EPA Human Studies Review Board
October 25–27, 2022 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A)
Date and Time: Wednesday, October 25–27, 2022, 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

Table of Contents

EPA Human Studies Review Board
October 25–27, 2022 Meeting Minutes

Tuesday, October 25, 2022

A. Meeting Topic and Charge Questions

Topic: Anderson and Molhave (1983): Chapter 14: Controlled Human Studies with Formaldehyde. In: Formaldehyde Toxicity, James E. Gibson ed. Hemisphere Publishing Group, Washington D.C. Open literature study.

Charge to the Board – Science: Is the research described in Formaldehyde Toxicity, Chapter 14 (Controlled Human Studies with Formaldehyde) by Ib Andersen and Lars Molhave, under the section titled "A Five-H Exposure Study," scientifically sound, providing reliable data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposures to formaldehyde?

Charge to the Board – Ethics: Does available information support a determination that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

B. Convene Public Meeting and Introduction of Members

Tom Tracy, Designated Federal Officer, EPA Human Studies Review Board (HSRB), Office of the Science Advisor, Policy and Engagement (OSAPE)

Mr. Tom Tracy, Designated Federal Official (DFO) for the 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 the meeting participants. The following members and observers were present:

HSRB members	Lisa Corey, Ph.D., Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (Colorado State University) 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) Srikumaran Melethil, Ph.D. (University of Missouri-Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Siecean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) Eun Um, Ed.D. (AMSTAT Consulting) David Williams, Ph.D. (Oregon State University)

EPA staff members	Michelle Arling (EPA, Office of Pesticide Programs (OPP)) Tom Tracy (EPA, Office of Science Advisor, Policy and Engagement (OSAPE)) Tim McMahon (EPA, OPP) Judy Facey (EPA, OPP) Rochelle Bohaty (EPA) Deborah Burgin (EPA, OPP) Lexie (Mary) Burns (EPA, OSAPE) Lisa Christ (EPA, OPP) Elizabeth Donovan (EPA, OPP) Robert Mitchell (EPA, OPP) Anita Pease (EPA, OPP) Doritza Pagan-Rodriguez (EPA, Office of Pollution Prevention and Toxics (OPPT)) Dana Sackett (EPA, OPP) Susanna Wegner (EPA, Office of Chemical Safety and Pollution Prevention) Kim Wilson (EPA, OPP)
Members of the public, representatives of research sponsor and research team	Emily Sokol (Eastern Michigan University) Jonathan Cohen (ICF, Contractor Support) Afroditi Katsigiannakis (ICF, Contractor Support) Angelina Guiducci (ICF, Contractor Support) Aishwarya Javali (ICF, Contractor Support) Katie Lenae (ICF, Contractor Support)

C. Meeting Administrative Procedures

Tom Tracy, Designated Federal Officer, EPA HSRB, OSAPE

Mr. Tom Tracy reviewed Zoom's tools and features and stated the purpose of the meeting was to review the paper by Anderson and Molhave (1983): Chapter 14: Controlled Human Studies with Formaldehyde. In: Formaldehyde Toxicity, James E. Gibson ed. He noted minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of October 27, 2022.

D. Opening Remarks

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

Dr. Julia Sharp welcomed everyone to the EPA HSRB meeting and discussed the agenda. She noted that the purpose of the meeting was to discuss the Anderson and Mohave paper and the agenda included two other studies for the following two days. Dr. Sharp reminded everyone to vote using the "reactions" option while responding to charge questions and to mention their names before speaking. Dr. Sharp then called on Ms. Michelle Arling to enlist updates and Dr. Timothy McMahon to discuss EPA Science Review highlights before addressing questions of clarification from the Board. Dr. Sharp noted there were no public comments to discuss.

E. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Michelle Arling announced there were no updates on the research discussed at the last meeting. She then discussed the agenda for the upcoming meetings.

- In December, the regular meeting will be extended to finalize the report from the ongoing meeting, and discussion will focus on a completed study of a skin-applied tick repellent that was brought to the HSRB last April at a protocol stage.
- In early 2023, the protocol for the skin-applied repellent will be discussed.
- For the following 2 days, the next two studies on formaldehyde assessment will be the topic of focus.

F. EPA Science Review Highlights

Timothy McMahon, Ph.D., OPP Antimicrobials Division

Dr. Timothy McMahon thanked HSRB for reviewing and commenting on the human study set titled "Use of Human Studies for Derivations of an Acute Inhalation Reference Concentration (RfC) for Formaldehyde." He provided an outline of the presentation.

Dr. McMahon detailed the role of OPP and OPPT in evaluating (under their respective statutes) the risks from exposure to formaldehyde. He explained that the Agency was seeking HSRB's recommendations on the scientific and ethical acceptability of human studies examining responses to short-term inhalation exposures to formaldehyde to support derivation of the RfC for both OPP and OPPT assessments for two of four human studies presented at the ongoing meeting.

Dr. McMahon described the background of formaldehyde as a highly water-soluble chemical that can exist as a liquid or gas and as a naturally occurring substance that can be found in plants and animals and in rural and urban environments. He also mentioned inhalation exposure being a significant route of exposure.

Dr. McMahon explained the development of a draft OPP risk assessment as part of the registration review process under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which governs the registration, distribution, sale, and use of pesticides in the U.S. to ensure they continue to meet the standard of "no unreasonable adverse effects on human health and the environment." Dr. McMahon announced that their use sites under FIFRA for formaldehyde included a variety of equipment and premises.

Dr. McMahon then discussed the regulatory overview for OPPT, which works under the Toxic Substances Control Act (TSCA). OPPT provides EPA with authority to require reporting, record keeping, testing requirements, and restrictions relating to chemical substances or mixtures, under the TSCA statute, to determine whether formaldehyde presents an unreasonable risk to health or the environment under their conditions of use. He informed the group that in the risk assessment, they were required to evaluate the hazards and exposures that are consistent with the requirements of TSCA. He enlisted the substances generally excluded from TSCA including among others food, drugs, cosmetics,

and pesticides.

Dr. McMahon acknowledged the different conditions of use and the statutory authorities of FIFRA and TSCA as reasons for OPP and OPPT conducting separate risk evaluations. He maintained, however, that both program offices were coordinating the development of the hazard characterization that would be referenced by the FIFRA risk assessment and the TSCA evaluation and mentioned that the release of draft documents for public comment was currently scheduled for the end of 2023. He added the contribution of IRIS to the development of an assessment of formaldehyde and announced the release of the IRIS Toxicological Review of Formaldehyde by Inhalation for public comment in April 2022. He reported that this assessment was currently under review by an independent, external scientific Peer Review Board managed by the National Academies of Sciences (NAS), under contract with EPA.

Dr. McMahon explained the role of IRIS in performing extensive characterization of chronic cancer and noncancer hazards from inhalation exposure to formaldehyde and how OPP and OPPT defer to the IRIS assessment for evaluating chronic inhalation risks. He noted that acute inhalation, dermal, and oral routes of exposure were beyond the scope of IRIS's formaldehyde assessment. He reminded the group that both EPA offices were working jointly to derive a point of departure (POD).

Dr. McMahon discussed sensory irritation as an adverse effect observed in human and animal studies examining effects from short-term inhalation exposures to formaldehyde. The studies provide quality data for determining eye, nose, or throat irritation from inhalation exposure to formaldehyde. He acknowledged the exposure-response relationship being more precise and the potential confounders being less of a concern in controlled exposure studies. He also mentioned OPP's description of sensory irritation as an adverse effect for antimicrobial pesticides and other risk assessments.

Dr. McMahon noted the two studies being discussed by the group, as chosen by OPP and OPPT toxicologists, include sensory irritation effects. He recognized that more than one study was being used for this derivation and that weight-of-evidence (WOE) assessments were routinely used in EPA with the following considerations:

- Quality of data and extent to which effects can be replicated within a laboratory and across different laboratories.
- Strengths and limitations of the evidence.
- Effects induced and the potency, magnitude, and severity of effects.
- Consistency, pattern, range, and interrelationships of effects observed across studies, species, strains, and sexes.
- Conditions under which the effects occur, such as dose, route, duration, and life stage.
- Understanding of any adverse outcome pathway or mode of action and biological plausibility of the response, when applicable.

Dr. McMahon continued to explain details about the first study under discussion: Andersen and Molhave (1983), including the experimental design:

- Measurement of the effects of formaldehyde vapor exposure on nasal mucociliary flow, nasal

airflow, resistance, forced expiratory vital capacity and irritation.

- Sixteen healthy students (five females and eleven males).
- Twenty to 33 years old (average age: ~23 years).
- No history of chronic or recent respiratory disease.
- Five smokers; only one was a heavy smoker (i.e., 20 cigarettes per day).
- Groups were exposed for 5 hours to formaldehyde vapor at 0, 0.3, 0.5, 1, and 2 mg/m^3 (0, 0.2, 0.4, 0.8, and 1.6 ppm) on four consecutive days.
- Control chamber data were generated each day during a 2-hour period prior to the exposures.
- Three identical series of measurements took place during control exposures, after 2 to 3 hours of exposure, and after 4 to 5 hours of exposure.
- Each series of measurements consisted of nasal mucociliary flow, nasal airflow, resistance, forced expiratory vital capacity, and odor threshold.
- Degree of airway irritation was assessed in each subject throughout the exposure period by asking him/her to adjust a pointer on a machine, expressing the degree of irritation on scale of 1 (complete comfort) to 100 (severe discomfort).
- Subject performance was assessed using numerical addition, multiplication, and card-punching tasks. Each task lasted 15 minutes.

Dr. McMahon mentioned the contribution of Dr. Jonathan Cohen in performing statistical analysis of the data. He explained how Fisher's exact test was used to determine whether the response rates at different doses were equal, and the Cochran-Armitage trend test was used to compare the null hypothesis that the response rates were the same at every dose against the alternative one-sided hypothesis that the response rate increased with dose. He added that discomfort and sensory irritation data were also analyzed for probability of response as a function of dose, using EPA's benchmark dose modeling software (BMDS) and a benchmark response (BMR) of 10%.

Dr. McMahon then presented the results,

- Chamber exposures to formaldehyde were within 20% of target values.
- A significant decrease in mucus flow rate was observed in the anterior portion of the nasal turbinates at the lowest (0.3 mg/m^3, 0.2 ppm) concentration of formaldehyde, with no further apparent reduction in flow rate at the 0.5 mg/m^3 or 0.4 ppm concentration and above.
- After 2 hours, no discomfort or irritation (conjunctival irritation and dryness of the nose and throat) was reported after exposure to 0.3 or 0.5 mg/m^3 (0.2 or 0.4 ppm) formaldehyde. In the remaining part of the exposure period (4–5 hours), conjunctival irritation and dryness of the nose and throat were reported at the 0.2 and 0.4 ppm concentrations.
- At the 1.0 and 2.0 mg/m^3 (0.8 and 1.6 ppm) exposure concentrations, test subjects reported conjunctival irritation and dryness of the nose and throat in the first hour of formaldehyde exposure.
- Airway resistance measurements showed no significant effect of formaldehyde inhalation exposure on vital capacity, forced expiratory flow, or forced expiratory volume at any concentration tested.

- No effects on performance of mathematical tests or number-transfer tasks were noted at any concentration tested.
- Complaints of nose and throat dryness and conjunctival irritation were reported at all concentrations tested.
- For sensory irritation responses (assuming 0 responses in control), the modeled BMD and BMDL (lower confidence limit) were determined to be 0.208 and 0.091 mg/m^3, respectively, using the Gamma model. As stated in Dr. Cohen's memo, "Although the Dichotomous Hill model had the lowest AIC [Akaike's Information Criterion], the p-value for that model was not available and BMDS determined this model as questionable. Therefore, we excluded that model and selected the model with the second lowest AIC instead."
- BMD/BMDL values for discomfort at 2.5 hours were calculated as 0.217 and 0.151 mg/m^3, respectively, and 1.542 and 0.250 mg/m^3 for discomfort at 5 hours, respectively.

Dr. McMahon visualized these results using a graph of the Gamma model with the lower 95% confidence interval (CI) and illustrating the two values that were derived from the model. He then compiled the strengths and limitations of the study:

- Strengths
    - Both males and females were represented in the study.
    - Study used multiple exposure concentrations to examine concentration-response.
    - Parameters measured were relevant to assessing acute adverse effects from inhalation exposure to formaldehyde.
    - Results characterized both the incidence and severity of the concentration-response and time dependence of responses based on concentration exposures.
- Limitations
    - Males and females were not represented equally.
    - Study had a low number of participants.
    - Relative sensitivity of smokers versus nonsmokers to formaldehyde exposure was not assessed.
    - Authors reported no change in performance in addition (speed and accuracy), multiplication, or transfer of numbers to punch cards, but data were not provided.
    - Study participants were young, healthy volunteers and not representative of the general population.

Dr. McMahon concluded by noting that:

- The study provided concentration-response data for assessing adverse effects from acute/short-term inhalation exposures to formaldehyde.
- The data are amenable to deriving a POD for acute/short-term inhalation exposures to formaldehyde for use in regulatory risk assessment.
- The Agency is in agreement with the results of this study. The study was well conducted and provides quantitative information for derivation of an RfC value for formaldehyde.

Dr. McMahon proposed a question to the HSRB, asking whether the research described in the published study was scientifically sound and provided reliable data.

G. Board Questions of Clarification

Lisa Corey, Ph.D., HSRB Chair

Dr. Lisa Corey asked whether there were any questions of clarification regarding the study.

- **Sri Melethil:** There was a graph presented that looked like a dose-response curve, and I am not sure of what the axes were on the graph.
    - **Jonathan Cohen:** The x-axis is the dose, and the y-axis is the probability of a response.
- **Lisa Corey:** Tim, do you know if the study was peer reviewed?
    - **Tim McMahon:** The study had been assessed for low and high confidence, and we started focusing on the high-confidence results. Not necessarily peer reviewed by an external source but by them and us.
    - **Lisa Corey:** Was the study randomized and blinded to exposures?
    - **Tim McMahon:** Yes, they were randomized and blinded.
- **Michelle Arling:** It does appear that it went through the appropriate peer-review process for the time that it was published.
- **Weiying Jiang:** I have a question about the study design. In the study design, the author mentioned all the human subjects were exposed to different levels of formaldehyde for four consecutive days. So, has EPA considered the effects of previous day exposure on the full day response? The other study mentioned separate exposures to make sure there were no carryover effects from previous exposures.
    - **Tim McMahon:** I can verify there was a period of a break between these exposures. I do not think they exposed one after the other.
    - **Weiying Jiang:** The study said consecutive days, so I am assuming that it is 4 days continuously with different exposure on each day.
    - **Tim McMahon:** It was consecutive days, and I do not think there was a wash-up here. The other study we will be discussing – there is a break between exposures, but you are right about there being consecutive days of exposure.
- **Lisa Corey:** I was wondering about the use of the nasal mucus flow rate as an adverse endpoint. Is that common, and is it a validated endpoint that is often used? I would guess it would be the same exposure rate for irritation. Can you tell me more about the standardization across studies?
    - **Tim McMahon:** Formaldehyde will cause damage to the cilia and affect nasal flow rate. This measure seems to be one of the common measures taken. We were focused more on the irritation; however, one could say this is an irritation as well. I cannot answer the question completely, other than it was included as a measurement because of how formaldehyde reacts.
- **David Williams:** How did they control for odor? Or was odor detected at these concentrations?
    - **Tim McMahon:** I think there was a mention of the odor threshold, and they had used the chemical for seeing how the odor threshold of formaldehyde was affected. I am not

certain whether they measured that in that particular study, or they just measured that or just an effect on that, because there was some limited data on this study.

H. EPA Ethics Review of Highlights

Michelle Arling, J.D., OPP

EPA did reach out to the authors of the study in a variety of ways but did not get any responses regarding contact information, raw data, or study ethics. There were 16 participants (5 females and 11 males) who had healthy upper airways and nasal breathers. There was no information about the consent process. Looking at risk minimization, formaldehyde can cause eye, nose, and throat irritation. Individuals with asthma or other breathing problems may be more sensitive to the effects of formaldehyde. According to the publication, the risks were minimized by selecting levels of formaldehyde that were below the existing substantive acceptance and ethical standards, by enrolling subjects who asserted they were healthy, and by prohibiting individuals from smoking during the test period. The subjects were not identified in the publication, so their confidentiality was maintained. There was no information on subjects receiving compensation. There was no information about whether the study was overseen by an ethics board. Ms. Arling then turned to the substantive Acceptance Standards, 40 CFR 26.1706, 40 CFR 26.1704, and FIRFRA 12(a)(2)(P). She stated that EPA regulations prohibit the Agency from relying on data that involve intentional exposure of pregnant or nursing women or children. For research that was conducted before 2006, EPA is prohibited from relying on the data if there is clear and convincing evidence that the conduct of the research was fundamentally unethical or was deficient relative to the ethical standards prevailing at the time. She then stated that the crux of the review is the time when the research was conducted; the ethical standards prevailing over the research would most likely have been the Declaration of Helsinki (1975), whose requirements Ms. Arling proceeded to list. With these standards in mind, Ms. Arling found minimized risks to subjects, no evidence of coercion, no pregnant or nursing women, and no indication subjects were at increased risk of harm. The lack of documentation does not indicate that standards were not met. Based on the available information, there is no clear indication that the research was unethical or placed the subjects at harm. Ms. Arling then moved on to the charge questions.

I. Board Questions of Clarification

Lisa Corey, Ph.D., HSRB Chair

Dr. Corey asked whether there were any questions for the ethics review. There were no clarifying questions.

J. Public Comments

Dr. Corey asked whether any members of the public had comments. There were none.

K. Break

L. Board Discussion

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

Dr. Julia Sharp welcomed everyone back and held a quick roll call for the HSRB board. Dr. Sharp then opened the floor for questions from the science discussants, Dr. Thomas Lewandowski and Dr. Lisa Corey.

- **Lisa Corey:** I am going to focus on the limitations of this study. This is an older study, and differences in presentation of data are expected (e.g., statistical details). Additionally, one of the things that was brought up during the question period is the idea of using odor perception and the use of ethyl valerate to determine odor or thresholds, but the significance of that in the experimental design wasn't described at all in the study. The two endpoints with unresolved major issues are the mucociliary flow rate and irritation. There is a lack of temporal and dose response with both. Looking at the flow rate, there could be some change at 0.5, but flow rate was not impacted at the highest concentration. This leads us to question the reliability of the test. Moving onto irritation, no dose response exists. The lowest dose group (0.3 mg/m^3) shows a higher discomfort, which is concerning. And then we are seeing temporal changes, as well, wherein the highest dose groups are kind of peaking and then decreasing, whereas the two lower dose groups are just continuing to increase. The interpretation of this is complicated and looking at the paper at face value, it is difficult to understand how to use these data. I believe EPA is proposing to use the lowest dose group data and base it on both the mild irritation and the decrease in mucus flow. But I guess maybe that is what I would like to open up for discussion at this point.
    - **Sri Melethil:** I am thinking about the relationship between nasal pressure drop and mucus flow, which confused me because I was thinking it would go the other way. If there is a decrease in mucociliary flow, that means they should be more resistant to flow. What is the connection between mucus flow and nasal pressure? For the dose response, would the dose response presented earlier help with this issue? And is WOE a quantitative thing? I am sure EPA has standards on that. So, I would like clarification on what exactly "weight-of-evidence" means in terms of deciding in the quantification and information of a value. There was a previous study showing a reasonable dose-response curve starting as low as 0.05. By starting with 0.3, we may be ignoring data below this concentration. Additionally, this study is older (1970s). Are there more recent studies we can look at? There are no crossover effects in the study. Symptoms had disappeared by the following morning.

Dr. Sharp asked to view the slide about WOE for HSRB members to review. Dr. McMahon shared the slide.

- **Tim McMahon:** It is some of these WOE parameters that we would discuss, and some of which we had presented. It is all to the point of looking at the data, which I know we have not seen all

of it yet. So, looking at all those data and synthesizing that evidence into the characterization where we can support a POD after looking at all the data.

Dr. Sharp asked whether there were additional questions regarding WOE.

- **Sri Melethil:** Does EPA do any quantitative algorithms with respect to WOE?
    - **Tim McMahon:** No algorithms I am aware of, but EPA tries to gather data of high quality and synthesize data across multiple studies/endpoints. We can model data to determine if there is a dose response that can be ascertained and looking at multiple data sets for that effect and going from there.
    - **Sri Melethil:** That is very helpful. Thank you.

Dr. Sharp followed up on the prior question presented by Dr. Corey. Does the HSRB feel that the data are reliable? EPA proposed to use the 0.3 threshold.

- **Lisa Corey:** I do think EPA has the more conservative number in that. So going forward, using the study in that matter would still be health protective.
    - **Tim McMahon:** When we develop assessments, we recognize it is health effective for many downstream effects that would be the result of longer or higher exposures. As far as acute effects, it tends to be a little conservative, but we do feel it is health protective in that case.
    - **Lisa Corey:** I feel okay about the health-protection aspect, but as a WOE, there should be some discussion regarding following dose responses. Not having this information makes this study questionable. We should be careful with the amount of weight placed on the study.
- **David Williams:** How does EPA view not analyzing data from smokers separately? They are shown to be less sensitive at detecting the odor of formaldehyde. This could represent the general population possibly.
    - **Tim McMahon:** EPA will consider that during the uncertainty analysis stage. Uncertainty exists, and there is a smoker/asthmatics issue. We will look at available data and determine the amount of uncertainty. We would also consider any other data we can find on the relative dose response on several populations to influence our characterization in that arena.
- **George Milliken:** Complaints were mainly irritation and dryness in throat after exposure. Even at 0.3, three out of sixteen subjects had nose and throat irritations. I am wondering whether the heavy smoker was the one who did not have issues. 0.3 could be too high because almost 25% of subjects had issues at this level.

Dr. Sharp asked for any other comments on the scientific review.

- **Sri Melethil:** Since the smoker issue was raised, mucus flow reduction may be more pertinent to someone with a disease like asthma or cystic fibrosis. Is it too early to discuss these things?
    - **Julia Sharp:** This is an appropriate time to discuss this. Do you have a specific question?
    - **Sri Melethil:** We are planning future studies, so should there be a patient-selection

process for future studies? Are we contemplating the use of nonhealthy subjects?

- **Judy Facey:** We are not planning on doing additional studies.
- **Sri Melethil:** One thing that escaped me was the overall picture of formaldehyde exposure in Americans. Is there data on this? Or is there somewhere we can find that out?
- **Tim McMahon:** Current IRIS assessment discusses that in their hazard identification. You can find additional information there.
- **Sri Melethil:** Where is this available?
- **Tim McMahon:** It is available publicly on the EPA IRIS program webpage by searching for "formaldehyde."

- **Weiying Jiang:** How will this study be considered in the WOE approach? Will you derive a POD from another study and use the values in this study as a supporting piece of evidence? What is the WOE general approach, and how will this study be considered?
  - **Tim McMahon:** We will not use only one study by itself. We will go through many studies and look at multiple factors across studies. Factors such as concentration response, the effect of interest, how the data add up (are these values supportive of each other?) will all be examined. We look at various parameters and use our best judgement on what we feel is the appropriate POD after going through all the data sets.
- **Lisa Corey:** Can we look at the graph of BMR data?

Dr. Michelle Arling brought up the slide showing the graph of BMR data.

- **Lisa Corey:** Is this based on a certain time point?
  - **Jonathan Cohen:** Dose is on the x-axis, and probability of response is on the y-axis. We have measurements at different times for different doses, but the information in the paper was not specific, so it is hard to tell. We do not even know who was a smoker and who was not a smoker. There is no time stamp with any of the data in the paper.
  - **Sri Melethil:** It may be worth looking at Figure 1 because there is a dose-response curve, and it might help. The task was order related (presence of formaldehyde so there were lower concentrations starting at 0.05), and it looks similar to the curve on the slide.
- **Sinziana Siecean-Boose:** I also have a general question. Does EPA take into consideration international works on formaldehyde standards?
  - **Tim McMahon:** Yes. We are always looking at international agencies.

There were no further comments or questions for the science discussants. Dr. Sharp asked for input from the statistics reviewers, Dr. George Milliken and Dr. Chad Cross.

- **Chad Cross:** I am impressed they provided historic data and highlighted five studies that happened in the past. Those studies used different statistical designs, but they did inform the current study, so it was helpful. The experimental design used was likely acceptable at time of study publication but probably not today. Gender and age ratio was greatly unbalanced and unjustified. Inclusion of smokers and small study size could potentially have led to results in the analyses that were contaminated by confounding effects. Smokers were in fact significantly less sensitive than nonsmokers and we are unsure how that impacted the results. Because we do not

have individual data, we do not know how that impacted the results. The rate of smoking when the study was published was about 32%, which is like what was in the study; however, the current smoking rate is only about a third of this. We believe the historic data may be contaminated by the inclusion of smokers in the study. There is no justification for why multiple tests were used. The data transformation mentioned did not have any details of the analyses, so we cannot provide a statistical overview on the findings. No information was provided on the impact of using the same subject. We do not know whether independence can be assumed with these groups. We agree with the memo presented earlier. Additionally, we cannot validate data because raw data is not available to us. Multiple limiting assumptions exist. POD is not strongly supported because statistical validity is poor.

- **Sri Melethil:** Is age range of statistical concern?
- **Chad Cross:** Not statistically concerning, just acknowledging the range.
- **Sri Melethil:** Is smoking considered the same thing as vaping?
- **Chad Cross:** No. There are different health impacts associated with smoking versus vaping.

Dr. Sharp asked whether there were additional questions regarding the statistical analysis of the study.

- **Chad Cross:** George, is there anything you would like to add?
  - **George Milliken:** Yes. This type of data is not set up for Fisher's exact test because the test assumes that all subjects were independent. The subjects in this study were not (they were in groups of four).
- **Julia Sharp:** Can Dr. Cohen follow up on the Fisher's exact test and the Cochrane Armitage tests and how those assumptions were accommodated in those analyses?
  - **Jonathan Cohen:** We had to assume independence to allow us to do analyses but with many caveats. All the tests are needed to assume independence, and we just do not have the data. The only thing I could do is attempt to follow what IRIS did and make some adjustment in BMD analysis (e.g., using a factor of 2), but that is sort of a number picked out of the air. Without the data, it is hard to do any analysis. EPA tried hard to get the data and did not get any answers.
  - **Julia Sharp:** I appreciate the effort to try to get the individual data. These studies were conducted in the 70s and 80s, and this was before mixed modeling approaches were prevalent. We would love to have individual observations, but we do not in this case.
  - **Chad Cross:** The BMDL is constant at about 57% of the BMD. There is some literature evidence to support the division by approximately 2 for BMD analysis.
- **Sinziana Siecean-Boose:** While indeed there is mostly real power within our subjects of interest, there are also major problems from the statistical perspective or assuming the non-correlating nature of the data. I agree on the fact that they will tell you to correct the correlated nature of data, which can have a huge impact on the results. The new methodology now available for this type of analysis was far behind. The new methodology now available was not at the time or other approaches were available. For example, a two-way analysis of variance (ANOVA) would be slightly more appropriate by additionally removing some variability between subjects. My main

concern here is that the assumption of independence may substantially change the result, especially for the F test, which you know becomes non-significant when you are using the appropriate methodology.

Dr. Julia Sharp stated that the two charge questions would be separated.

- Dr. Julia Sharp had a recommendation in response to the science charge question. She read the question and added that the rest of it should include: "for use in a weight-of-evidence to determine a point of departure for acute inhalation exposures to formaldehyde." Dr. Sharp stated that the study does not have reliable data, so her recommendation in response to the science charge question would be to change the response so HSRB does not suggest that the data are sound and reliable but that they provide a qualitative limited use in a POD.
    - **George Milliken:** Can we change "scientifically sound" to say "somewhat scientifically sound"?
    - **Julia Sharp:** I have updated the response to say: "The research described in Formaldehyde Toxicity, Chapter 14 (Controlled Human Studies with Formaldehyde) by Ib Andersen and Lars Molhave, under the section titled 'A Five-H Exposure Study,' provides somewhat scientifically sound, qualitative data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposure to formaldehyde." This is a proposed response to the science charge question.
    - **Lisa Corey:** Are we allowed to change the charge question and respond in this way, or do we have to answer the one that was given?
    - **Julia Sharp:** Are we saying yes or no, or are we going in this grey area?
    - **Michelle Arling:** If you want to, say, "Yes, with qualifications." It provides reliable data. I think it would be hard to interpret the "somewhat scientifically sound." But "somewhat scientifically sound" with purpose would be easier to interpret moving on.
    - **Lisa Corey:** We can answer the question and include our list of qualifications.
    - **Albert John (A.J.) Allen:** Say that "this is subject to the limitations and recommendations discussed in the HSRB meeting."
    - **Julia Sharp:** I like those recommendations. The new response for consideration is: "The research described in Formaldehyde Toxicity, Chapter 14 (Controlled Human Studies with Formaldehyde) by Ib Andersen and Lars Molhave, under the section titled "A Five-H Exposure Study," provides scientifically sound data for qualitative use in a weight-of-evidence to determine a point of departure for acute inhalation exposure to formaldehyde, given the limitations and recommendations provided by the HSRB are considered.
    - **George Milliken:** Agree.
    - **Sinziana Siecean-Boose:** Perhaps we can add something about modeling the chance that an individual will be able to respond to exposures of increased dose (or without seriously adverse reactions) must be taken into consideration. Individuals might have different response levels, and for this reason, this study can accommodate the question.
    - **Julia Sharp:** We will include that in a recommendation in a report. Are there any other comments or concerns?

  - **Weiying Jiang:** Since we are considering using this study qualitatively, I was thinking about phrasing it as: "to support the determination of a point of departure" instead.
  - **Julia Sharp:** Updated charge question to state: "The research described in Formaldehyde Toxicity, Chapter 14 (Controlled Human Studies with Formaldehyde) by Ib Andersen and Lars Molhave, under the section titled 'A Five-H Exposure Study,' provides scientifically sound data for qualitative use in a weight-of-evidence to support the determination of a point of departure for acute inhalation exposure to formaldehyde, given the limitations and recommendations provided by the HSRB are considered." Are there any concerns with this statement? We will use the reactions button to approve or reject the changes to the scientific charge question. The updates to the question are approved. We will move on to the ethics charge question and the ethics reviewers, Philip and Joey.

- **Philip Day:** We all know what we are reviewing, so the charge to the board is: "Does available information support a determination that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent?" For our review, we reviewed the provided documents and accompanying documents from the EPA. We agree with the EPA: There is no indication of coercion, all participants are over the age of 18, specific inclusion and exclusion criteria were not included, six reported to be smokers, no information about compensation. The study provides no information about consent. Risks and benefits have been covered well so far. We do believe risks were adequately minimized. Reactions to the exposure included increases to discomfort in the slight to low discomfort range. Most did not report discomfort; based on the study discussion, this should be expected from formaldehyde exposure. Study participants are referred to as numbers, and no direct information is available. No information on independent ethics review. This study does not appear to be conducted unethically. While this lacks information, there is no evidence in the chapter that the study was conducted unethically. Our response to the charge question is yes. There is no clear and convincing evidence that the study was conducted unethically.
  - **Joseph Tuminello:** There are no further comments. Philip's comments reflect my position.
  - **Julia Sharp:** Are there any further questions?
  - **Albert John (A.J.) Allen:** To comment on the review, I agree the applicable standard in the 1970s would have been significantly less than today's standards. A lot of discussion we have on ethics would not have applied. The Helsinki court would have been highly influential. In Europe, they tend to be good at receiving informed consent.
  - **Julia Sharp:** I have formulated a response to the charge question. The proposed response is as follows: "The Board does not believe that the research described in Formaldehyde Toxicity, Chapter 14 (Controlled Human Studies with Formaldehyde) by Ib Andersen and Lars Molhave, under the section titled 'A Five-H Exposure Study,' provides clear

and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent." Are there any comments on the charge question response, or concerns? I am going to take a vote on the updated charge question.

- **Sri Melethil:** Should there be a "not" in this?
- **Julia Sharp:** The "not" is in the first four words. It looks like there is a yes consensus. That concludes the business for today.

M. Adjournment

Dr. Julia Sharp ended the meeting and thanked the board members.

Dr. Lisa Corey asked that the reviewers have the revised drafts, based on the recommendations discussed today, ready for the next meeting.

The meeting adjourned at 3:42 p.m., EDT.

Wednesday, October 26, 2022

A. Meeting Topic and Charge Questions

Topic: Kulle, T.J.; Sauder, L.R.; Hebel, J.R.; Green, D.J.; Chatham, M.D. (1987). Formaldehyde Dose-Response in Healthy Nonsmokers. JAPCA 37: 919-924. DOI: 10.1080/08940630.1987.10466285

Kulle, T.J. (1993). Acute Odor and Irritation Response in Healthy Nonsmokers with Formaldehyde Exposure. Inhalation Toxicology 5(3): 323-332. DOI: 10.3109/08958379308998389 (statistical re-analysis of data from Kulle et al. 1987 paper)

Charge to the Board – Science: Is the research by Thomas J. Kulle et al. described in the 1987 publication "Formaldehyde Dose-Response in Healthy Nonsmokers" and the 1993 publication "Acute Odor and Irritation Response in Healthy Nonsmokers with Formaldehyde Exposure" scientifically sound, providing reliable data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposure to formaldehyde?

Charge to the Board – Ethics: Does available information support a determination that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

B. Convene Public Meeting Day 2

Tom Tracy, Designated Federal Officer, EPA HSRB, OSAPE

Dr. Julia Sharp introduced Dr. Lisa Corey, Chair, and led the HSRB member roll call. Dr. Sharp invited members of the group to introduce themselves. Drs. Chad Cross and Kendra Lawrence were not in attendance.

Dr. Sharp invited Ms. Arling and Dr. McMahon, both from EPA, to introduce themselves. Although

additional EPA staff were in attendance, they did not introduce themselves.

HSRB members	Lisa Corey, Ph.D., Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (Colorado State University) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) 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. (University of Missouri-Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Siecean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) Eun Um, Ed.D. (AMSTAT Consulting) David Williams, Ph.D. (Oregon State University)
EPA staff members	Michelle Arling (EPA, OPP) Tom Tracy (EPA, OSAPE) Taylor Lass (EPA, OSAPE) Tim McMahon (EPA, OPP) Judy Facey (EPA, OPP) Deborah Burgin (EPA, OPP) Lexie (Mary) Burns (EPA, OSAPE) Elizabeth Donovan (EPA, OPP) An-Tsun Huang (EPA, OPP) Robert Mitchell (EPA, OPP) Doritza Pagan-Rodriguez (EPA, OPPT) Kim Wilson (EPA, OPP)
Members of the public, representatives of research sponsor and research team	Jonathan Cohen (ICF, Contractor Support) Afroditi Katsigiannakis (ICF, Contractor Support) Angelina Guiducci (ICF, Contractor Support) Aishwarya Javali (ICF, Contractor Support) Kaedra Jones (ICF, Contractor Support)

C. EPA Science Review Highlights

Timothy McMahon, Ph.D., OPP Antimicrobials Division

Dr. Timothy McMahon shared that he found that NAS provides a good overview and outline of the WOE approach used by EPA. It is not a one-size-fits-all approach.

EPA understands that the studies presented to the HSRB measure different exposures and endpoints and that four to five parameters are being considered. The focus is on sensory irritation response, which is strongly correlated with short-term exposures to formaldehyde. Four studies are being used as a WOE, but only two of these are being presented now. During the next meeting, EPA will be able to put something more definitive together and show this to the HSRB.

Dr. McMahon noted that participants have acknowledged there is always an alternate approach. In this case, that approach is to rely on the 2001 ACGIH TLV documentation for formaldehyde, which used the study of Horvath et al. (1988). Horvath et al. (1988) was an occupational study and questionnaire among particle board workers. An inhalation POD of 0.1 ppm for all durations was selected from this study. However, one reason why the group is having this discussion is that this POD value is not necessarily representative of the short-term exposure considered today. IRIS conducted a review of these studies and described confidence as medium to high. Focus was placed on the chronic endpoint, whereas the HSBR is currently focused on an acute inhalation POD.

Dr. Sharp thanked Dr. McMahon for this context. There were no questions from the HSRB.

Dr. McMahon moved on to discuss Study #2, which includes two studies by Kulle et al. (1987) and (1993). The study measured effects of formaldehyde vapor exposure on nasal airflow resistance, pulmonary function, eye irritation, and odor threshold. Kulle et al. (1987) was republished with additional analyses in 1993. The same data set is reflected in both papers. Dr. McMahon described the experimental design used by Kulle et al. on slide 29. He explained that 19 healthy nonsmoking male and female subjects received five separate 3-hour exposures to formaldehyde in an environmentally controlled chamber. Each subject served as his/her own control. Exposures were random and separated by 1 week. Exercise consisted of 8 minutes on a bicycle ergometer every 30 minutes during a 3-hour exposure duration.

Dr. McMahon provided an illustration of the inhalation chamber on slide 30. This illustration was provided by Anderson, but it is representative of the chamber used in Kulle et al. (1987).

Dr. McMahon reviewed the methods of Kulle et al. on slide 31. Some effects were measured objectively (i.e., pulmonary function, bronchial reactivity, and nasal resistance), whereas others were assessed via questionnaire (i.e., symptoms of nose, throat, or eye irritation; cough; headache; chest discomfort) at six intervals during the exposures. Symptoms were scored prior to, immediately following, and 24 hours post-exposure.

Dr. McMahon gave an overview on slide 32 of the statistical analysis of the data in Kulle et al. (1987, 1993), performed by Dr. Jonathan Cohen (ICF) and reported in a memorandum from January 28, 2022. BMD modeling was used to fit and plot dose-response models and to estimate the BMD as the dose at which there was a 10% extra risk above an assumed 0% risk for unexposed subjects.

Dr. McMahon summarized the results from Kulle et al. (1987, 1993) on slides 33, 34, and 35. Odor sensation, eye irritation, and nose/throat irritation were the most frequently reported symptoms from inhaled formaldehyde in this study. A linear trend for odor sensation and eye irritation responses was

[1]Horvath, A. O., & Greenberg, L. S. (1989). Development and validation of the Working Alliance Inventory. *Journal of Counseling Psychology*, *36*(2), 223–233. https://doi.org/10.1037/0022-0167.36.2.223

reported. No significant pulmonary function decrements or bronchial reactivity increments were observed after 3 hours of exposure to 0.5–3 ppm formaldehyde. One of 10 subjects reported a mild odor response at 0.5 ppm. There was a significant increase in nose/throat irritation at the 2.0 ppm concentration, when there was exercise in comparison to the effect without exercise. Dr. McMahon added that Dr. Cohen presented the following BMDL values in his memo: 0.182 ppm for odor sensation, 0.502 ppm for eye irritation, and 0.992 for nose/throat irritation. These values agreed with the values reported in the draft IRIS assessment published by EPA in 2022.

Dr. McMahon presented an illustration on slide 36 with BMD and BMDL values for modeling dose response.

Dr. McMahon identified the strengths and limitations of Kulle et al. (1987, 1993) on slides 37 and 38:

- Strengths:
    - The study included both male and female subjects, which were represented equally.
    - Measured parameters were relevant to assessing acute adverse effects from inhalation exposure.
    - Results characterized both the incidence and severity of the concentration-response and time dependence of responses based on concentration exposures.
- Limitations:
    - The number of study participants was low and consisted of young, healthy volunteers.
    - The participants were not representative of the age distribution and health status in the general population.

Dr. McMahon stated the overall conclusions from Kulle et al. (1987, 1993) on slide 39. This study provided concentration-response data for assessing adverse effects from acute/short-term exposures in a WOE determination. These data are amenable to deriving a POD for acute/short-term inhalation exposures for use in regulatory risk assessment. EPA is in agreement with the results of this study, which is considered well conducted and provides quantitative information relevant for deriving an acute RfC for formaldehyde.

D. Board Questions of Clarification

Lisa Corey, Ph.D., HSRB Chair

- **Thomas Lewandowski:** Does EPA have any comment on why the BMDL information was not part of the original package the HSRB received?
    - **Michelle Arling:** There was a miscommunication in what materials were originally sent over.
- **Thomas Lewandowski:** Seeing the BMD results is helpful. Does EPA plan to use the BMD analysis? Are these the data that established the RfC?
    - **Timothy McMahon:** Yes, EPA plans to consider the BMD results as part of our acute RfC value.
- **Lisa Corey:** How should the x-axis and y-axis be labeled on the modeling results presented on

slide 36?

  - **Jonathan Cohen:** The x-axis label is "dose (in ppm)," and the y-axis label is "probability of eye irritation." Dose-response modeling results are detailed in the memo provided to the HSRB and available on the HSRB website.

- **Julia Sharp:** Do these analyses account for repeated measures on the subjects?
  - **Jonathan Cohen:** We do not have individual data on the subjects' responses. Assumptions were made on independence.
- **Weiying Jiang:** In general, I agree with EPA's conclusion of using this as a WOE to support determining the POD. There might be concerns about whether it is appropriate to use the sensory irritation endpoint to derive the POD because we are talking about health risk assessment. We should include a health effect for determining the POD. A sensory effect was observed in this study, with the most sensitive being eye irritation. How is that related to inhalation exposure? The eye irritation could be caused by eye contact with the vapor.
  - **Timothy McMahon:** That is a good question, and one would assume that eye irritation was part of that investigation. EPA's approach has been to look at known mode of action data on response related to irritancy. EPA has used irritancy as a health protective measure for noncancer adverse effects. EPA recognizes that we are focused on an acute exposure in this scenario, which would differ from what happens with long-term exposures, when the respiratory tract is more affected. Kulle et al. were not just looking at what would happen if the eye was directly exposed, but they did include some measures of irritancy response.
- **Weiying Jiang:** Did EPA ever use irritation or odor sensation as a POD in previous risk assessments?
  - **Timothy McMahon:** Yes, EPA has used irritancy responses for assessments of pesticides and for antimicrobials because a large portion of these types of chemicals show irritation as a primary response. EPA developed draft guidance on irritancy based on either a NAS or National Research Council publication that described uncertainty analyses around these endpoints. EPA finds this approach more relevant for antimicrobial pesticides.
  - **Thomas Lewandowski:** Irritation, but not sensory, data have been used to set POD values.
  - **Weiying Jiang:** Could EPA share some of these assessments with the HSRB?
  - **Timothy McMahon:** Yes, these assessments can be shared.
- **Sinziana Siecean-Boose:** Does Timothy McMahon have any information related to tolerance when assessing the sensory issue? How do you control for higher level of sensory tolerance and variability, which can be quite high? How was this managed in other studies?
  - **Timothy McMahon:** We address these variables using the available data as part of risk characterization. We would consider using default or targeted assumptions related to these variables, which would ultimately affect the value selected as an RfC. There is a bit of uncertainty with this step, but we do recognize these variables as factors. We look for

specific data that help inform risk characterization. EPA has default assumptions available, but these can be modified if the data allows.

- **Sinziana Siecean-Boose:** What study design approach was used for randomization? The results do not overlap with the randomization described in the study.
    - **Jonathan Cohen:** It is difficult to understand randomization without detailed data by subject. We did not have all the information we would have liked to have. I assumed EPA tried to get these data but was unsuccessful. We are assuming blocks are the subjects.
    - **Sinziana Siecean-Boose:** It looks like the randomized variable was the gender of patients, but this is an assumption based on results. There is a peculiar reporting of random selection of exposure during the control experiment; however, there are exactly the same number of exposures for each participant.
    - **Julia Sharp:** These observations should be included in the detailed HSRB reviews.
- **Srikumaran Melethil:** Are there any type II errors or concerns with respect to the reliability of the data? I point to Figure 2 in Kulle et al. (1987), where results for rest and exercise for nose and throat are presented. When visually looking at the results, there appears to be a two-fold difference, but the results are shown to be statistically insignificant. What is the probability you detect even if there is a real difference?
    - **Julia Sharp:** I did not see anything like that. Please hold this question for the HSRB science and statistics review.
- **Srikumaran Melethil:** Regarding the modeling in the Kulle et al. (1987) paper, why was one group modeled as a linear dose response and the other group a log dose response?
    - **Julia Sharp:** With one group, exposures were equally spaced, and with the other group, exposures were unequally spaced. A log transformation approach was used for the group with unequally spaced exposures.

E. EPA Ethics Review of Highlights

Michelle Arling, J.D., OPP

Ms. Arling presented the ethical conduct of the study. On slides 1 and 2, an outline of the presentation was provided. On slide 3, subject information was provided. There were 19 subjects in the study, all over 18 years old. They were all nonsmokers and willing to undergo a screening examination prior to the study. On slide 4, the consent process was discussed. All subjects signed consent forms. On slide 5, risk and risk minimization were presented. Risks were minimized by enrolling healthy subjects and spacing the test days weeks apart. On slide 6, it is noted that subjects were compensated for participation in the study, and the subjects' privacy was protected. On slide 7, an independent ethics review was presented. The protocol was approved by the Human Volunteers Research Committee at the University of Maryland. On slide 8, the substantive acceptance standards were presented. On slide 9, the prevailing ethical standards were discussed (e.g., Declaration of Helsinki (1979)). Looking into these standards, the study was required to adhere to regulations set forth by the Department of Health and Human Services. Multiple ethical parameters, such as ethical informed consent and ensuring benefits of research outweigh the risks to participants, were discussed. On slide 10, the findings of the study were discussed. An

independent ethics review board approved the research. On slide 11, conclusions were provided. Available information does not indicate this was unethical research. On slide 12, the charge question was presented.

F. Board Questions of Clarification

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

Dr. Sharp asked the group whether anyone had questions of clarification for the board.

- **A.J. Allen:** Were there participants younger than 18 years old in the study?
    - **Michelle Arling:** The articles gave age range and average range, and there was no indication that any participant was less than 18 years old.
    - **Philip Day:** Age and standard deviation is given in the study. The youngest and oldest participants were 21 and 31, respectively.

Dr. Sharp asked the group whether there were any additional questions of clarification for the board. There were none.

G. Public Comments

Dr. Sharp asked whether any members of the public had comments. There were none.

H. Break

I. Board Discussion

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

Dr. Julia Sharp welcomed everyone back, did a quick roll call, and announced the board discussion after the science, statistics, and ethics review team presentations.

Dr. Thomas Lewandowski shared general agreement with EPA's conclusions. He agreed with the acceptability for WOE to support acute inhalation risk assessment. However, he noted that:

- Subjects were healthy, nonsmoking young adults and did not include people with pre-existing conditions.
- It also excluded smokers, who might be expected to be somewhat more resistant to the effects of formaldehyde.

Dr. Lewandowski acknowledged the study's advantages, including a balanced sex ratio and the use of two methods of evaluating exposure, gas monitors and impingers. He listed the limitations as the absence of raw data and the impact of this absence in evaluating intervariability. He mentioned how generalization due to self-reporting with respect to perception of irritation disregarded individual variability or degree of irritation and symptoms. He also mentioned that the study noted measurement of functional residual capacity, but those results were not presented in either publication. Dr. Lewandowski reiterated the benchmark dose information in EPA's analysis and noted that there was confusion if EPA used the results of BMD analysis or the results from a No Observed Adverse Effect Level. Although

presented in the slide, he stressed the need for further clarification on this issue. Dr. Lewandowski highlighted the possibility of irritation, including odor sensation and irritation due to direct eye contact with formaldehyde, and requested clarification on whether the RfC considered the other sources as well.

- **Sri Melethil:** My question was relating to the reliability of the data, and I was looking at the 1987 paper; the intrasubject variability (on Figure 2) visually appears to have increased two-fold but was not statistically significant. Are there any type II errors here? What is the probability of detecting a difference? I do not see a discussion of this anywhere.
    - **Julia Sharp:** We do not typically compute type II error from a data set, so I am unclear what you are asking.
    - **Sri Melethil:** Are we avoiding the possibility of type II errors?
    - **Weiying Jiang:** It depends on what EPA selects to derive its POD as well as supporting PODs. The most sensitive endpoint is eye irritation. As mentioned, it may be caused by inhalation. If EPA decides to use that as the POD, then this is not our concern.
    - **Thomas Lewandowski:** It is a little vague. I suppose the dividing line between statistics review and science review. This question would fall into statistical review. The effects shown in Figure 2 are at the 2-ppm concentration, and the Lowest Observed Adverse Effect Level was 1 ppm for eye irritation. So, I do not really see that having a significant effect on the data that would be used to derive a value.
    - **Sri Melethil:** We are asked to say they are reliable data. When I see data like these, I think we should discuss it.
    - **Thomas Lewandowski:** We are looking at historic data, and obviously they are 30 to 40 years old, so it is not ideal. Is the data good enough to be used? They are being used as WOE, so they are useful. From my perspective, while they have some issues, they have some reasonable methods of measuring exposure, quantifying exposure, and assessing response such that they could be used as part of a larger way for evidence analysis.
    - **George Milliken:** Generally, while talking about type II, we are relating to power analysis and there is nothing to talk about that in these papers.
- **Sinziana Siecean-Boose:** When we are talking about study design flow, is that scientific or statistical?
    - **Thomas Lewandowski:** If you are asking about how the data were gathered, then it should be appropriate for this moment.
    - **Sinziana Siecean-Boose:** I struggle with randomization. Within every block group 1 and group 2, there are five separate exposures or formaldehyde doses. One issue about a different randomization scenario: 0.5 verses 3. Based on the results in Table 3, it appears that every participant was exposed to different doses of formaldehyde. In my opinion, this will not give good results. The same participant should be exposed to the same dose multiple times. It seems like there is no randomization. I would appreciate hearing your thoughts.
    - **George Milliken:** The person or subject is a block, and the five time periods that each person was exposed – they were randomly assigned the dose in these time periods.

- **Sinziana Siecean-Boose:** Yes, but if it is a random design of the same size, you would not have all five like values for the same participant. You would expect that participant to be exposed at least twice to the same dose because it is random.
- **Thomas Lewandowski:** The order is randomized, not the doses. Everyone gets the same dose but in a different order.

Dr. Julia Sharp moved on to statistical review, the next item on the agenda. She discussed the statistical analysis conducted in the paper and commented that it was unclear whether block with observed participants was included in the model. She noted that these studies were conducted before mixed models were prevalent in the statistics realm, so they could have included block in the model (but it was unclear). She commented further about the lack of statistically significant relationships with the different concentrations, as indicated by the F test, and this could be an erroneous result due to the independence assumption not being satisfied.

Dr. Sharp reiterated the re-examination that occurred in 1993 to quantify threshold concentrations using McNemar's test. She commented on the tables not being reproducible as they do not indicate the individual subjects in each exposure reporting symptoms. Dr. Sharp concluded with the decision that the analyses were limited and non-reproducible due to the absence of raw subject-level data analyses presented in the manuscripts. She reported that analyses relying on the assumption of independence and multiple exposure, like Fisher's exact test and Cochran-Armitage tests, should be interpreted with caution as the underlying correlation between observations cannot be accounted for, which could lead to type I errors.

Dr. Sharp recommended that a mixed model would be most appropriate for analyzing the original data, but it could not be considered due to lack of access to the raw data. She also suggested EPA express more prevalently in the report that the tests should be interpreted with caution. She also mentioned an unclear statement about odor sensation and eye irritation, which she suggested EPA break into shorter sentences to make comprehensive.

- **George Milliken:** If they randomized block analysis before mixed method was around, this analysis would be okay.
    - **Julia Sharp:** I agree, George. It was not clear whether they were doing a one-way ANOVA or including the subject as another factor in the analysis.

Dr. Sharp proceeded to the charge questions.

Dr. Sharp expressed no large concerns about the publication not providing scientifically sound reliable data and proposed a response in the chat.

Response: "The research described in the 1987 publication "Formaldehyde Dose-Response in Healthy Nonsmokers" and the 1993 publication "Acute Odor and Irritation Response in Healthy Nonsmokers with Formaldehyde Exposure" is scientifically sound, providing reliable data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposure to formaldehyde, given the recommendations provided by the HSRB are considered."

- **George Milliken:** I have an issue. They did not do reliable analysis of the data, but the data is reliable, analysis is not reliable (the authors' analysis, not EPA's analysis).
    - **Julia Sharp:** I think part of the data question relates to the data that was collected but also to the data that are resulting from the analyses, so it is hard to untangle those two things in my mind. Do you have a recommendation for how to change the response?
    - **George Milliken:** I would say something like: "providing reliable data and extracted reliable information."
    - **Lisa Corey:** These are explicitly covered that our recommendations need to be considered.

Dr. Sharp received unanimous agreement on the response and proceeded to the ethics review discussion, requesting that Dr. Philip Day and Ms. Nicole Deming take the lead.

Dr. Day agreed with EPA on their comments and ethics review. He focused on the lack of delineation between inclusion and exclusion criteria in the articles with respect to smoking status and recent history of allergy, asthma, or upper respiratory infection. He mentioned that although not clearly stated, there were potentially disqualifying elements of medical history related to the physical exam, electrocardiogram, and pulmonary function. He noted that risks were not detailed in either article, but investigators minimized risk to participants by selecting a formaldehyde exposure concentration in line with the accepted Occupational Safety and Health Administration standards of the day. Dr. Day confirmed there was no evidence to indicate that recruitment, selection, or screening was unethical or inequitable.

Dr. Sharp thanked them for their ethics review and the response to the ethics charge question was unanimously passed by all members, without questions or comments.

Response: "The Board does not find that the research described in the 1987 published article "Formaldehyde Dose-Response in Healthy Nonsmokers" and the 1993 publication "Acute Odor and Irritation Response in Healthy Nonsmokers with Formaldehyde Exposure" provides clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent."

J. Adjournment

Mr. Tom Tracy reminded the members about the 2023 meeting. Dr. Julia Sharp ended the meeting and thanked the board members.

The meeting adjourned at 4:00 p.m., EDT.

Thursday, October 27, 2022

A. Meeting Topic and Charge Questions

Topic: Field Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray Against Mosquitoes. Study Report MIM-006. May 12, 2022.

Charge to the Board – Science: Did the research summarized in "Field Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray Against Mosquitoes" generate scientifically reliable data, useful for estimating the amount of time that product tested repels mosquitoes?

Charge to the Board – Ethics: Does the available information support a determination that the research was conducted in substantial compliance with the applicable requirements of 40 CFR part 26, subparts K and L?

B. Convene Public Meeting Day 3

Tom Tracy, Designated Federal Officer, EPA HSRB, OSAPE

Dr. Tom Tracy led the HSRB member roll call. He invited members of the group to introduce themselves. Dr. Julia Sharp invited Dr. Michelle Arling from EPA to introduce herself. Additional EPA staff in attendance were invited to introduce themselves.

HSRB members	Lisa Corey, Ph.D., Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (Colorado State University) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Philip Day, Ph.D. (University of Massachusetts, Chan Medical School) Chad Cross, Ph.D. (University of Nevada-Las Vegas) 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. (University of Missouri-Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Siecean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) Eun Um, Ed.D. (AMSTAT Consulting) David Williams, Ph.D. (Oregon State University)
EPA staff members	Michelle Arling (EPA, OPP) Tom Tracy (EPA, OSAPE) Taylor Lass (EPA, OSAPE) Lexie (Mary) Burns (EPA, OSAPE)

	Dana Sackett (EPA, OPP) Clara Fuentes (EPA, OPP) Robert Mitchell (EPA, OPP) Stephanie Watson (EPA, Tribal Water Protection Office) Brandall Ingle (EPA, OPP) Kaitlin Saunders (EPA, OPP) Elizabeth Andrews (EPA, OPP) Virna Stillwaugh (EPA, OPP) Angela Myer (EPA, OPP) Kathryn Korthauer (EPA, OPP) Rebecca Lasko (EPA, OPP)
Members of the public, representatives of research sponsor and research team	Dana Lateulere (Bergeson & Campbell) Scott Carroll (Carroll-Loye Biological Research) Shawn King (Good Laboratory Practice Consultant) Laura Hall (Bergeson & Campbell) Afroditi Katsigiannakis (ICF, Contractor Support) Angelina Guiducci (ICF, Contractor Support) Aishwarya Javali (ICF, Contractor Support) Emily Pak (ICF, Contractor Support)

Dr. Corey reviewed the agenda and overview for the day. She also reviewed Zoom's tools and features and stated the purpose of the meeting was to review the paper "Field Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray Against Mosquitoes." She noted the minutes of the meeting, and a report will be prepared, certified, and posted on the website within 90 days of October 27, 2022.

C. EPA Science Review Highlights

Timothy McMahon, Ph.D., OPP Antimicrobials Division

Dr. Clara Fuentes presented the science review highlights.

On slide 1, the title of the presentation was provided. On slide 2, the study overview and objective were given. On slides 3 and 4, the submission history was addressed. The study was submitted to EPA for review in 2020. One slide 5 points of clarification were provided. Mosquito density and landing thresholds in subject attractiveness testing was discussed. On slide 6, endpoints and definitions of terms used in the study were discussed. The endpoint is "First Confirmed Landing." Repellency was measured by "Complete Protection Time" (CPT). On slides 7 and 8, information regarding conformity with amended protocol was discussed. On slide 9, an overview of the study design was summarized. Two testing sites were selected from California, and field testing was conducted with 13 treated subjects/field sites. On slide 10, the study objective was given: determine the median complete protection time (mCPT) of the proposed product against wild adult mosquitoes in the field using volunteer human subjects. On slide 11, an overview of field sites used in the study was given. Site 1 was a flooded forest, and site 2 was an open wetland. On slide 12, field site monitoring was reviewed. The field sites were

monitored weekly for 2 months prior to study initiation. On slide 13, the trap collection days were discussed. Collection days differed at sites 1 and 2. On slide 14, an overview of the attractiveness test was provided. The data showed all test subjects passed attractiveness with two landings/minute. On slide 15, an overview of aspirator training was provided. Subjects practiced in the lab following the attractiveness testing.

On slide 16, randomization was discussed. Total enrollment increased from 40 to 46. Randomization was stratified by gender at each field site. On slides 17 and 18, a product application was described. The product was applied onto the forearm. The time of product application differed by less than 20 minutes among subjects. On slide 19, field testing was described, and test days and sites were provided. Exposures were conducted between midday and evening. On slide 20, the subject's arrangement at field sites was discussed. Exposure areas were 30 meters in size for occupancy of 20 subjects and four staff members. On slide 21, field testing and data collection were discussed. Controls monitored landing pressure during exposure periods preceding treated subjects' exposure periods. On slides 22 and 23, field testing and collected mosquitos were addressed. Data for total number of mosquitos landing and collected from controls and treated subjects were provided. On slide 24, the study results were presented. The mCPT was undetermined (>9 hours). On slide 25, an overview of the statistical analysis was given. EPA's analysis was performed using SAS and log-log transformation for determination of the 95% CI.

On slide 26, protocol deviations were discussed. Some examples included gloves being replaced by finger cots for dose application, the lack of measurement of lower legs for testing efficacy, and enrollment increasing from 40 to 46 participants. On slides 27, 28, and 29, the responses to points of clarification were provided. For example, clarification was provided on the site-monitoring procedure, the attractiveness test, and aspirator training. Additionally, responses to proximity of test field sites and overlap of predominant species between the field sites were discussed. EPA found all rationales acceptable. On slide 30, a graph of species landing at sites 1 and 2 at different times of day was provided. On slide 31, field monitoring trapping data was shown. Two EPA-generated plots were presented, displaying trapping data at the two sites. On slide 32, a graph displaying distinction between field sites was highlighted. Differences in trapping data at the sites were shown on the graphs. On slide 33, conclusions from EPA's principal component analysis on site similarity was provided. The analysis concluded the two sites were different and distinct habitats.

On slide 34, various reliability measurements were discussed (no participants withdrew or were replaced, etc.). On slide 35, risk minimization was discussed. Field sites were monitored for detection of pathogens 1 month prior to field testing (among other minimization techniques). On slides 36 and 37, recommendations to future studies were discussed. Future studies should select field sites that include mosquitos EPA requires for general mosquito claims and applicable disease vector claims. Future studies should also provide detailed descriptions of study conduct in the report. On slide 37, recommendations to the amended protocol were noted. For example, "Biting Pressure" should have been removed from the protocol. Additionally, certain references should have been added. On slides 38, 39, and 40, the EPA science review conclusion was provided. The data support an overall mCPT of 8 hours

against mosquitoes. The conclusion was based on the review and implementation of results consistent with the amended study protocol. On slide 41, EPA's policy on determining mCPT was discussed. EPA follows the "Repellency Awareness Guidelines on Skin Applied Insect Repellent Producers" in setting mCPT. On slide 42, the charge question was presented.

D. Board Questions of Clarification

Lisa Corey, Ph.D., HSRB Chair

Dr. Lisa Corey opened the discussion for questions of clarification from the board.

- **Lisa Corey:** Are there any requirements for which species are measured, or is the genus level sufficient for labeling and registration requirements?
    - **Clara Fuentes:** It was our policy until the rule this year to have representative vectors different from the main general ones. Specific vector species of pathogens against Zika, Dengue, West Nile, and encephalitis must be tested.
- **Sinziana Siecean-Boose:** I was wondering, in terms of subject variability, if you had collected any data related to perspiration during the experiment or the blood type of the subjects and also if you had any specific requirement in terms of body hygiene?
    - **Clara Fuentes:** There is preparation ahead of the field-testing day, wherein for 48 hours, subjects cannot be using cigarettes, perfumes, or repellents in preparation for the test.
- **Sinziana Siecean-Boose:** I think it was a good thing that this was a block gender randomization design.
- **George Milliken:** Yes, you talked about 40–46 subjects. Did you use the six new subjects to have 16 per treated group? What happened to the six new subjects?
    - **Clara Fuentes:** From these 46 subjects, they selected 13 who were testing the repellent, two untreated as controls, and five as alternates; others were dismissed.
- **Sri Melethil:** What happens once the mosquito lands on the site of the body? Is that when aspiration comes in, when the subject removes the mosquito before it bites?
    - **Clara Fuentes:** The area of the skin that is exposed – that is where aspirators are used when those mosquitos land there.
    - **Sri Melethil:** How exactly is the mosquito removed?
    - **Clara Fuentes:** An aspirator is used, which has a piece of mesh at the end to trap the mosquito.
- **Sri Melethil:** Was there any concern about dermal absorption in these studies?
    - **Clara Fuentes:** The risk of rate of application for the hours the subjects would have the substance on their skin was calculated. It was below the levels of concern. There was no issue with having irritation, no concern.
- **David Williams:** In terms of site selection, I think EPA was correct to allow the investigators to use the two sites they did. EPA requires sites to be separated by 15 km, which is about the distance the mosquitoes can travel. I thought they were correct.
- **Sinziana Siecean-Boose:** You showed the graph of the longitudinal data collection of the

mosquito types, and I was wondering whether you did any sensitivity analysis – and if you are sure of the reliability of the data, whether you validated the data related to the data collection.

- **Clara Fuentes:** The dropping data that is collected during site monitoring prior to field testing, and that is very important because it is used to determine whether there are pathogens in the area prior to field testing.
- **Sinziana Siecean-Boose:** My question is: Were there any differences in who collected the data, or is there any reason why the data should be changed?
- **Clara Fuentes:** I do not know specifically who collected the data but just know that it was done by the lab and technicians there.

E. EPA Ethics Review of Highlights

Michelle Arling, J.D., OPP

Ms. Michelle Arling presented an ethics review to the board. She outlined her overview and provided information about recruitment via craigslist, listserv, newsletter, and word of mouth, as well as informed consent taken from all participants. Ms. Arling listed the requirements for subject eligibility. She noted that out of 57 respondents, 46 consented to enroll, comprising 20 males and 26 females ranging from 19 to 54 years of age.

Ms. Arling mentioned pretesting procedures, such as when subjects should arrive and what they should wear. They also were asked not to apply materials on their skin prior to testing. She noted that each subject's skin was prepared by washing with soap and water and rinsing with ethanol, after which a trained researcher applied the material. Testing continued until seven subjects experienced product failure; at that point, their arms were washed, and their skin checked, and they received their compensation. She noted the subjects received compensation consistent with the protocol. She assured subjects were asked to follow and use items for personal safety, and medical professionals were on site to monitor subjects and check skin for disqualifying conditions. Subject privacy and respect were also maintained.

Ms. Arling reported protocol amendments took place three times, with several inclusions and corrections. They were all approved by the institutional review board (IRB) with different dates of approval. She reported there were deviations from the protocol in terms of subject pool and unequal gender distribution. She reminded the group about the review of the protocol, which took place in April 2021, when the HSRB concluded the research was likely to meet applicable ethical requirements, if EPA recommendations were addressed.

Ms. Arling listed the findings in detail and EPA's recommendations on the conducted study. She concluded that the available information indicated that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

F. Board Questions of Clarification

Lisa Corey, Ph.D., HSRB Chair

There were no questions of clarification.

G. Public Comments

Dr. Lisa Corey provided the platform for this public comment:

- **Scott Carroll:** It is a great pleasure for us to be here discussing work that we have been involved with for years. I thought it would be informative to respond to the cogent question about other factors behind the sudden shift in the constituency of mosquito species. At one of our field sites, there was a strong difference between the two, and the methodology remained consistent throughout the entire period. We feel confident about the data records for a couple of reasons:
    - There is a discrete set of about 10 species, three of which are most common, and those are the most fundamental ones that are listed in EPA's new rule of species. They are the most abundant in the region in general. The bloom of Culex in site 2 is something we look forward to every year, related to flooding of wildlands. They are reliably not vectoring West Nile. The Culex in North America is not as reliable. The summer generation carries West Nile; the fall generation does not.
    - The downside might be our expectation that we would start to find 10,000 Culex mosquitoes in our Carbon Dioxide traps, where there had been only scores in the prior week, but the shift is very striking to any mosquito biologist.
    - So entomologically, it matched all expectations, and there is a wildlife spectacle at the micro level that occurs annually and is the fundamental basis for us being able to do a really good job.

H. Break

I. Board Discussion

Lisa Corey, Ph.D., HSRB Chair

Lisa Corey summarized the agenda for board discussion, which began with the science categories and moved on to statistical considerations and recommendations for the board to consider. Dr. Corey outlined the objective of the study, explained the repellant formulation, noted the seven protocol deviations, and how they, along with the study locations, were well described. EPA's overall conclusions were reported by Dr. Corey, who stated that the assessment found the study results acceptable to support the CPT of 8 hours against mosquitoes for the proposed spray repellant. In addition, based on the HSRB's review of the materials, they agreed with EPA conclusions that the study does provide reliable, scientifically sound data to support the CPT. EPA and sponsor revisions were noted to be much stronger than the original report. The protocol deviations were not found to undermine the conclusions, and HSRB agreed with the future considerations noted, as well. The main recommendation for the study report, Dr. Corey noted, concerned an inconsistent use of scientific references to support scientific statements. Making a claim about something that is known scientifically should be consistently referenced in each section, which was not the case; Dr. Corey noted that this continued to be a recommendation after issues were pointed out earlier in the process. Dr. Corey then invited David Williams to share his review.

Dr. David Williams thanked Lisa Corey for her work and pointed out that in the questions of clarification (question number 3), his comment was a mistake as he was examining a different study, which did have a skewed gender ratio. He noted that his other concerns were addressed by the presentation, as was a question on demographics and the role of ethnicity in landing behavior. Dr. Williams concluded that he agreed with EPA about the distinct site locations and that they had to refrain from labeling the product effective against certain pathogens because testing with other species was not included.

Dr. Lisa Corey opened up the presentation to clarifying questions.

- **Sinziana Siecean-Boose:** This question is for EPA. I know it was stated that you would like to see in the future the collection of more demographic characteristics, which I think is actually a great idea because those also can be important confounders. I was wondering whether EPA is looking at including disadvantaged populations in these studies and, if yes, whether there are any thoughts on how well you can monitor this.
    - **Michelle Arling:** Yes, I can answer that. We do not conduct the studies, so we do not have control over this.
    - **Sinziana Siecean-Boose:** That is correct. I was talking about guidelines**.**
    - **Michelle Arling:** We want our testing to be demographically representative of the population, so we are not planning on issuing guidelines for specifically targeting minority populations for participation in this kind of test.
    - **Sinziana Siecean-Boose:** Okay, yes, it is just a matter of percentages because disadvantaged populations are often a large portion of the general population, but yes, I understand.

Dr. Lisa Corey reminded the group that they will be looking particularly at the charge questions to formulate responses.

- **Sri Melethil:** I never received the memo. In the future, should I be expecting to examine other resources to find it?
    - **Michelle Arling:** Yes, it was included in the SharePoint.
    - **Sri Melethil:** Thank you. For the study, what happened to the 46 subjects? In the report, it ended up being only 26. Could you clarify this difference?
    - **Michelle Arling:** Yes, a total of 46 subjects consented to do the study, but on each study day, only 20 subjects were needed (under the protocol, they needed 13 test subjects, two control subjects, and five alternate subjects). More individuals were asked to consent in order to have additional subjects available in case an individual was not available on a particular day or dropped the study.
    - **Sri Melethil:** As a suggestion, it should be made more clear that this was the case.
    - **Michelle Arling:** Okay, thank you for that feedback.

Dr. Lisa Corey transitioned to the statistical review, introducing Eun (Ann) Um to do the summary. Dr. Um stated that the statistical analysis was done within each half-day; thus, protocol deviation could not compromise the results. Kaplan-Meier survivor analysis was done using 95% CI and log transformation;

thus the statistical mapping was appropriate and the study reliable. However, Dr. Um noted the findings cannot be generalized to other states. Because of this, she recommended that researchers add other states. Dr. Corey then opened the presentation for questions or comments.

- **Julia Sharp:** Ann, was your recommendation to add to the HSRB report that the results cannot be generalized to other populations?
    - **Eun (Ann) Um:** Yes, there was a limit to the studies conducted, so I recommend that researchers add additional states.
    - **Lisa Corey:** I would like to go into this further because it may influence our response. To clarify: Would that be for future studies or does this limit our ability to respond to the charge today?
    - **Eun (Ann) Um:** Future studies.
- **George Milliken:** Ann, did they have the 95% lower CI on the CPT? I did not find those in the documentation.
    - **Eun (Ann) Um:** They provided a 95% CI that differed from the 95% CI reported for site 2 because of default transformations in the statistical programs.
    - **George Milliken:** So, did you find those lower CIs? I did not.
    - **Julia Sharp:** I am looking at the EPA Science Review, page 15. EPA did an analysis, and the BMDL was 454 seconds, and the upper confidence limit was 584 seconds for site 1. On page 15, it is listed as seconds; maybe that should be minutes. Can EPA clarify?
    - **Clara Fuentes:** Could you repeat the questions?
    - **Julia Sharp:** We were wondering what the values for the 95% CI are. In the table on page 15, it is listed as minutes, and in the interval, it is listed as seconds.
    - **Clara Fuentes:** In the study report? That must be a mistake.

Lisa Corey asked whether there were any other points of discussion and said they could now look at the charge questions. She asked the charge question: "Did the research summarized in 'Field Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray Against Mosquitoes' generate scientifically reliable data, useful for estimating the amount of time the product tested repels mosquitoes?" Dr. Corey asked whether there were any suggestions for edits or changes; seeing none, she went ahead with the vote. All 13 voted to show approval.

A.J. Allen then began to speak and introduce the ethics questions, noting he made additional changes to what was submitted and will send the written revisions. He noted he wanted to go through the important aspects of the ethics review question and emphasized the weight of ethical guidelines and what they explicitly state, highlighting the importance of complying with common rules, informed consent, and the exclusion of pregnant women and children. Dr. Allen acknowledged that the youngest participant was 19 years of age, and that the study excluded pregnant women and used extensive pregnancy testing throughout the study, meeting the requirements for 26-1703. In terms of 26-1705, Allen discussed the common rule, stating the most relevant parts indicated the research must be scientifically sound and the protocol and materials must be reviewed by an IRB, and he discussed how this study specifically met

these requirements. He went on to highlight the IRB reviewer, Advarra, and how it met the rules, adding that EPA and HSRB performed their own reviews. The researchers tried to minimize the risks, and Dr. Allen added that there were no direct benefits of the research to the individual subjects; thus, it is important to see how societal benefits may come from this study and relate to the participants. Deviation from the protocol was not viewed as having caused any additional risk to subjects. One limitation highlighted was the English-language requirement, which in Northern California may have limited the equitability of the study due to large numbers of Spanish-language speakers; however, this was not possible to determine due to limited data. During the HSRB review, questions were raised about diversity, and information was requested on how diverse populations were recruited; however, this was not conducted and researchers instead indicated that ethnicity has not been found to be related to biting. Gender balance was attempted despite higher female response, and there was a scientific justification for this as there may be differences in mosquito attractiveness. Dr. Allen thought there should be some effort made, so the study population would be in line with the demographics of the state or area. He recognized that this study follows the common rule, but due to limited information in their report, determination of ethical selection of subjects was not possible. The variety of ways subjects were recruited from a community was highlighted. In addition, they had to independently respond to the announcement and participate in an informed consent session and additional steps, which further enhanced the consent requirements. The recruitment of students was noted, although there is no guideline against it. Dr. Allen noted the subjects were compensated, which was consistent with the IRB protocol, and that such compensation did not unduly influence subjects' participation. Additionally, Dr. Allen noted that report formatting matters, and he found this report difficult to review for comprehension; thus, better organization would be advised. Lisa Corey opened up the floor to ethics-related questions:

- **Sri Melethil:** Commenting on student coercion, around 1970, a course at the University of Buffalo was cancelled because students were required to take a prescription (even though there was informed consent), so I wanted to make note of that. What happens in a situation where there is a protocol breach and yet, the study director finds it is okay (though fails to notify the IRB)? Should we say something that in the future, in such situations, the IRB should be notified?
    - **A.J. Allen:** Well, spelled out in the regulations with IRBs and in terms of their monitoring studies, there are conditions for when you need to report study deviation and also when you need to report an adverse event, particularly if it is a serious adverse event or such, so I am not sure we need to say that. I believe this is reflected in the common rule policy requirements. This is a great point to make.
    - **Sri Melethil:** Okay, thank you.

Dr. Lisa Corey opened the vote after no suggestions or comments were made to the response below. The ethics-related question: "Does the available information support a determination that the research was conducted in substantial compliance with the applicable requirements of 40 CFR part 26, sub part K and L?"

Dr. A.J. Allen crafted the following response to the charge question: "Based on its review of the materials provided by EPA and subject to any limitations or recommendations of EPA or the HSRB, the HSRB concludes that the 'Field Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray Against Mosquitos' was conducted in substantial compliance with the applicable requirements of 40 CFR part 26, subparts K and L." All 13 individuals indicated their approval. Dr. Allen noted his two additional recommendations for EPA: "The HSRB recommends that EPA require future study reports to contain more information regarding demographics of subjects selected for study, including breakdowns according to age, gender, AND minorities and ethnicities (while not ideal, the U.S. Census categories are a good starting point) in order to improve EPA and HSRB's ability to evaluate the equitable selection of subjects."

- **George Milliken:** Could we include "ethnicity" or something similar? Though it is difficult to get a distribution of ethnicities with 13 subjects.
    - **A.J. Allen:** The idea is that "minorities" is a Census category, which is a well-known starting point, although not ideal. Technically, you are dealing with both minorities and ethnicities. This particular study had only "male" and "female," but you could potentially have additional categories in terms of gender.
- **Julia Sharp:** Can "minorities" be replaced with "race"? And if there is another mechanism besides being entered into the report, that would be a better approach.

Dr. A.J. Allen responded it may be consistent with the report. Dr. Michelle Arling thought it would be fine to include in the report and noted that it applies more broadly than just this study, as previous HSRB recommendations are examined when conducting reviews.

- **Sinziana Siecean-Boose:** I thought using "Census category" instead of stating minority, race, or ethnicity would be more helpful and sufficiently broad, perhaps including information such as income and poverty levels.
    - **A.J. Allen:** I do not have a problem including this information but am not sure whether Census categories specifically will be continued to be used, so it may be less relevant.
    - **Tom Lewandowski:** I am concerned that in putting these recommendations in this particular report, it seems like we are targeting or have a problem with this report (instead of making a broader comment), implying it was not actually acceptable but we are letting it slide.
    - **Lisa Corey:** A proposition: EPA has "recommendations for future studies." I propose we move this to a separate section that includes all future recommendations so as not to limit or target this study.

The new proposal was stated as follows: "The HSRB recommends that EPA require all future study reports to contain more information regarding demographics of subjects selected for study, including breakdowns according to age, gender, race, and ethnicity (while not ideal, the Census categories are a good starting point) and potentially other characteristics in order to improve the EPA and HSRB's ability to evaluate the equitable selection of subjects."

J. Closing Comments and Next Steps

Lisa Corey, Ph.D., HSRB Chair

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

Dr. Julia Sharp stated that all the reports from the past few days will be combined into one, so that all comments can be concatenated in this report and have a separate section for future studies.

Dr. Lisa Corey set a timeframe for comments to be submitted by members, November 11th, and that they will reconvene. She indicated HSRB will be reporting one large packet and another study that will be reviewed at that future meeting. Dr. Corey then said that unless there was anything else, the meeting was concluded, thanking everyone at EPA and HSRB. She noted that this was a large amount of work and appreciated everyone's efforts (and also ICF for hosting). Tom Tracy expressed appreciation, too, to all of the board members and the EPA participants, hoping everyone received an invitation to the future meeting.

K. Adjournment

The meeting adjourned at 4:00 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.	Associate Professor	Colorado State University 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	Principal	Gradient Seattle, WA
Srikumaran Melethil, Ph.D.	Professor Emeritus	University of Missouri-Kansas City Kansas City, MO
George Milliken, Ph.D.	President	Milliken Consultants Manhattan, KS
Sinziana Siecean-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–9328–01–ORD]

Human Studies Review Board; Notification of Public Meetings

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 the 2022 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. January 25–27, 2022;
2. April 26–28, 2022;
3. July 19–21, 2022; and
4. October 25–27, 2022.

Meetings will be held each day from 1 p.m. to 5:00 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 2 p.m. to 4 p.m. Eastern time on the following dates: March 17, 2022; June 16, 2022; September 14, 2022; and December 14, 2022.

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 the Office of Pesticide Programs (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 pre-register 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 pre-registered 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.