentative about discussing or incorporating public input, as appropriate, in their report and comments to EPA. Public input is an important part of the process.

Finally, because the EPA is asking the HSRB for their review, and because public comments during the HSRB meeting are addressed to the HSRB for their consideration, EPA will not be providing any separate responses to the public in response to comments sent to the HSRB. If the HSRB report to EPA does not incorporate public comments and does not explicitly recommend that EPA consider and incorporate public comments into their approach, the public comments will most likely go unaddressed. If HSRB agrees with public comments, HSRB should note its agreement and recommend that EPA incorporate the comment into its evaluation.

Statutory and Regulatory Requirements for Scientific Standards

During the May 18, 2023 HSRB meeting, questions were raised regarding EPA's requirement to use the best available science. While EPA has Information Quality Guidelines[7] and guidelines for evaluating the quality of scientific and technical information,[8] EPA must also ensure they are meeting the standards of the relevant environmental statutes. The HSRB is reviewing information to inform EPA assessments under both FIFRA and TSCA. As such, the standards of both these statutes, and their implementing regulations and guidance, apply.

To implement FIFRA, EPA has developed many guidance documents and guidelines that speak to the quality of studies and data that will be considered acceptable by the pesticides program.[9] Because FIFRA has many data requirements, EPA provides guidance for the different types of data that are submitted and considered. In addition, when information is not required or is not part of a standardized testing protocol, OPP provides guidance on evaluating and selecting studies from the open literature.[10] These guidance documents and guidelines help to ensure that evaluations conducted to inform pesticide regulations meet the highest science standards.

TSCA, which was amended in 2016, speaks directly to the quality of information EPA should use and consider in TSCA assessments. TSCA requires that EPA use the "best available science" and also consider the "independent verification or peer review of the information or of the

[7] See EPA Information Quality Guidelines available at: https://www.epa.gov/quality/epa-information-quality-guidelines.
[8] See EPA Guidance for Evaluating and Documenting the Quality of Existing Scientific and Technical Information, available at: https://www.epa.gov/risk/guidance-evaluating-and-documenting-quality-existing-scientific-and-technical-information.
[9] See for example, data requirements available at: https://www.epa.gov/pesticide-registration/data-requirements-pesticide-registration.
[10] See EPA OPP guidance available at: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-identifying-selecting-and-evaluating-open.

procedures, measures, methods, protocols, methodologies, or models.[11] As part of the requirement to use "best available science," EPA must consider, among other elements, the variability and uncertainty in data and EPA must also make decisions considering the "weight of the scientific evidence."[12] EPA has defined "weight of the scientific evidence" to mean "a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance."[13]

In the document provided to the HSRB, entitled "*Weight of Evidence for Acute and Peak Inhalation Endpoints*" EPA describes the approach OCSPP has taken to evaluation sensory irritation as being "health protective."[14] EPA staff, in responding to questions from the HSRB during the May 18, 2023 meeting, also described their approach as "health protective."[15] While the ACC Panel supports the goal of ensuring that chemical substances do not present unreasonable risks of injury to health and the environment, consistent with the mission of TSCA, it is important to note that TSCA requires that scientific evaluations be based on the best available science. TSCA does not tell EPA to simply apply "health protective" approaches. Dr. Melethil had a very valid question when he asked what the EPA response was to concerns regarding use of the best available science. We encourage the HSRB to keep in mind the important scientific standards that EPA must follow when evaluating, assessing and using information to inform decisions under both TSCA and FIFRA.

The ACC Panel has also previously provided detailed comments on the charge, statement of task, and scope of the peer review for the ongoing National Academies of Sciences, Engineering, and Medicine (NASEM) committee review of EPA's draft assessment of formaldehyde.[16] These comments laid out the legal, scientific quality, and EPA policy justifications for avoiding a narrow or leading charge, which EPA failed to follow for NASEM. These comments may have applicability for HSRB's consideration in light of the EPA peer review process on the weight-of-evidence request.

In addition, EPA's weight of evidence approach should have triggered additional standards for peer review and information quality as these determinations are influential scientific

[11] 15 U.S.C. 2625(h).
[12] 15 U.S.C. 2625(i).
[13] 82 Fed. Reg. (July 2017) 33748.
[14] See EPA Weight of Evidence for Acute and Peak Inhalation Endpoints, at page 13, available at: https://www.epa.gov/system/files/documents/2023-04/3a.%20Formaldehyde%20WOE%20for%20Acute%20and%20Peak%20Inhalation%20Endpoints_2023-04-23.pdf.
[15] On May 18, 2023, Dr. Burgin, in describing the EPA approach, stated "OCSPP has taken a health protective approach and has assumed that sensory irritation from formaldehyde at lower concentrations adheres to Haber's law," and in responding to HSRB questions about why EPA believes Haber's law applies to formaldehyde, Dr. Burgin began her explanation by stating "[w]e've taken a health protective approach."
[16] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment.

information[17] or highly influential scientific assessments.[18] In addition to determining the peer review venue, the requirements associated with such information include peer review and charge documentation as well as inclusion in the public-facing Peer Review Inventory.

The HSRB Should Not Comment on a Weight of Evidence Conclusion That Includes Studies the HSRB Was Not Asked to Evaluate

OCSPP has asked the HSRB to comment on the use of four studies in OCSPP's weight of evidence evaluation for acute inhalation endpoints for formaldehyde. However, EPA's weight of evidence evaluation predominantly relied on six studies.[19] As was pointed out by HSRB members, the HSRB cannot comment on studies that they were not asked to review. The ACC Panel agrees with these comments from the HSRB. The HSRB should remain focused on the utility of the four studies that were reviewed and provide recommendations for how they should be considered in a future weight of evidence evaluation. It would be impossible for the HSRB to weigh or consider these studies against other studies which it did not evaluate. Furthermore, a true weight of evidence evaluation should also include consideration of the toxicokinetics and toxicodynamics of formaldehyde, which EPA did not ask the HSRB to consider. Additionally, if the HSRB makes recommendations to EPA based on the four studies evaluated, the HSRB should make clear to EPA that the weight of evidence evaluation only considered four studies and that the HSRB has no comment on whether the additional two studies are better or worse.[20]

The Best Available Science Shows That Formaldehyde Does Not Follow Haber's Law

The observation that neither formaldehyde sensory or tissue irritation adhere to Haber's law has been noted in several publications in the peer-reviewed literature, including in evaluations conducted by the National Academies of Science (NAS 2007).[21] For sensory irritation, which was considered to be a primary health effect of concern by the NAS, the NAS agreed with the literature that found that concentrations that do not produce short-term sensory irritation also do not produce sensory irritation after repeated exposure.[22] Tissue irritation only occurs at concentrations higher than those that elicit sensory irritation. Recognizing the sequence of effects at increasing air concentrations, NAS also stated that at air concentrations that did not produce chronic tissue irritation, risk of cancer and other health effects appeared negligible.[23]

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[17] EPA's Peer Review Handbook identifies several factors to consider in determining if a work product is influential scientific information and explains: "As defined by the OMB Peer Review Bulletin, the term 'influential scientific information' means scientific information the agency reasonably can determine will have or does have a clear and substantial impact on important public policies or private-sector decisions."

[18] EPA and OMB definition of "highly influential scientific assessments include weight-of-evidence analyses or hazard determinations that are "novel, controversial, or precedent-setting or has significant interagency interest."

[19] *Id*. at Section 2 where EPA presents the six studies considered.

[20] Should the HSRB feel compelled to comment on other studies, the HSRB should consider the comments that were submitted to the panel, on May 17, 2023, by Ramboll on the Hanrahan et al. 1984 study.

[21] See comments submitted to the HSRB, May 16, 2023, by Dr. Holm on behalf of the American Forest & Paper Association and the American Wood Council. See also NAS 2007, *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants Volume 1*, 2007, available at: https://nap.nationalacademies.org/download/11170#.

[22] See NAS report *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants Volume 1*, 2007, at page 105, available at: https://nap.nationalacademies.org/download/11170#.

[23] *Id*.

During HSRB discussions on May 18, 2023, in response to HSRB questions asking EPA to explain why they disregarded information about the inapplicability of Haber's law, EPA relied on two arguments. The first argument cited limited low concentration data from the Andersen and Mølhave (1983) study which indicated symptoms may increase over time at low concentration, and higher concentration data that indicated symptoms may decrease over time. However, the HSRB review of the Andersen and Mølhave (1983) study, among other concerns, raised questions about the reliability of the study due to the lack of details presented and expressed concerns with the small sample size, highly variable responses, the lack of dose-response, and the inclusion of potential confounders in the data. Based on these concerns, the HSRB final report recommends that EPA only use this study qualitatively.[24] In flagrant disregard of your recommendation, EPA is now using this study quantitatively to justify concerns about spurious effects seen only at low concentrations in one study of questionable reliability.[25] This argument should be rejected.

EPA's second argument for disregarding Haber's Law is based on OCSPP's choice to take a health protective approach.[26] While a conservative, or precautionary approach, may be appropriate in the absence of data and scientific understanding, it is not appropriate in this situation. Because there is scientific data, as presented above and in comments submitted to the HSRB, an overly conservative health protective approach to modeling and liberal application of uncertainty factors should be rejected. This overly conservative approach to setting exposure limits is also inconsistent with the TSCA requirements to use the best available science. Using this argument to justify a dramatic lowering of existing occupational exposure limits should also be rejected. We note that EPA's position could be used to justify any level no matter how disconnected from the body of scientific information.

While EPA described their reasoning at the May 18, 2023, meeting, the HSRB discussions for a recommendation to EPA focused on suggesting that EPA explain their approach. This recommendation is not sufficient. The EPA staff have already explained the reasoning for the agency's approach which as described above is not scientifically sound. The HSRB should recommend that EPA recognize that Haber's Law does not apply to formaldehyde sensory irritation. As such, the HSRB, consistent with approaches taken by the WHO and EU, should recommend that EPA not apply any duration adjustment to the point of departure (POD) when deriving acute and sub-chronic exposure values.

[24] See HSRB Final Report, Mar. 31, 2023, available at: https://www.epa.gov/system/files/documents/2023-03/HSRB%20Oct%20Report%20Final.pdf.
[25] See EPA May 18, 2023 presentation to the HSRB at slide 28 where EPA cites the low concentration data from the Andersen and Mølhave (1983) to support the need for duration adjustment, available at: https://www.epa.gov/system/files/documents/2023-06/HSRB%205-18-2023%20WOE%20acute%20inhalation%20HCHO%20discussion.pdf.
[26] See EPA WOE Acute Inhalation HCHO Discussion slides, at slide 29, available at: https://www.epa.gov/system/files/documents/2023-06/HSRB%205-18-2023%20WOE%20acute%20inhalation%20HCHO%20discussion.pdf and also see EPA Weight of Evidence for Acute and Peak Inhalation Endpoints, at page 13, available at: https://www.epa.gov/system/files/documents/2023-04/3a.%20Formaldehyde%20WOE%20for%20Acute%20and%20Peak%20Inhalation%20Endpoints_2023-04-23.pdf.

Healthy Young Adults Are the Sensitive Subpopulation for Formaldehyde Irritation

An evaluation of the best available science, including consideration of the mechanism by which formaldehyde causes sensory irritation, supports the fact that healthier and younger populations will be more sensitive to formaldehyde irritation than older adults.[27] As Dr. Dalton, an expert in odor and sensory irritation, describes in her comments that because there is a decline in olfactory and trigeminal (chemesthetic) sensitivity with age and age-related diseases, a younger and healthier population will have lower thresholds for odor detection and sensory irritation.[28] Studies have also shown that asthmatics are not more sensitive to formaldehyde.[29] In agreement with this understanding of the science, in EPA's assessment of the pesticide chloropicrin, where sensory irritation was the endpoint used to set a regulatory level, EPA acknowledged that young adults were the most sensitive subpopulation.[30]

We recommend that the HSRB take this important and unique information into account when providing final comments to EPA on the shortcomings of studies that included only healthy younger populations. The best available science, consistent with OPP's previous evaluations, tells us that these populations will indeed be the most sensitive to formaldehyde's irritancy effects.

When Using Sensory Irritation as a Critical Effect, Uncertainty Factors Are Not Necessary

Consistent with the fact that controlled human exposure studies that measure sensory irritation are routinely approved by academic institutions and human subject review boards throughout the US, sensory irritation is considered to be a mild reversible effect that does not meet the EPA definition of an adverse health effect, but can be used to set a lower bounding on potentially adverse effects, without the application of uncertainty factors.[31]

This determination has precedent in other OPP determinations, as exemplified in the amended Clororpicrin RED[32] where it is stated:

> Based on the human study, a margin of exposure (MOE) of 1 defines the Agency's level of concern (LOC) for acute inhalation exposure. The uncertainty factors have been removed due to a) chloropicrin's mode of action (MOA) of sensory irritation,[2] and b) evaluation of the most sensitive human subpopulation to sensory irritants (young adults, average age 23).[3] The Agency has high quality data that shows at 0.15 ppm (which corresponds to an MOE of 0.50) humans

[27] See comments from Dr. Dalton, provided to EPA on June 13, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0086
[28] *Id*.
[29] *Id*.
[30] See EPAs *Amended Registration Eligibility Decision(RED) for Chloropicrin*, 2009, at page 21, where EPA states "[t]he uncertainty factors have been removed due to a) chloropicrin's mode of action (MOA) of sensory irritation, and b) evaluation of the most sensitive human subpopulation to sensory irritants (young adults, average age 23)," available at: https://www.regulations.gov/document/EPA-HQ-OPP-2007-0350-0396.
[31] For additional information, see presentation from Dr. James Sherman presented to the HSRB May 18, 2023, and also submitted to the HSRB Designated Federal Official, Tom Tracy on May 18, 2023.
[32] *Id*.

> begin to sense chloropicrin without leading to more serious effects. While there are uncertainties about the effects of chloropicrin at higher concentrations and at exposure durations longer than 1 hour, data do suggest that effects would not become more severe unless the concentration of chloropicrin increases. Therefore, the Agency is confident that the human study provides high quality information regarding the dose-response in humans at the levels that lead to minor, reversible effects.

When PODs are derived using sensory irritation as the critical effect, EPA and the public can be assured that preventing exposures above this level will also prevent the occurrence of adverse effects that only occur progressively at higher air concentrations. PODs derived using sensory irritation endpoints should be considered to be No Observed Effect Levels (NOELs), rather than No Observed Adverse Effect Levels (NOAELs). In the case of the EU and the WHO, these endpoints were considered sentinel effects. As EPA shows in their background documentation, no uncertainty factors are needed when using a sentinel effect or NOEL.[33]

Using sensory irritation as the POD is a health protective approach. Considering this and the strong database that exists showing when sensory irritant sentinel effects occur in sensitive subpopulations, the HSRB should recommend to EPA that the POD for sensory irritation can be used as a lower bounding on potential adverse effects and no additional uncertainty factors need to be applied when using sensory irritation as the critical effect.

HSRB and EPA Should Seek to Coordinate Peer Review Activities related to Formaldehyde

As noted by public commenters on May 18, EPA's effort to conduct joint risk assessment activities for formaldehyde under the IRIS, FIFRA, and TSCA programs should be accompanied by a more coordinated approach to peer review of key issues of common interest. These include the Congressionally directed roles of the Science Advisory Committee on Chemicals (established in Section 26(o) of TSCA to "provide independent advice and expert consultation… with respect to the scientific and technical aspects of issues related to implementation" of TSCA), the Science Advisory Board, SAB's Agricultural Science Committee (required to conduct peer review activities of certain EPA work products under TSCA and FIFRA pursuant to the Environmental Research, Development, and Demonstration Authorization Act), as well as the ongoing NASEM review of EPA's formaldehyde assessment. Part of this coordination should focus on the inclusion of statutorily relevant and scientifically significant charge questions to satisfy scientific standards under multiple laws.

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[33] See EPA Weight of Evidence for Acute and Peak Inhalation Endpoints, at page 3-4, available at: https://www.epa.gov/system/files/documents/2023-04/3a.%20Formaldehyde%20WOE%20for%20Acute%20and%20Peak%20Inhalation%20Endpoints_2023-04-23.pdf.

Thank you again for your service to the HSRB. Should you have any questions, I would welcome the opportunity to speak with the HSRB and provide any additional information that may be helpful. I can be contacted at sahar_osman-sypher@americanchemistry.com.

Regards,

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On Behalf of the ACC Formaldehyde Panel