EPA Human Studies Review Board (HSRB)
July 26, 2023 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A.)
Date and Time: Wednesday, July 26, 2023, 1:00 to 4:00 p.m. EDT.
Location: Via Zoom
Purpose: The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subjects research.
HSRB Website: https://www.epa.gov/osa/human-studies-review-board

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Wednesday, July 26, 2023:

A. Meeting Topics and Charge Questions

Topic: EPA Weight of Evidence for Acute and Peak Inhalation Endpoints

> **Weight of Evidence Charge**: OCSPP has developed a weight of evidence for acute inhalation endpoints for formaldehyde that considered multiple studies and proposed acute inhalation PODs for three durations (15-minute peak, 8-hour, and 24-hour PODs). Please comment on the use of the four studies reviewed by the HSRB (Kulle et al. 1987; Andersen and Mølhave 1983; Lang et al. 2008; Mueller et al. 2013) in the weight of evidence from OCSPP for acute inhalation endpoints and the proposed PODs in Table 3.

Topic: May 16-18, 2023 HSRB Report

- Mueller, J.U., Bruckner, T., and Triebig, G. (2013) Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males. Int Arch Occup Environ Health 86:107–117. DOI 10.1007/s00420-012-0745-9
- Lang, I., Bruckner, T., and Triebig, G. (2008) Formaldehyde and chemosensory irritation in humans: A controlled human exposure study. Regulatory Toxicology and Pharmacology 50:23–26. DOI:10.1016/j.yrtph.2007.08.012

B. Convene Meeting and Introduction of Members

Tom Tracy, DFO, EPA HSRB, OSAPE

Mr. Tom Tracy, DFO for HSRB, called the meeting to order at 1:00 p.m. EDT. He introduced the meeting, outlined the Federal Advisory Committee Act procedures, and performed a roll call of meeting participants. The following members and observers were present:

HSRB members
Lisa Corey, Ph.D., Co-Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (National Institute of Standards and Technology) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Chad Cross, Ph.D. (University of Nevada – Las Vegas) Philip Day, Ph.D. (University of Massachusetts, Chan Medical School) Nicole Deming, J.D., M.A. (Case Western Reserve University, School of Medicine) Thomas Lewandowski, Ph.D. (Gradient) Srikumaran Melethil, Ph.D., J.D. (University of Missouri – Kansas City) Sinziana Seicean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) David Williams, Ph.D. (Oregon State University)
EPA staff members
John Allran (EPA, OPP) Michelle Arling (EPA, OPP) Rochelle Bohaty (EPA, OPP) Deborah Burgin (EPA, OPP)

HSRB members
Lexie Burns (EPA, OSAPE) Jeffrey Dawson (EPA, OPP) Timothy Dole (EPA, OPP) Elizabeth Donovan (EPA, OPP) Judy Facey (EPA, OPP) Myles Hodge (EPA, OPP) Monique Perron (EPA, OPP) Colleen Rossmeisl (EPA, OPP) Dana Sackett (EPA, OPP) Monique Tadeo (EPA, PHREO) Tom Tracy (EPA, OSAPE) Susanna Wegner (EPA, OPP)
Members of the public, representatives of research sponsor, and research team:
Nancy Beck (Hunton Andrews Kurth LLP) Pamela Dalton (Monell Chemical Senses Center) James Damewood (Dupont Chemical) Stewart Holm (American Forest and Paper Association) Angelina Guiducci (ICF, Contractor Support) Debra Kaden (Ramboll) Afroditi Katsigiannakis (ICF, Contractor Support) Sahar Osman-Sypher (American Chemistry Council) Emily Pak (ICF, Contractor Support) James Sherman (Celanese) Clint Woods (Hexion)

C. Meeting Administrative Procedures

Tom Tracy, DFO, HSRB, OSAPE

Mr. Tom Tracy reviewed the Zoom platform tools and features and stated the purpose of the meeting was to review the EPA Weight of Evidence for Acute and Peak Inhalation Endpoints and the paper by Mueller et al., "Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males." He noted that minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of July 26, 2023.

D. Meeting Process

Lisa Corey, Ph.D., HSRB Co-Chair
Julia Sharp, Ph.D., HSRB Co-Chair

Dr. Lisa Corey welcomed the Board and outlined the goals of the meeting. The goals were to (1) review EPA's Weight of Evidence for Acute and Peak Inhalation Endpoints report and reach a response consensus to EPA's charge question and (2) review and approve the final draft of the

May report.

E. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Michelle Arling shared there were no updates from OPP. Ms. Arling added that EPA is reviewing two dermal patch studies for potential review by the Board in October. EPA will share these studies with the Board about a month before the meeting.

F. Public Comment

Mr. Tom Tracy briefly introduced the public commenters. Mr. Tracy then invited the first public commenter, Mr. Clint Woods, to begin.

Mr. Woods introduced himself as the Global Director of Product Services and Regulatory Affairs at Hexion Inc. Mr. Woods thanked the Board for their consideration of public comments and noted his presentation focuses on the draft HSRB interim weight-of-evidence report on formaldehyde point of departure (POD).

Mr. Woods discussed key points taken from the May HSRB meeting public comment period related to consistency and coordination. Mr. Woods emphasized the critical role of the HSRB under its charter to provide advice on human research used for regulatory purposes under the Federal Insecticide, Fungicide, and Rodenticide Act and section 408 of the Federal Food, Drug and Cosmetic Act. He also emphasized the differences between EPA and its peer review venues and highlighted the broader scope of the HSRB under the updated Toxic Substances Control Act (TSCA).

Mr. Woods supported two recommendations in the HSRB draft report. The first recommendation indicated that EPA should take a more coordinated approach with other entities in establishing PODs for formaldehyde. Consequently, Mr. Woods suggested coordination with the National Academy of Sciences, Engineering, and Medicine (NASEM) committee on Review of EPA's 2022 Draft Formaldehyde Assessment. Mr. Woods also mentioned that TSCA has established EPA's Science Advisory Committee on Chemicals (SACC), a likely venue for review of other aspects of formaldehyde risk evaluation through EPA's standing Science Advisory Board. Mr. Woods also mentioned the existence of standing committees that review proposed actions under TSCA and agricultural regulatory developments, e.g., the Agricultural Science Subcommittee that could play an important role in EPA's hazard and risk assessment activities.

Mr. Woods also reflected on a second recommendation from the draft HSRB report that focuses on how other agencies have chosen to use different studies for the basis of their acute exposure guidelines. These guidelines include Lang et al. (2008) with support of other studies. Other agencies have also opted to use low or no uncertainty factor in their assessments based on Lang et al. (2008). Mr. Woods provided a list of additional federal and state regulatory programs with existing short-term exposure limits. It was noted that the HSRB could help EPA with TSCA coordination requirements by encouraging the Agency to engage with other parts of the federal

government and state government. Mr. Woods also mentioned relevant executive orders and key provisions of TSCA that encourage EPA to move in the direction of interagency coordination.

Dr. Lisa Corey asked if the Board had questions for Mr. Woods. There were none. Dr. Corey then invited Dr. James Sherman to begin his public comment.

Dr. Sherman introduced himself as a Science Fellow, Toxicology and Product Stewardship for Celanese Corporation. Dr. Sherman provided additional support for his previous public comments related to sensory irritation, specifically OPP's risk evaluation for chloropicrin reregistration eligibility decision (RED). Dr. Sherman started his presentation by thanking the HSRB for their efforts in helping OPP maintain a reputation for conducting scientifically sound weight-of-evidence determinations. Dr. Sherman noted that Celanese fully supports the HSRB's draft recommendations and that the report is further supported by OPP precedent.

Dr. Sherman reviewed chloropicrin's RED. He emphasized that "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, and b) evaluation of the most sensitive human subpopulation to sensory irritants (young adults, average age 23)." It was also highlighted that "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."

Dr. Sherman concluded his presentation by asking the HSRB to consider including a recommendation that the formaldehyde assessment be consistent with prior EPA OPP determinations for chloropicrin with respect to an MOE of 1 for sensory irritation effects, receptor mediated sensory irritation is concentration and not time dependent, and young healthy adults are the most sensitive subpopulation for sensory irritation.

Dr. Corey asked if the Board had questions for Dr. Sherman.

- **Thomas Lewandowski**: Do we have evidence to indicate similar MOAs between chloropicrin and formaldehyde?
    - **James Sherman**: I believe the MOA for both chemicals involves the TRP receptors family. Sustentacular cells in the epithelium are involved for formaldehyde. Formaldehyde can be detected in the mucus layer via external receptors.

Dr. Corey then invited Dr. Debra Kaden to begin her public comment.

Dr. Kaden introduced herself as a Toxicologist at Ramboll U.S. Consulting. Dr. Kaden disclosed that she is speaking at the request of the American Chemistry Council (ACC) but the ideas and opinions in her presentation on studies examining sensory and irritating effects of formaldehyde on humans are her own. Dr. Kaden thanked the HSRB for consideration of her past public comments and stated the present comment's purpose was to compare study designs across the three studies she discussed during the previous meeting. These include the two chamber studies

with human volunteers (Mueller et al., 2013; Lang et al., 2008) and one observational study in adult and teens (Hanrahan et al., 1984).

Dr. Kaden indicated that exposure differs greatly between chamber studies and observational studies. Exposure was controlled, measured, and contrasted to contemporary health symptoms (i.e., symptoms that occur during the time of exposure) in the chamber studies. This strengthened the link between exposure and the symptoms observed. Additionally, exposures were higher than those typically found in the environment and co-exposures were known in the chamber studies. Exercise was also included in these study designs to consider the impact of breathing rates in cumulative doses. In contrast, the exposure was inferred through measurements in a residence on a single day in the observational study. The latter assumes exposures during the study were the same as exposures that occurred previously. Co-exposures were assessed by a questionnaire based on recall and most likely did not reflect reality, and exercise status and time outdoors were unknown for this study.

Another difference in these study designs was the number of participants. While it is easier to include a larger number of participants in observational studies, the Hanrahan et al. (1984) study did not. Only 61 individuals from 42 homes returned the questionnaire and 20 individuals were smokers (a source of formaldehyde) and more probably lived with smoker. Thus, the number of participants in this observational study is comparable to the combined number of participants in the two chamber studies and the typical advantage from an observational study with a larger sample size was not present in Hanrahan et al. (1984).

Dr. Kaden mentioned that measured health endpoints also differed between the chamber and observational studies. The chamber studies measured both objective and subjective symptoms which were assessed at the time of exposure. In comparison, the observational study was dependent upon recall of symptoms of past exposure at any time since moving into the home. It was unclear what the exposures were at the time symptoms were experienced (including potential co-exposures). The only recalled symptom to show significant association with the single day recent formaldehyde concentration was eye burning and irritation. Additionally, half of the exposure measurements were below the second data point in the dose-response graph, which weakens the model.

Dr. Kaden concluded that controlled human exposure studies are the gold standard of toxicology studies due to careful control of exposure parameters and contemporary assessment of symptoms. Both chamber studies used multiple exposure scenarios for each participant and each participant served as their own control group, strengthening these studies. Many other agencies recognize these chamber studies as the most relevant in terms of formaldehyde risk assessment.

Dr. Corey asked if the Board had questions for Dr. Kaden. There were none. Dr. Corey invited Ms. Sahar Osman-Sypher to begin her public comment.

Ms. Osman-Sypher introduced herself as a Senior Director at the ACC and mentioned that she is speaking on behalf of the ACC Formaldehyde Panel. Ms. Osman-Sypher thanked the HSRB for

their attentiveness to public comments during the May meeting. The ACC Formaldehyde Panel followed up on the May meeting with a letter outlining additional information that Ms. Osman-Sypher presented during the current meeting.

Ms. Osman-Sypher reminded the HSRB that TSCA requires EPA to "use scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed in a manner consistent with the best available science." Key points from the best available science relating to formaldehyde exposure were discussed, including the fact that formaldehyde does not follow Haber's Law and that healthy young adults are the most sensitive subpopulation for irritation. It was also reiterated that controlled chamber studies are considered the gold standard for deriving safe exposure limits for humans. Ms. Osman-Sypher indicated that both chamber studies (Mueller et al., 2013; Lang et al., 2008) have been considered the best available science by multiple authoritative bodies.

Lastly, Ms. Osman-Sypher discussed the importance of public input in all Federal Advisory Committee Act (FACA) committees, including the HSRB. She thanked the Board for their consideration of public comments and providing sound scientific recommendations that are clear and actionable.

Dr. Corey asked if the Board had questions for Ms. Osman-Sypher.

- **Srikumaran Melethil**: You made a statement that formaldehyde does not follow Haber's Law. Is this true for all concentrations of formaldehyde?
    - **Sahar Osman-Sypher**: The next presentation will address this question.
    - **Stewart Holm**: There is no evidence that formaldehyde follows Haber's Law at low or high concentrations. EPA has used a particular study to support this statement which will be covered in my presentation.

Dr. Corey invited Mr. Stewart Holm to begin his public comment.

Mr. Holm introduced himself as Chief Scientist at the American Forest and Paper Association, American Wood Council. Mr. Holm recalled that other boards and committees have discussed the issues regarding formaldehyde irritation and Haber's Law. Other bodies have also investigated this relationship, including the Draft 2022 IRIS Assessment and the EU Scientific Committee on Occupational Exposure Limits (SCOEL). The IRIS assessment concluded that there was no evidence of a time-dependent relationship with formaldehyde. The EU SCOEL concluded sensory irritation is a concentration- rather than a cumulative dose-driven effect.

Mr. Holm indicated that EPA has relied on Anderson and Mølhave (1983) to support the idea that lower concentrations of formaldehyde adhere to Haber's Law. Mr. Holm then presented NASEM's decision upon their review of Anderson and Mølhave (1983), concluding that they found no compelling evidence of Haber's Law at lower concentrations of formaldehyde.

Mr. Holm concluded his public comment by offering support of the HSRB's recommendation that OCSPP change their approach, which assumes that Haber's Law would apply at low doses

and not high doses. Additionally, Mr. Holm indicated that a duration adjustment should not be applied.

Dr. Corey asked if the Board had questions for Mr. Holm.

- **Thomas Lewandowski**: My understanding is that formaldehyde is not the only chemical where Haber's Law does not relate to sensory irritation. Instead, it is a general property of irritation as a toxicological phenomenon. Is this correct?
    - **Stewart Holm**: That is my understanding as well.
    - **Thomas Lewandowski**: Therefore, we are not talking about a formaldehyde specific situation, but instead anything relating Haber's Law to irritation is questionable.
    - **Stewart Holm**: In terms of general contact irritation, that is correct.

Dr. Corey then invited the last public commenter, Dr. Pamela Dalton, to begin.

Dr. Dalton introduced herself as Principal Investigator at Monell Chemical Senses Center. Dr. Dalton disclosed that she was speaking at the request of the ACC but the ideas and opinions in her presentation were her own. Dr. Dalton thanked the HSRB for their review of the formaldehyde literature and stated that she wanted to provide additional evidence to address the inclusion of young participants in the chamber studies. She indicated that the inclusion of young individuals in these controlled human exposure studies is scientifically justified because aging is associated with a sensitivity decline to odor and irritant sensation. Dr. Dalton then explained sensory irritation threshold. This threshold is the concentration at which an individual can identify which nostril has been stimulated when clean air and a chemical are being applied to different nostrils at the same time. She stated that this threshold declines with age. Dr. Dalton then provided additional evidence that older individuals require higher concentrations to detect formaldehyde. Dr. Dalton concluded that the HSRB should not be biased against the use of young individuals in the controlled exposure studies under review. Lastly, Dr. Dalton recommended the HSRB review the literature on sensitive populations for chemosensory irritation, as it will apply to a broad range of chemicals.

Dr. Corey asked if the Board had questions for Dr. Dalton.

- **Thomas Lewandowski**: Can you address sensory irritation in asthmatic individuals?
    - **Pamela Dalton**: I have tested individuals with moderate persistent asthma for the sensory irritation threshold of many chemicals and have found no difference except for age-related differences. I have not found that asthmatic individuals are more or less sensitive to sensory irritation than individuals without asthma.
    - **Thomas Lewandowski:** Any thoughts on why there is no difference in sensitivity to sensory irritation between individuals with and without asthma?
    - **Pamela Dalton**: The respiratory issues involved with asthma are independent of the response of the TRP receptors and trigeminal nerve response in the eyes and the nose.

- **Stewart Holm**: Another study included asthmatic individuals as a sensitive subpopulation and the outcome was similar to non-asthmatic individuals up to 3 ppm.
- **Debra Kaden**: The WHO working group on formaldehyde also concluded that asthmatic individuals were not more sensitive to formaldehyde than were non-asthmatic individuals.

Dr. Corey thanked the public commenters and reminded the HSRB that they have access to the previous presentations and letters from public commenters.

G. Review and Finalize HSRB Report on Weight of Evidence (WoE)

Lisa Corey, Ph.D., HSRB Co-Chair
Julia Sharp, Ph.D., HSRB Co-Chair

Dr. Lisa Corey discussed the goals from the previous meeting and shared the May meeting document. Dr. Corey outlined the purpose of the current smaller working group: to address EPA's charge question and develop a consensus document with recommendations. Dr. Corey then introduced Dr. Chad Cross to review the WoE agenda. Dr. Cross read the WoE charge to the Board regarding acute inhalation endpoints for formaldehyde. Dr. Cross noted that the Board's initial response was that the four studies discussed in the document appeared to be appropriate in the use for the WoE for determining the PODs for formaldehyde. Additionally, EPA should consider limitations that the Board has identified. Dr. Cross then introduced the next section in the WoE document, which provides an overview of formaldehyde. Dr. Cross emphasized definitions relevant to the meeting, including the EPA IRIS definitions for adverse effect and acute exposure. Dr Cross summarized the four studies previously reviewed by the HSRB to provide context for their recommendations.

Dr. Cross summarized the Kulle et al. (1987) study including methods and findings and the HSRB findings that it was scientifically and ethically sound and noted EPA's medium confidence level. The HSRB reached similar conclusions for Andersen and Mølhave (1983) and Lang et al. (2008), though some endpoints in Andersen and Mølhave (1983) could not be evaluated due to issues with unavailable data and inclusion criteria. The HSRB determined the findings from Mueller et al. (2013) provided reliable semi-quantitative data for determining a POD for inhalation exposures to formaldehyde.

Dr. Cross mentioned the two other studies reviewed by EPA, Hanrahan et al. (1984) and Liu et al. (1991). EPA did not charge HSRB to review these studies because they were not intentional human exposure studies, though Dr. Cross summarized each for completeness of the Working Group's WoE evaluation. He then introduced Dr. Corey and Dr. Julia Sharp to discuss HSRB comments.

Dr. Corey explained the importance of answering the WoE charge question by EPA even for the studies done by Hanrahan et al. (1984) and Liu et al. (1991) for appropriate context. Dr. Corey provided a summary of the HSRB comments for these studies regarding endpoints and studies

used. Dr. Corey identified the term "adverse" as unclear when describing sensory endpoints versus acute human health exposure risk. Dr. Corey emphasized the HSRB felt chamber studies and controlled studies are stronger for use as the basis for PODs or WoE. Dr. Corey reviewed comments regarding flaws in study design and data collection for the Hanrahan et al. (1984), Liu et al. (1991), and Mueller et al. (2013) studies and noted the use of the Lang et al. (2008) study by other agencies.

Dr. Corey introduced the next category, POD Derivation Assumptions. She indicated that EPA determined Haber's Law to be applicable to formaldehyde at low levels based on findings from Andersen and Mølhave (1983), but not at high levels of formaldehyde. Dr. Corey emphasized that the discussion should be if the Board agreed with EPA, noting that the initial discussion during the May meeting suggests that the Board does not agree with EPA regarding low levels and Haber's law and a duration adjustment. Dr. Corey then asked for input on discussion points.

- **Albert J. Allen:** I would like to first thank those who gave public comment. I think that there are three items that we may consider adding to the recommendations based on the comments:
    - Addressing the inclusion of younger participants involved in sensory irritation studies, if that is appropriate. I found the information presented by Pamala Dalton very helpful.
    - How to approach the absence of Haber's Law in Jim Sherman's comments aligned with our recommendation in terms of the analysis without Haber's Law. This has already been addressed through EPA's Office of Pesticide Programs.
    - Finally, to ensure a collaborative approach, sharing the report with the National Academies of Sciences to consult with other agencies and other committees.
- **Srikumaran Melethil:** Would you clarify something on formaldehyde at low concentrations and Haber's Law? Are we changing that?
    - **Lisa Corey:** Yes, EPA made a distinction that there is a difference, saying formaldehyde applies to Haber's Law at low levels, but that it did not at high levels. Our disagreement is that we did not see that Haber's Law applies at low levels of formaldehyde based on the one study from Andersen and Mølhave (1983). We did not see their findings as strong enough to support this conclusion.
- **Thomas Lewandowski:** I agree with what Dr. Allen said. In parallel, I noticed we do not reach a conclusion regarding the Hanrahan et al. (1984) study. Also, we should put page numbers in this document. We say that EPA should provide a rationale regarding this study, and we did not fully evaluate this study. It is not a study we would normally evaluate to the full extent. Commenting on this study, which is normally outside our charge, felt like a slippery slope, but we are not being very specific in terms of what we would say about the Hanrahan et al. (1984) study. Lastly, the benchmark concentration (BMC) divided by two was not clear to me. Normally, a benchmark concentration has a response rate specified and this one does not.

- **Julia Sharp:** This is part of the review, and we have specific recommendations about BMC/2 that Dr. Corey will discuss.
- **Thomas Lewandowski:** You do. That is what I was flagging. Normally for BMD you would say, e.g., "BMD 10," and this is instead BMC without any response rate specified.
- **Lisa Corey:** The concern that we had with this was that there was more information in the ICF statistical analysis. However, EPA's document stated this was not a common practice but there was no discussion of what is common practice or how this differed. In the separate document from Dr. Cohen, he noted that it was arbitrary. That was a missing a point of clarity.
- **Julia Sharp:** It was unclear where the BMC/2 came from. It was unclear why the denominator was two, and what is common practice. Could you help me further address your question, Dr. Lewandowski?
- **Thomas Lewandowski:** Yes. Normally a BMC is the result of modeling and working with a concentration that is associated with a specific response rate. For example, you may have a BMD 10. Typically, there might be some indication of what the response rate of that concentration would be. I am unclear with what that BMC/2 means.

Dr. Sharp noted they would return to the ICF document, asking EPA directly to respond later in the meeting. She also asked Dr. Lewandowski to reiterate his concerns with the Hanrahan et al. (1984) study review.

- **Albert J. Allen:** We may want to add to the paragraph regarding Hanrahan et al. (1984), stating that the HSRB did receive a public comment from Dr. Kaden, who indicated the advantages of a chamber interventional study approach over an observational epidemiological study. I would agree with those observations and thought she laid out the differences clearly. Maybe we can acknowledge that in the report.

Dr. Corey recognized Dr. Allen's points, noting that it is one of their recommendations. Dr. Lewandowski asked that the recommendation list the studies by name when noting the chamber studies that should be included, helping with the vagueness of the language. Dr. Cross agreed with Dr. Allen's suggestions and the comments in Dr. Kaden's slides that made the distinctions. Dr. Corey returned to a point made by Dr. Allen about the sensitive subpopulation, asking if there is anything the Board wants to add in terms of recommendations, reading Dr. Allen's additions. Dr. Corey recommended the Board specify the distinction of younger versus older participants. Dr. Sharp shared the ICF statistical analysis review of Andersen and Mølhave (1983) and Kulle et al. (1987, p. 25), which states that the use of BMD/2 is arbitrary, and that the true BMDL is a lower confidence for the dose at which the extra risk is 10%. Dr. Lewandowski noted that it was an omission of the authors to not include the information, and the document should specify the BMC of 10. Dr. Monique Perron of EPA confirmed it was a BMC 10, and that this approach was taken from the IRIS assessment to ensure a single Agency approach for consistency. Dr. Perron noted the original report specified nuances in differences between studies

and that there is an explanation in the IRIS assessment concerning the correlated measures not being accounted for, thus impacting the confidence level and the initial decision.

- **Thomas Lewandowski:** So, the BMC 10 is based upon the observation of mild irritation, and it was a limited irritation threshold seen in these studies?
    - **Monique Perron:** Correct, this is all based off the sensory irritation effects that we are seeing.
    - **Thomas Lewandowski:** So, a 10% response rate of something that is considered mild which goes to the adverse effect question.
        - **Monique Perron:** Correct, and I want to remind everyone that because that is part of the IRIS review, it is also undergoing review by NASEM, and we anticipate seeing comments from that review.
        - **Thomas Lewandowski:** Thank you.
- **Julia Sharp:** Is what I have written sufficient, or should we make a recommendation in the EPA and IRIS document that they use BMC 10?
    - **Thomas Lewandowski:** I feel like that is the normal process.
    - **Monique Perron:** The BMC is not the lower limit; that is the central estimate. It is the concentration at which subjects reported a 10% increase in their symptoms above the clean air exposure background. You might also want to use concentration instead of dose for consistency. To specify, I do not want to have confusion over the BMC/2 that is in parenthesis, so benchmark concentration is the estimate for the concentration, not for the BMC divided by 2. If you are trying to define BMC, benchmark concentration is the estimate for that. BMC/2 was IRIS's approach to defining a lower limit.
        - **Thomas Lewandowski:** Julia you could actually say in the parenthetical say "where BMC is the benchmark concentration" basically saying what BMC is.

Dr. Corey read through the recommendations of the Board. HSRB recommends that EPA adopts a more coordinated approach with other entities, such as NASEM and TSCA SACC, to establish PODs for formaldehyde. HSRB suggests that EPA provides clarification on the use of sensory endpoints as adverse effects in the WOE review, considering sensory irritation PODs as a lower bound for potential adverse effects without the need for uncertainty factors. Dr. Corey noted that HSRB was not tasked with determining the uncertainty factors and that this may need to be discussed further. Additionally, HSRB advises EPA to justify its use of the BMC/2 value from the Kulle et al. (1987) study for 15-minute peak exposure PODs, as this value was originally derived for a 3-hour exposure period. HSRB disagrees with EPA's assumption of Haber's Law for formaldehyde and advises against making duration adjustments to develop the PODs. HSRB recommends using exposure levels from controlled chamber studies rather than observational studies due to their preferred study design and greater scientific rigor.

Dr. Allen provided an addition to the first recommendation, stating that the HSRB recommends that EPA shares this report with NASEM and TSCA SACC, and that EPA consults with other state and federal agencies, as appropriate, when working on formaldehyde guidance. Dr. Corey

and Dr. Sharp agreed with Dr. Allen's addition and asked for the Board to address EPA's comment regarding the agency's PODs. Dr. Corey specified that the NASEM committee is looking at the BMC/2 approach, emphasizing that coordination is important, agreeing with the second section of EPA's addition, and agreed that Dr. Allen's addition provides more clarification.

- **Srikumaran Melethil**: To address Dr. Sharp's question on what defines "young," the American Psychological Association defines young adulthood as 20 to 35 and middle adulthood as 36 to 64, so maybe we just need to put an age range instead.
    - **Albert J. Allen**: Even if you do that, you will want to use what the data suggests, which is 18 years old up to the fifth decade. You should not use an arbitrary range when you have data that points to a range of ages that are more sensitive.
    - **Srikumaran Melethil**: I agree we could use the data that she presented but specify a range. That is what I meant by using an age group.
        - **Albert J. Allen**: I think you must use "young" to some extent, because that is what the public comments used, but specify the range as well. The problem is we only have the fifth decade, which is vague.
        - **Lisa Corey**: Dr. Sharp has "aged <50 years old" in a comment of the document. I agree this needs to be based on specific data for formaldehyde and not just a generic age range for categorization.

Dr. Lisa Corey returned to the first recommendation to confirm the Board thought it was actionable. Dr. Allen specified the language by adding "regarding advice on establishing PODs." Ms. Arling elaborated that, in addition to considering future coordination with other governing bodies, EPA should also consider recent recommendations from other bodies, as many peer and independent reviews have occurred for formaldehyde. Additionally, specificity about what a coordinated approach between entities might look like would be helpful, specifically for OPP and OCSPP.

- **Srikumaran Melethil**: I agree with the concept, but I wonder if we are asking EPA to do the impossible. Is the number of organizations they need to consult too much?
    - **Julia Sharp**: I believe our first public comment has a list of recommendations.
        - **Albert J. Allen**: Yes, there was a list of organizations to consult. That was Clint Woods.

Dr. Sharp reviewed the list of organizations from Clint Woods' presentation and added to the document, recommending providing a copy of the HSRB report to NASEM and TSCA SACC in addition to potentially hosting a public workshop.

- **Julia Sharp**: Here are the three items from Clint Woods. Did I capture that?
        - **Clint Woods:** You did, thank you.
    - **Lisa Corey**: Should we include more agencies?
        - **Srikumaran Melethil**: Could we leave this to EPA to consider, because this is more a policy matter than a science matter.

    - **Thomas Lewandowski**: I think we need to specifically mention NASEM, because there is active work there that overlaps with ours. Beyond that, I tried to tie it to state and federal agencies, but there may be others as well.
    - **Srikumaran Melethil**: My concern is that we have not looked at those documents. We are using a third party to tell us what to recommend.
    - **Albert J. Allen**: Which documents? We looked at the draft report from TSCA SACC and referenced some material from NASEM.
- **Michelle Arling:** I want to clarify that we will take into consideration the recommendations from all the federal panels as we move forward within the OPPS and OPPT, and our assessment will go out for public comment again. So, we already have planned to look at the recommendations that have been made by other bodies. Our decisions will be documented and discussed moving forward if there are overlapping or conflicting recommendations. Does that help?
    - **Albert J. Allen**: It was helpful to us to have the draft recommendation from TSCA SACC to review, as well as past recommendations from NASEM. It may be helpful for them to review our draft. The concern is that all of these are running parallel, so it would be best to have each group aware. Another piece that I am hearing from the public comments is that there are lots of groups that look at this, and the concern from different sectors is that too many recommendations may result in diverging regulations. To me, that is a concern and a reason for us to share this information with these groups.

Dr. Corey asked if there were any additional suggested edits for clarification from the written recommendation. Dr. Allen mentioned considering a public workshop for additional feedback, if possible. Dr. Perron recognized the intentions of the Board's recommendations but noted that not all may be possible. The NAS will finalize their report soon and will not be able to review HSRB's recommendations before doing so. What goes to the TSCA SACC is still being considered, but having all the different review panels will not be possible with the current timeline and restrictions. Ultimately, the timing issues of this recommendation limit its feasibility and should be kept in mind. Dr. Allen responded that they were presented their charge in an unclear way, which left a lot of questions, and this challenge may be addressed in the future by coordination within the Agency. Dr. Perron clarified that EPA hopes to not have overlapping review, noting that the HSRB is the most appropriate external review panel given the subject matter. Dr. Allen's expressed the issue of the Board not being equipped to review two of the studies considered by the EPA, which is problematic for the final review. Dr. Corey recognized this concern and included this concern under future recommendations. Dr. Allen added one more modification to the fourth recommendation related to chloropicrin, and Dr. Sharp recognized it was a suggestion from Jim Sherman. Dr. Corey asked about the wording of the recommendations related to EPA coordination with other entities. No additional comments were made on the topic.

Dr. Corey then asked if the Board would like to make a specific recommendation related to uncertainty factors, considering it was not specifically part of the Charge and the limited information. Dr. Sharp read an EPA comment stating that this is a policy question and asking for clarification. Dr. Corey suggested language such as "consider" instead of "recommend." Dr.

Lewandowski emphasized the lack of clarity regarding EPA's goals, suggesting that the language be kept in place. Dr. Williams agreed with Dr. Lewandowski, stating the more definitive language of the recommendation should be left in, and it is a science issue. Dr. Perron specified that study selection is one thing, the application of different uncertainty factors is another, and rather a policy question. The study selection and PODs are what the Board's charge is. The current language tells EPA to state something, and Dr. Perron suggested rewording. Dr. Lewandowski asked for clarification about what EPA would not like to be addressed in the with the charge in the future.

Dr. Corey asked the HSRB if members would change the word from "recommends" to "considers", and whether any additional specificity is needed. Dr. Williams suggested that they remove "EPA state that" language, and the Board agreed. Dr. Corey reconfirmed the observations about BMC/2 and Haber's Law, duration adjustment, and chamber studies versus observational studies. The Board gave no additional suggestions for clarifications or new recommendations. Dr. Corey read the charge question and drafted response, and noted some editing would be done, but the conceptual issues would not change. The Board voted on the current response using zoom responses to agree or disagree. There was unanimous approval. Dr. Corey thanked the Board and appreciated the effort members contributed.

H. Review and Finalize HSRB Report on the research article by Mueller, Bruckner, and Triebig (2013)

Lisa Corey, Ph.D., HSRB Co-Chair
Julia Sharp, Ph.D., HSRB Co-Chair

Dr. Corey stated the next task for the HSRB was to finalize the May meeting report document. Dr. Sharp shared her screen with the draft report.

- **Julia Sharp**: There is a comment from Dr. Williams regarding hyper- and hypo-sensitivity. David, do you recommend we add clarification to this comment?
    - **David Williams**: No. I was confused when I went back and read that because the authors took measurements all the way through but only used the last measurement to make the median division between hyper- and hyposensitivity. I am okay with ignoring this comment since we have already criticized the use of "hyper" and "hypo" for other reasons.
    - **Lisa Corey**: The designation of "hyper" and "hypo" was confusing in comparison to the general population. However, it did not end up impacting the data for EPA's weight of evidence.
    - **David Williams**: No change needed.
- **Julia Sharp**: There is a comment from EPA that was also in the July weight-of-evidence comment period. The comment reads: "Where recommendations are made for EPA to provide additional information or clarification, is it the HSRB's intention that it is up to the Agency to determine the appropriate place for providing any additional justification/information?" Does the HSRB want to add page numbers to make this

clearer? Or is the HSRB satisfied with being vague?

- **Lisa Corey**: I am okay with allowing EPA the flexibility to choose where the most appropriate place to include clarification is in the final document.
- **Albert J. Allen**: When EPA uses the data, they need to justify that it is relevant to the general population.

- **Julia Sharp**: David had an additional comment on the HSRB response, but I believe this is the wording of the response the HSRB voted on in May. We do not normally change the responses after voting on them.
  - **David Williams**: That is fine. It was more of a comment than a suggested edit.
- **David Williams:** I had an additional comment. It appeared the no observed effect level (NOEL) was used for the 0.5 continuous and the adverse effect level (AEL) was used for the variable. I had thought it was referring to the same thing, but I see now that the NOEL is for objective eye irritation and the AEL is for variable exposures. No changes are needed.
  - **Lisa Corey**: You explained it correctly.
  - **Julia Sharp**: Thank you.
- **Lisa Corey**: There were some recommendations to evaluate additional studies. This was added to the Recommendation for Future Studies section of the report.
  - **David Williams**: Is this inconsistent with what we have said elsewhere?
  - **Albert J. Allen**: This goes back to the question of whether young adults are more sensitive than older adults to sensory irritation.
  - **David Williams**: I think we can still recommend this; however, remove the sentence discussing humans with asthma or preexisting skin sensitization.
  - **Albert J. Allen**: Although this is a recommendation that we voted on last time, the new information we have received justifies the change.
  - **Julia Sharp**: I am fine with updating recommendations. I prefer to not change the responses to the charge questions the HSRB has already voted on.

Dr. Corey asked the Board if there were additional comments on the draft report. There were no additional comments. The Board voted to approve the report as final, and a consensus was reached. Dr. Corey thanked the Board, EPA, and public commenters for their time and efforts. Mr. Tracy announced the next HSRB meetings will be held on August 23rd and October 11th – 13th.

I. Adjournment

Mr. Tom Tracy thanked the Board. The meeting adjourned at 3:49 p.m. EDT.

Attachment A: HSRB Current Committee Membership

Name	Title	Affiliation
Lisa Corey, Ph.D.	Senior Toxicologist	Intertox, Inc. Seattle, WA
Julia Sharp, Ph.D.	Mathematical Statistician	National Institute of Standards and Technology Fort Collins, CO
Albert J. Allen, M.D., Ph.D.	Consulting Specialist	Self-employed
Chad Cross, Ph.D.	Associate Professor In-Residence	University of Nevada Las Vegas, NV
Philip Day, Ph.D.	Assistant Professor	University of Massachusetts, Chan Medical School Worcester, MA
Nicole Deming, J.D., M.A.	Assistant Dean, Faculty Affairs and Human Resources	Case Western Reserve University, School of Medicine Cleveland, OH
Weiying Jiang, Ph.D.	Staff Toxicologist	California Environmental Protection Agency, Department of Pesticide Regulation Sacramento, CA
Thomas Lewandowski, Ph.D.	Principal	Gradient Seattle, WA
Srikumaran Melethil, Ph.D., J.D.	Professor Emeritus	University of Missouri-Kansas City Kansas City, MO
George Milliken, Ph.D.	President	Milliken Consultants Manhattan, KS
Sinziana Seicean-Boose, M.D., Ph.D., M.P.H.	Assistant Professor	Case Western Reserve University Cleveland, OH
Joseph Tuminello, Ph.D.	Assistant Professor	McNeese State University Lake Charles, LA
Eun Um, Ed.D.	President and CEO	AMSTAT Consulting San Jose, CA
David Williams, Ph.D.	Distinguished Professor	Oregon State University Corvallis, OR

Attachment B: Federal Register Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10408-01-ORD]

Human Studies Review Board (HSRB) Meetings—2023

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of public meeting.

SUMMARY: The Environmental Protection Agency (EPA), Office of Research and Development (ORD), gives notice of 2023 public meetings of the Human Studies Review Board (HSRB). The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of third-party human subjects' research that are submitted to the Office of Pesticide Programs (OPP) to be used for regulatory purposes.

DATES: Four three-day virtual public meetings will be held on:

1. February 15–17, 2023; and
2. April 18–20, 2023; and
3. July 26, 2023; and
4. October 11–13, 2023.

Meetings will be held each day from 1 p.m. to 4 p.m. Eastern Time. For each meeting, separate subsequent follow-up meetings are planned for the HSRB to finalize reports from the three-day meetings. These meetings will be held from 1 p.m. to 4 p.m. Eastern Time on the following dates: March 23, 2023; May 18, 2023; August 23, 2023; and November 16, 2023.

ADDRESSES: These meetings are open to the public and will be conducted entirely virtually and by telephone. For detailed access information and meeting materials please visit the HSRB website: *https://www.epa.gov/osa/human-studies-review-board*.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact the HSRB Designated Federal Official (DFO), Tom Tracy, via phone/voicemail at: 919-541-4334; or via email at: *tracy.tom@epa.gov*.

SUPPLEMENTARY INFORMATION:

Background

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act 5 U.S.C. App.2 section 9. The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of third-party human subjects research that are submitted to OPP to be used for regulatory purposes.

Meeting access: These meetings will be open to the public. The full agenda with access information and meeting materials will be available seven calendar days prior to the start of each meeting at the HSRB

website: *https://www.epa.gov/osa/human-studies-review-board*. For questions on document availability, or if you do not have access to the Internet, consult with the DFO, Tom Tracy, listed under **FOR FURTHER INFORMATION CONTACT**.

Special Accommodations. For information on access or services for individuals with disabilities, or to request accommodation of a disability, please contact the DFO listed under **FOR FURTHER INFORMATION CONTACT** at least 10 days prior to each meeting to give EPA as much time as possible to process your request.

How May I Participate in this Meeting?

The HSRB encourages the public's input. You may participate in these meetings by following the instructions in this section.

1. *Oral comments.* To preregister to make oral comments, please contact the DFO, Tom Tracy, listed under **FOR FURTHER INFORMATION CONTACT**. Requests to present oral comments during the meetings will be accepted up to Noon Eastern Time, seven calendar days prior to each meeting date. To the extent that time permits, interested persons who have not preregistered may be permitted by the HSRB Chair to present oral comments during the meetings at the designated time on the agenda. Oral comments before the HSRB are generally limited to five minutes per individual or organization. If additional time is available, further public comments may be possible.

2. *Written comments.* For the Board to have the best opportunity to review and consider your comments as it deliberates, you should submit your comments prior to the meetings via email by Noon Eastern Time, seven calendar days prior to each meeting date. If you submit comments after these dates, those comments will be provided to the HSRB members, but you should recognize that the HSRB members may not have adequate time to consider your comments prior to their discussion. You should submit your comments to the DFO, Tom Tracy listed under **FOR FURTHER INFORMATION CONTACT.** There is no limit on the length of written comments for consideration by the HSRB.

Topics for discussion. The agenda and meeting materials will be available seven calendar days in advance of each meeting at *https://www.epa.gov/osa/human-studies-review-board*.

Meeting minutes and final reports. Minutes of these meetings, summarizing the topics discussed and recommendations made by the HSRB, will be released within 90 calendar days of each meeting. These minutes will be available at *https://www.epa.gov/osa/human-studies-review-board*. In addition, information regarding the HSRB's Final Reports, will be found at *https://www.epa.gov/osa/human-studies-review-board* or can be requested from Tom Tracy listed under **FOR FURTHER INFORMATION CONTACT**.

Dated:

Mary Ross, Director, Office of Science Advisor, Policy and Engagement.