EPA Human Studies Review Board (HSRB)
August 23, 2023 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A.)
Date and Time: Wednesday, August 23, 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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August 23, 2023 Meeting Minutes

Wednesday, August 23, 2023:

A. Meeting Topics and Charge Questions

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

> **Weight of Evidence Charge**: The Office of Chemical Safety and Pollution Prevention (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.

B. Convene Meeting and Introduction of Members

Tom Tracy, DFO, EPA HSRB, OSAPE

Mr. Tom Tracy, the designated federal official (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) Weiying Jiang, Ph.D. (California Environmental Protection Agency) Thomas Lewandowski, Ph.D. (Gradient) Srikumaran Melethil, Ph.D., J.D. (University of Missouri – Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Seicean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) David Williams, Ph.D. (Oregon State University)
EPA staff members
Michelle Arling (EPA, OPP) Elizabeth Donovan (EPA, OPP) Monique Perron (EPA, OPP) Monique Tadeo (EPA, PHREO) Tom Tracy (EPA, OSAPE)

Members of the public, representatives of research sponsor, and research team:
Nancy Beck (Hunton Andrews Kurth LLP) James Damewood (Dupont Chemical) James Hamrick (Kronos Pan USA) Stewart Holm (American Forest and Paper Association) Angelina Guiducci (ICF, Contractor Support) Denyse Marquez Sanchez (ICF, Contractor Support) Ali Goldstone (ICF, Contractor Support) Julianne Ogden (American Chemistry Council) 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 (WoE) for Acute and Peak Inhalation report. He noted that minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of August 23, 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, which included reviewing the proposed changes to EPA's Weight of Evidence for Acute and Peak Inhalation Endpoints report and then voting to approve the draft HSRB report.

E. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Michelle Arling noted that the National Academy of Sciences (NAS) released its peer review report on formaldehyde. EPA is currently reviewing the NAS and HSRB draft recommendations and discussing how to incorporate them into future work. Two additional published studies on formaldehyde patch tests will be presented to the HSRB for discussion in October.

F. Public Comment

Dr. Lisa Corey asked Mr. Tom Tracy if there were any public commenters. Mr. Tracy confirmed there were no registered public comments and asked if anyone had an unregistered public comment. There were none.

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. Julia Sharp shared the draft HSRB report. Dr. Lisa Corey stated that EPA's comments included adding additional meeting dates on the report's cover letter. She also noted that many of ICF's edits were editorial. Dr. Corey then recalled a comment regarding the use of "formaldehyde" versus "HCHO" consistently throughout the report and confirmed "formaldehyde" was chosen. Dr. Corey introduced a comment regarding language updates in the study summaries to be consistent across studies. Dr. Corey then agreed that language should be consistent and explained the differences are due to how the HSRB wrote the charge questions throughout different meetings. Her recommendation was to keep the original language and make the wording around it as consistent as possible. Dr. Corey asked if the Board members had additional thoughts on this.

- **Chad Cross:** You are correct. I want to clarify that when I wrote these bullet points, I used the language from previous reports.
    - **Lisa Corey:** Thank you. If there are no objections, the language will be as similar as possible but remain with the agreed upon responses to charge questions.

Dr. Corey asked the Board if there were any comments, questions, or suggestions from the Board. She described the next steps which included her and Dr. Sharp accepting tracked changes and fixing typos as needed. No substantive changes or updates will be made.

- **Srikumaran Melethil:** I have a clarifying question. Why is it stated in the report that the definition of adverse effects is unclear in relation to sensory irritation?
    - **Lisa Corey:** There was discussion around whether a sensory endpoint should be considered adverse. The HSRB added a definition for an adverse effect. The request is for EPA to clarify what the endpoint was in the document.
    - **Srikumaran Melethil:** Is the new definition in the report redefined by EPA?
    - **Lisa Corey:** The new definition is from IRIS. The second half of the definition discusses whether or not an endpoint is adverse.
    - **Srikumaran Melethil:** The sentence says "or," so it could be any one of those listed in the definition, correct?
    - **Lisa Corey:** Yes.
    - **Srikumaran Melethil:** I am still unclear on why the HSRB is unsure if this is an adverse effect.
    - **Lisa Corey:** Is your recommendation to remove that from the report?
    - **Srikumaran Melethil:** Yes. When I read the definition, there was no confusion about the endpoint.
    - **Julia Sharp:** Can someone on the working group add to this conversation? There were several discussions about this.

- **David Williams:** This is important when discussing the point of departure (POD) and using sensory effects as a baseline. A biochemical change includes many things. EPA should tighten the definition of adverse effects so that similar studies are not as confusing in the future.
- **Lisa Corey:** Yes. The HSRB is not arguing that there is an effect. A biochemical change could be adverse, or it could not be. Any measurable biochemical change in the body is not necessarily adverse. The question is how these changes get treated, since an adverse effect should be treated differently than a non-adverse effect in risk assessment. This is where extra clarification becomes important.
- **Julia Sharp:** There was a public comment that described that issue in detail. Dr. Corey's description aligns with my memory. The definitions of adverse and acute effects are conflated in EPA's WoE report.
- **Srikumaran Melethil:** This still troubles me. We start the report by stating the definition is confusing but continue to discuss them later. I propose deleting that paragraph.
- **Lisa Corey:** We are not arguing whether there is an effect. We are discussing whether it is adverse or not. How do others feel about deleting this paragraph?
- **Chad Cross:** I do not agree with removal of that paragraph. The HSRB is asking for clarification. The question here is not about whether there is a biochemical change, it is whether that biochemical change is adverse. Are watering eyes associated with an adverse event or are they simply a reaction? We are simply asking for clarification.
- **Lisa Corey:** I also feel it is important to keep it, because it was not clear in the original documentation.
- **Albert Allen**: The fact that the HSRB spent time reviewing this speaks to the need for clarification. I agree we should include this.
- **Sinziana Seicean-Boose**: I agree, it should be included.
- **Chad Cross**: It is a comment, not a recommendation. Thus, EPA can decide to do what they want with this.
- **Julia Sharp**: There is a recommendation about this. The HSRB recommends EPA provide clarification on the use of sensory endpoints as adverse effects in the context of this WoE review. Additional information is provided regarding what is needed for clarification.
- **Albert Allen:** The fact that the HSRB spent time clarifying this speaks to the need for clarification in the report as well. Therefore, future readers will not need to do the same background reading.
- **David Williams:** Another component is whether this effect is reversible. In terms of formaldehyde, the effect is reversible.
- **Julia Sharp:** I agree we should include this. Dr. Melethil, is there a way to make this clearer for you?

- **Srikumaran Melethil:** Clearly there is an adverse effect. We could clarify that even though there is an adverse effect, it does not meet EPA's definition. And the recommendation should be at the end of the report.
- **Lisa Corey**: We are saying that this is not an adverse effect. It is a measurable effect, but it is not necessarily adverse based on the definition. Part of this relates to the reversibility that David just mentioned. The second half of the definition is what the HSRB does not agree with and has an impact on downstream risk assessments.
- **Srikumaran Melethil:** I have a problem with the grammar. When saying "or" it means any of the following as opposed to "and."
- **Chad Cross:** But are they impacting the performance of the whole organism? That is the important part of the sentence.
- **Srikumaran Melethil:** Yes, I understand that. However, the endpoint may not fit the last part of the definition, but it fits several other parts. I feel the definition is clear to me because it meets one of the points in the definition.
- **Julia Sharp:** You are thinking the first part is a biochemical change. Is that correct?
- **Srikumaran Melethil:** Yes.
- **Julia Sharp:** The definition states the biochemical change that affects the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge. I believe others are saying that this biochemical change is not affecting the performance of the whole organism, nor is it reducing an organism's ability to respond to an additional environmental challenge. Therefore, sensory irritation does not fit this definition of an adverse effect.
- **Srikumaran Melethil:** Thank you, I understand. The organism's ability to respond applies to everything. I agree with that. The placement of commas confused me. I understand now.

Dr. Sharp mentioned when the subgroup finalized the draft of the report, there was discussion around the recommendation regarding future studies. There is a recommendation for additional clarity on the scope and charge of the HSRB. Dr. Corey asked for additional comments or questions.

- **Weiying Jiang**: I was unable to attend the July HSRB meeting. I have a clarifying question related to page 11 of the draft report. Why does the HSRB recommend that the uncertainty factor is unnecessary for deriving the POD? Uncertainty factors are oftentimes used to account for data gaps and health protection purposes.
    - **Lisa Corey:** This is not an adverse effect, and thus, the same uncertainty factor that is applied to an adverse effect is not warranted here. Additionally, it was recognized that this is outside of EPA's request to the HSRB. Therefore, this commentary is provided on presented PODs, but additional clarity on the

definition of an adverse effect is still needed. From the group's interpretation, no adverse effect occurred, and the same uncertainty factor is not needed.
    - **Julia Sharp:** I have highlighted the HSRB's comments related to that recommendation on page 11.
    - **David Williams:** With respect to uncertainty factors, one component of that response dealt with the population being studied. Young and healthy individuals participated in this study, which were shown to be the most sensitive population. Normally, an uncertainty factor is used to protect the most sensitive population. However, the most sensitive population was tested here.
    - **Thomas Lewandowski**: Another aspect of uncertainty factors relates to species' differences in sensitivity. The literature suggests that irritation does not vary by species. It is a direct chemical effect. That is an additional consideration related to the lack of need for uncertainty factors.
    - **Lisa Corey:** Dr. Jiang, what do you think?
    - **Weiying Jiang**: Thank you for the clarification.

- **George Milliken:** Could we add concrete examples to the report? For instance, watering eyes is not considered an adverse effect but something else is. Examples may help clarify.
    - **Julia Sharp**: The report contains examples of sensory endpoints in the comments section. When discussing sensory later in the report, examples could be added. Would that be helpful?
    - **David Williams:** An example provided by a public commenter was watering eyes from chopping onions. I am not sure we need to add examples though, it may be better to leave that decision to EPA.
    - **George Milliken**: Okay.
    - **Julia Sharp**: I will add it once since it is already in the comments, and hopefully that will be clearer in the different sections.

Dr. Corey asked for additional questions. There were none. She then explained that minor grammatical, non-substantive edits will be made to the document. The HSRB then voted to approve the report and a consensus was reached.

H. Adjournment

Mr. Tom Tracy thanked the HSRB for their efforts and noted that a poll will be sent to assess members' 2024 meeting availability. Ms. Michelle Arling also thanked the Board for their efforts.

- **Thomas Lewandowski**: Can EPA give a sense of how long the formaldehyde project will continue?
    - **Michelle Arling**: Things may change in the future, but currently there are two patch studies involving formaldehyde coming. In January, a skin applied repellant

protocol will be presented. Multiple meetings are not anticipated for these future studies.
    - **Thomas Lewandowski**: Thank you.
    - **Lisa Corey**: Thank you, hearing the big picture is helpful.
    - **Michelle Arling**: Things are constantly evolving, and I will provide updates as I receive them.
- **Tom Tracy**: Ms. Arling, you mentioned two studies for October. I assume the three-day meeting could be scaled back to two days. Would October 11th and 12th accommodate discussion of these two studies?
    - **Michelle Arling**: Yes, that works on our end.
    - **Tom Tracy**: Okay, I will update the calendar invite.

The meeting adjourned at 1:48 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 subject's 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.