EPA Human Studies Review Board (HSRB)
May 16–18, 2023 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A.)
Date and Time: Tuesday, May 16, 2023, Wednesday, May 17, 2023, and Thursday, May 18, 2023, 1:00 to 5:00 p.m. EDT.
Location: Via Zoom
Purpose: The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subjects research.
HSRB Website: https://www.epa.gov/osa/human-studies-review-board

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EPA Human Studies Review Board (HSRB)
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Tuesday, May 16, 2023:

A. Meeting Topic and Charge Questions

Topic: Mueller, J.U., Bruckner, T., and Triebig, G. (2013) Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males. Int Arch Occup Environ Health 86:107–117. DOI 10.1007/s00420-012-0745-9

Charge to the Board – Science: Is the research described in "Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males" by Joerg U. Mueller, Thomas Bruckner, and Gerhard Triebig scientifically sound, providing reliable data for use in a weight of evidence to determine a point of departure (POD) for acute inhalation exposures to formaldehyde?

Charge to the Board – Ethics:

- Does available information support a determination that the conduct of the research was not fundamentally unethical?
- Does available information support a determination that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted or conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

B. Convene Meeting and Introduction of Members

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

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

HSRB members
Lisa Corey, Ph.D., Co-Chair (Intertox, Inc.) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Chad Cross, Ph.D. (University of Nevada – Las Vegas) Philip Day, Ph.D. (University of Massachusetts, Chan Medical School) Nicole Deming, J.D., M.A. (Case Western Reserve University, School of Medicine) Weiying Jiang, Ph.D. (California Environmental Protection Agency) Thomas Lewandowski, Ph.D. (Gradient) Srikumaran Melethil, Ph.D., J.D. (University of Missouri – Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Seicean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) Eun Um, Ed.D. (AMSTAT Consulting) David Williams, Ph.D. (Oregon State University)

EPA staff members
Michelle Arling (EPA, Office of Pesticide Programs (OPP)) Rochelle Bohaty (EPA, OPP) Deborah Burgin (EPA, OPP) Lexie Burns (EPA, OSAPE) Madison Clark (EPA, OSAPE) Jeffrey Dawson (EPA, OPP) Timothy Dole (EPA, OPP) Elizabeth Donovan (EPA, OPP) Judy Facey (EPA, OPP) Timothy McMahon (EPA, OPP) Monique Perron (EPA, OPP) Santhini Ramasamy (EPA, Center for Public Health and Environmental Assessment (CPHEA) Colleen Rossmeisl (EPA, OPP) Dana Sackett (EPA, OPP) Monique Tadeo (EPA, Program in Human Research Ethics and Oversight (PHREO)) Tom Tracy (EPA, OSAPE) Susanna Wegner (EPA, OPP)
Members of the public, representatives of research sponsor, and research team:
Sorina Eftim (ICF, Contractor Support) Angelina Guiducci (ICF, Contractor Support) Debra Kaden (Ramboll) Afroditi Katsigiannakis (ICF, Contractor Support) Katie Lenae (ICF, Contractor Support) Lucas Rocha Melogno (ICF, Contractor Support) James Sherman (Celanese)

C. Meeting Administrative Procedures

Tom Tracy, DFO, HSRB, OSAPE

Mr. Tom Tracy reviewed the Zoom platform tools and features and stated the purpose of the meeting was to review the paper by Mueller et al., "Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males." He noted minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of May 18, 2023.

D. Opening Remarks

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

Dr. Lisa Corey welcomed everyone to the EPA HSRB meeting, briefly introduced the studies under discussion, and outlined the meeting process. She then asked for updates from OPP.

E. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Michelle Arling stated there was nothing to update the committee on for the study that was discussed at the meeting in April, and there were no new updates on any research that had previously been considered by HSRB members.

F. EPA Science Review Highlights

Deborah Burgin, Ph.D., DABT, OPP Antimicrobials Division

Dr. Deborah Burgin thanked the committee and introduced the study, "Use of Human Studies for Derivation of an Acute Inhalation Reference Concentration (RfC) for Formaldehyde" while sharing the slides. Slide 2 had acknowledgements of members of EPA OPP, EPA Office of Pollution Prevention and Toxics (OPPT), and ICF, who had worked on the science review. Dr. Burgin turned it over to Ms. Arling to review slide 3, which provided an overview of the Human Studies Rule.

Ms. Arling provided an overview of the Human Studies Rule, which outlines the requirements for consultants with the HSRB. Intentional exposure studies initiated after April 2006, studies conducted prior to April 2006 with the intent to identify or measure a toxic effect, and all proposals for intentional exposure studies initiated after April 2006, have to be reviewed at both the protocol stage and before the research is initiated. The Human Studies Rule applies to research involving intentional exposure of human subjects but does not cover observational research.

Slide 4 introduced the difference between intentional exposure and observational exposure studies. Intentional exposure studies are defined in the Human Studies Rule; they are limited to adults and non-pregnant, non-nursing women; they are evaluated from scientific and ethical perspectives; and under the Human Studies Rule, consultation with HSRB is required prior to EPA's reliance on the research. Observational studies are non-intentional exposure studies. They have no Human Studies Rule restrictions on participants' ages and pregnancy status, they are evaluated from a scientific and ethical perspective, and there is no requirement under the Human Studies Rule for consultation with HSRB prior to EPA's reliance on the research.

Slide 5 provided an outline for the presentation, which included an introduction and purpose, background, and the presentation order for the next three days.

Slide 6 provided the introduction and purpose of the review. The OPP and OPPT are evaluating the risks from exposure to formaldehyde under their respective statutes. The Agency is consulting with the HSRB on the scientific and ethical conduct for two of four intentional human exposure studies that examined responses to short-term inhalation exposures to formaldehyde. The Agency previously presented the two other studies to the HSRB in October 2022. It is also consulting with the HSRB on its weight of evidence of human studies to support the derivation of the acute reference concentration for the OPP and OPPT assessments.

Slide 7 provided background on the chemical of interest, formaldehyde. Formaldehyde is a highly water-soluble chemical that can exist as a liquid or a gas. It is a naturally occurring substance and can be found in the living systems of both plants and animals. Given the high vapor pressure of formaldehyde and registered use patterns, inhalation is expected to be a significant route of exposure.

Slide 8 described the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) under which OPP operates. FIFRA governs the restoration, distribution, sale, and use of pesticides in the United States. Under FIFRA, registered pesticides are required to undergo periodic re-evaluation to ensure they continue meeting the standard of no unreasonable adverse effects on human health and the environment. Slide 9 continued describing FIFRA and the registered use sites for formaldehyde. Those sites include agricultural, food handling, and veterinary premises and equipment; commercial/industrial/institutional premises and equipment; industrial processes and water systems; and material preservation of industrial and household products.

Slide 10 detailed the Toxic Substances Control Act (TSCA). OPPT works under TSCA, which requires reporting, record-keeping and testing, and restrictions related to chemical substances and/or mixtures. TSCA requires a risk evaluation to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment. It was noted that certain substances are generally excluded from TSCA, including food, drugs, cosmetics, and pesticides.

Slide 11 described the TSCA conditions of use for formaldehyde. Those conditions include use of formaldehyde as a reactant, incorporation of formaldehyde into articles, and incorporation into formulation, mixture, or reaction products for various industrial, commercial, and consumer applications. Further conditions of use include textiles, foam bedding/seating, semiconductors, resins, glues, composite wood products, paints, coatings, plastics, rubber, resins, construction materials, furniture, toys, and various adhesives and sealants.

Slide 12 detailed OPP and OPPT coordination on formaldehyde. Given the different conditions of use and the statutory authorities of FIFRA and TSCA, OPP and OPPT will conduct separate risk evaluations for formaldehyde. However, both offices are coordinating on the development of the hazard characterization that will be referenced by FIFRA risk assessment and TSCA risk evaluation and on the schedule for releasing the draft documents. Both OPP and OPPT rely upon work already completed by EPA's Integrated Risk Information System (IRIS) whenever possible.

Slide 13 described IRIS's role within the formaldehyde assessment. IRIS is a human health assessment program that characterizes the health hazards of chemicals found in the environment. It is located within the Center for Public Health and Environmental Assessment in the Office of Research and Development. The IRIS toxicological review of formaldehyde inhalation was published for public comment in April 2022 and is currently under review by an independent external scientific peer-review board managed by the National Academies of Sciences, Engineering, and Medicine (NASEM), under contract with EPA.

Slide 14 continued the description of the IRIS formaldehyde assessment. IRIS performed extensive characterization of chronic non-cancer and cancer hazards from inhalation exposure to formaldehyde. Shorter inhalation duration (acute, short-term) exposures are not the focus of the assessment. Lastly, OPP and OPPT toxicologists are currently jointly working to derive points of departure for acute inhalation hazard from formaldehyde.

Slide 15 continued the description of the IRIS formaldehyde assessment. The published literature contained a multitude of human studies relevant to acute and short-term exposure to formaldehyde. IRIS has identified several observational and controlled human exposure studies for their chronic reference concentrations. There were several endpoints considered, including sensory irritation, pulmonary function, immune-mediated conditions, and respiratory tract pathology. Sensory irritation was selected due to rapid onset and rapid resolution when exposure ceases. Sensory irritation is appropriate for acute inhalation point-of-departure derivation. It was noted that it was appropriate for selection because of anticipated exposure, according to the Office of Chemical Safety and Pollution Prevention's (OCSPP's) registered uses and conditions of use.

Slide 16 detailed sensory irritation as an acute effect. Sensory irritation is an adverse effect observed in human studies of short-term inhalation exposures to formaldehyde. Controlled human exposure studies provide quality data for determining eye, nose, or throat irritation from inhalation exposures to formaldehyde. The exposure-response relationship is more precise, and potential confounders are less of a concern in controlled exposure studies.

Slide 17 detailed the sensory irritation dataset and how study selection occurred. OPP and OPPT toxicologists examined the IRIS inhalation dataset and determined that four intentional exposure chamber studies with sensory irritation effects were appropriate for use. Two studies were reviewed by HSRB in October 2022 (Andersen and Mølhave 1983, and Kulle et al. 1987), and the remaining two studies by Mueller et al. (2013) and Lang et al. (2008) were set to be reviewed during the current HSRB meetings.

Slide 18 introduced the current study to be discussed by the HSRB, "Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males" by Mueller et al. (2013).

Ms. Arling discussed some of the background on the Mueller et al. study on slide 19. It was stated that OPP made multiple attempts to request the raw data and documentation of the ethical conduct of the study. Dr. Mueller did not respond to any emails. Dr. Bruckner was retired and could not be contacted. However, Dr. Triebig responded and provided a copy of the approval letter from the ethics committee. It was noted that the study sponsor was unable to locate any of the files related to the study. The institute where the research was conducted was closed within the University of Heidelberg, and German law requires research records be kept for only 10 years. Documentation of the efforts to gain access to the raw data was provided in the EPA's ethics review memo.

Dr. Burgin described the purpose of the Mueller et al. study on slide 20. The Scientific Committee on Occupational Exposure Limits (SCOEL) was set up by the European Commission to evaluate the potential health effects of occupational exposure. In 2008, SCOEL concluded that the time-weighted average (TWA) occupational exposure limit for formaldehyde should be kept at or below the no-observed-adverse-effect level for sensory eye irritation. It also proposed an inductive occupational exposure limit of 0.2 ppm with peak excursions of 0.4 ppm to account for possible interindividual differences in susceptibility to irritation by formaldehyde. Mueller et al. developed this study to address the issue of interindividual susceptibility to chemosensory formaldehyde effects.

Slide 21 detailed the Mueller et al. experimental design. The study measured irritant effects of formaldehyde on male volunteers, who were defined as hypo- or hypersensitive for sensory irritation based on nasal sensitivity to carbon dioxide as a surrogate. Forty-one healthy, non-smoking, male subjects, with a mean age of 32±9.9 years, participated in the study. The exclusion criteria included an eye-blinking frequency of greater than 2 times/min; allergy and/or skin diseases; drug abuse; consumption of alcohol greater than 50 g/day; exposure to formaldehyde at the workplace or at home; diseases of the respiratory tract, metabolism, or heart; and inadequate vision without visual aids.

Slide 22 continued the description of the experimental design. Each subject received five separate 4-hour exposures to formaldehyde vapor (0, 0.5, 0.7, 0.3 ppm with peak exposures of 0.6 ppm, or 0.4 ppm with peak exposures of 0.8 ppm). It was noted that exposures were completed on five consecutive days, and the exposure sequence was determined by blinded randomization. Peak exposures occurred four times during the exposure period for 15 minutes each. During the exposure period, subjects exercised on a cycle ergometer at 80 watts for 15-minute intervals at predefined times. Lastly, the subjects were instructed not to eat shortly before examination and during exposure and could not drink non-sparkling bottled water.

Slide 23 detailed the parameters assessed, which included the following objective measurements: conjunctival redness, eye-blinking frequency, and nasal resistance and flow. The authors also assessed self-reported tear film break-up time. Subjects' symptoms and complaints were measured by the Swedish Performance Evaluation System (SPES) questionnaire. Ratings of symptom strength or severity were also documented using a visual analog scale from 0 to 1,000. Questionnaire symptoms were gathered prior to exposure and shortly before the end of exposure, inside the chamber.

Slide 24 listed more parameters assessed. Mueller et al. also assessed nasal sensitivity to carbon dioxide, which was used as a surrogate for individual chemosensitivity. These effects are mediated by the trigeminal nerve, which is distinct from activation of the specialized chemical sense such as olfaction or taste. Measurements were taken using a visual analog scale. They were taken daily before and after exposure to formaldehyde and during three follow-up tests at one-week intervals after the end of exposure. Using the median of the carbon dioxide sum score, participants were classified as either hyposensitive or hypersensitive. In total, 20 participants

were classified as hyposensitive and 21 were classified as hypersensitive.

Slide 25 detailed the experimental order. Subjects were examined approximately 1 hour before the start of exposure and 1 hour after the end of exposure. Measurements of nasal flow rates and self-reported tear film breakup time were recorded, along with the detection of carbon dioxide sensitivity (through photo documentation of conjunctival redness), eye-blinking frequency both outside the chamber and during the last 15 minutes inside the chamber (through video recording), and subjective symptoms and complaints reported on the SPES questionnaire before exposure and during the last 15 minutes inside the chamber.

Dr. Burgin then presented slide 26 with an Inhalation Chamber Diagram from another study but stated it was fairly representative of inhalation chambers used in the present study. She described how an inhalation chamber worked. The participant sits inside the large box on the bottom of the chamber. The chemical of interest is introduced on the right of the diagram and goes through several filters before exiting on the left. The air then leaves the chamber on the left and goes through a series of carbon filters before exiting.

Slide 27 provided an overview of the statistical analysis completed by Dr. Sorina Eftim from ICF. ICF assumed independence between responses at different doses, and several statistical approaches were used due to a lack of raw data. Fisher's exact test was used to test whether the response rates at different doses were equal. Mean differences before and after exposure to formaldehyde, or between any exposure scenario and control condition, were tested using a Student's t-test. Discomfort and sensory irritation data were also analyzed for the probability of a response as a function of dose using EPA's Benchmark Dose Modeling Software. A benchmark response (BMR) of 10% was assumed during analysis.

Slide 28 described results from the statistical analysis. It was reported that the measured formaldehyde concentrations were in close agreement with target values.

Slide 29 discussed the sensory irritation results. There was an apparent (non-significant) increase in conjunctival redness in hyposensitive groups at 0.5 and 0.7 ppm (this was not confirmed by ICF). Eye-blinking frequency was unaffected in all treatment groups, although there was large variability in individuals. This result was confirmed by ICF. Tear film break-up time significantly increased in both hyposensitive and hypersensitive individuals in the 0.4/0.8 ppm and 0.5 ppm exposure groups compared to pre-exposure and in hypersensitive individuals at 0.4/0.8 ppm and 0.5 ppm compared to 0 ppm. It was also reported that nasal flow rates increased in hypersensitive subjects at 0.7 ppm.

Slide 30 detailed the subjective symptoms reported in the study. Hyposensitive individuals were found to have a significant increase in olfactory irritation at 0.4/0.8 ppm and 0.5 ppm. The hypersensitive individuals reported more subjective symptoms than the hyposensitive individuals. The SPES sum score significantly increased in hypersensitive subjects at 0.3/0.6 ppm and 0.4/0.8 ppm; the perception of impure air increased with hypersensitivity. Eye irritation increased in most groups with exposure. It was found that olfactory irritation was

significantly increased when compared to the control for all hypersensitive exposure groups.

Slide 31 listed the strengths of the study, which included an adequate number of participants and the inclusion of hypo- and hypersensitivity to irritant responses in the study design. The study employed several concentrations to examine concentration response. The parameters measured were relevant to assessing acute adverse effects from inhalation exposure to formaldehyde, and the results characterized both the incidence and the severity of the concentration response, as well as the time dependence of responses based on exposure concentrations.

Slide 32 listed the limitations of the study, which included (1) the use of only males; (2) all study participants being young, healthy volunteers (and thus not representative in terms of age and health status); (3) the results of exercise on responses measured in the study were not reported; and (4) a large degree of variation for some parameters measured in this study, which limited the interpretation of the results.

Slide 33 listed the overall conclusions. The study was well conducted and provides quantitative information for deriving an acute reference value for formaldehyde as part of a weight-of-evidence determination. This study also provided concentration response data for assessing adverse effects from acute/short-term exposures to formaldehyde.

Slide 34 detailed the scientific charge question for the study: *"Is the research described in the published study "Joerg U. Mueller, Thomas Bruckner, Gerhard Triebig (2013): Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males. Int Arch Occup Environ Health 86:107-117" scientifically sound, providing reliable data for use in a weight of evidence to determine a point of departure for acute inhalation exposures to formaldehyde?"*

G. Board Questions of Clarification

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

- **Thomas Lewandowski**: Slide 30 shows the frequency of adverse effects. Is there also information on the severity of effects? How much eye irritation was there at 0.5 ppm?
    - **Deborah Burgin**: Unfortunately, the authors did not specify severity. They presented several box and whisker plots, which made it difficult to extract information. Irritation values are in the minimal to moderate range.
    - **Thomas Lewandowski**: In terms of benchmark dose (BMD) modeling, it was noted that ICF assumed independence, but then it was violated. Was BMD modeling conducted?
    - **Deborah Burgin**: ICF attempted to conduct BMD modeling; however, the inability to obtain the raw data limited the analysis since individuals acted as their own controls. This is similar to a repeated measures analysis of variance (ANOVA), wherein individuals are exposed to multiple doses.
    - **Thomas Lewandowski**: It was unclear because of the assumption that a benchmark analysis would be performed. It sounds like a benchmark analysis was

not performed. Is that the correct conclusion?

- **Deborah Burgin**: Yes, that is right. It is important to know that ICF had to assume independence, but without access to the raw data, no benchmark analysis could be performed.

- **Srikumaran Melethil**: What is the difference between the eye blink test and the eye film breakup time?
  - **Deborah Burgin**: The eye-blinking frequency test measures how often a person blinks in a given period (e.g., 90 seconds). For the tear film breakup time test, participants are asked not to blink as long as possible while staring at a wall. The two tests measure opposite things, but they both relate to eye irritation. The tear film breakup test is for dry eye testing. The eye-blinking frequency is a measure of irritation or watering eyes.
  - **Srikumaran Melethil**: In the presence of an irritant, will the eye-blinking test be positive, whereas the tear film breakup will show the opposite effect?
  - **Deborah Burgin**: It depends. Those who suffer from allergies know their eyes can be watery as well as dry and itchy. In the literature, dry, itchy, and watery eyes have all been reported after exposure to formaldehyde. The two tests help characterize whether an individual's eyes are extra watery or dryer than normal. Does that help?
  - **Srikumaran Melethil**: Yes. Based on personal experience, I blink more often when my eye is irritated. What is the rationale behind the experimental design that includes changes or peaks in exposure rate during a given interval? This was only done for a few concentrations, as shown in Table 1. Is there an environmental exposure connection wherein the concentrations vary during a given interval of time?
  - **Deborah Burgin**: The peaks are modeled after occupational exposure conditions. In a workplace setting, there is often a background level of formaldehyde. Higher, short-term exposure can occur, as well (e.g., if workers start a process involving formaldehyde or open a container). Many agencies do not allow workers to be exposed to the highest acceptable level of formaldehyde for longer than 15 minutes. Authors chose the levels used in the study based on the SCOEL. In 2008, the SCOEL defined the occupational exposure limit at or below the no observed adverse effect level (NOAEL) for sensory irritation. They proposed an indicative occupational exposure limit of 0.2 ppm with peak excursions of 0.4 ppm.
  - **Srikumaran Melethil**: That is helpful. However, when looking at Table 1, the numbers do not change very much between B and C.
  - **Deborah Burgin**: Mr. Tim Dole, could you answer this?
  - **Timothy Dole**: I have a table that shows what the concentrations should be. It shows the average and peak concentrations that authors targeted and exposure

times. There was an average target of 0.3 ppm for 3 hours and the peak target of 0.6 ppm for an hour. For the total 4-hour exposure, the TWA is 0.38 ppm. That is somewhat less than the real-time monitoring results of 0.33 ppm. There are other similar situations shown in the table. It is unclear why this happened since the instrument should have responded accordingly if the authors truly held the peak exposure for 15 minutes. But, as you can see, there is a difference.
    - **Srikumaran Melethil**: Yes, there is. Were measurements made at peak exposure?
    - **Timothy Dole**: That is not clear. For the paper from Lang et al. (2008), it was stated that measurements were not taken at peak exposure, but it is unclear in this study.
- **Weiying Jiang**: My first question relates to the division of study subjects into two groups, which is based on the median of the reaction scores. This value varied very little among populations. Is this value representative of the general population?
    - **Deborah Burgin**: Yes. The authors determined what the median pain sensitivity to carbon dioxide was among subjects. In this case, the median splits up the group. However, some individuals in the general population will be more sensitive to carbon dioxide. Other studies determined that there is little inter-individual variability between the subjects in this study.
    - **Weiying Jiang**: I am wondering if this value obtained from the study subjects can represent a value for the general population.
    - **Deborah Burgin**: Yes. The pain you receive from carbon dioxide sensitivity is different from chemosensory senses, which are perceived by different parts of the brain and body.
- **Weiying Jiang**: My second question relates to the length and concentration of formaldehyde exposures. The study simulates an occupational exposure scenario of 4 hours. However, the general population is likely exposed for a longer period of time at a lower concentration. Is the chemosensory reaction related more to the concentration or to the duration of formaldehyde exposure?
    - **Deborah Burgin**: The authors did not go over this in the paper, but I believe they chose this sensitivity to carbon dioxide to test the responses to subjective surveys.
    - **Weiying Jiang**: My question is specific to formaldehyde, not carbon dioxide.
    - **Deborah Burgin**: For this assessment, I believe the authors used this sensitivity to check the subjective questionnaires. Most chamber studies that include subjective surveys do not have a way of cross-checking individual reports of high levels of sensitivity. This accounts for the fact that some individuals in the general population are more sensitive to pain, and chamber studies split the study subjects into two groups (hypo- and hypersensitive).
- **Timothy Dole**: I want to clarify that the high-performance liquid chromatography (HPLC) measurements did include the peaks.

H. EPA Ethics Review Highlights

Michelle Arling, J.D., OPP

Ms. Michelle Arling presented the EPA Ethics Review Highlights for this study. Slide 1 introduced the topic of the presentation, and slide 2 outlined its agenda. Slide 3 described the participant selection process (the article provides little information on participant selection). Slide 4 explained the informed consent process, noting that all subjects provided written informed consent. Slide 5 covered risk and risk minimization in the study. It was noted that formaldehyde exposure can cause eye, nose, and throat irritation. Risk was minimized through selection of formaldehyde levels based on existing standards and data and through enrolling healthy, non-smoking individuals. Slide 6 highlighted the respect and privacy of subjects, noting they were not identified in the research publication. Slide 7 described the independent ethics review process. The Ethics Committee of the Medical Faculty of the University of Heidelberg, which holds a Federal-Wide Assurance, approved the research. Slide 8 presented the substantive ethics standards for the study. It was emphasized that EPA cannot rely on data from a study that involves pregnant or nursing women or children, fundamentally unethical research, or research that was deficient relevant to the ethical standards at the time and place it was conducted. Slide 9 described the prevailing ethical standards present at the time the research was conducted. The study mentions the Declaration of Helsinki, which states, among other things, that research must be scientifically sound and conducted by qualified personnel. Slide 10 highlighted the study findings. All subjects were males and provided written consent. Authors conducted the research in a university setting by qualified personnel, and subject risk was minimized. An independent ethics body oversaw the research. Slide 11 listed the conclusions of the study's ethical review. Available information indicated the research was not fundamentally unethical. Slide 12 presented the charge questions to the Board.

- **Srikumaran Melethil**: Does EPA have a policy for when a study does not include women?
    - **Michelle Arling**: No, EPA does not have a policy for when women are not included in a study. Can you clarify your question?
    - **Srikumaran Melethil**: This study has general applicability. Women are not included, but they are subject to exposure in a given environment. Does the exclusion of women considerably reduce the value of a study? Not including women may not be unethical, but it may reduce the value of the study.
    - **Michelle Arling**: This evaluation and review is about the ethical acceptability of the study, and there is no issue with women not being included.
    - **Lisa Corey**: This point could be brought up in the science review.
- **AJ Allen**: I appreciated the inclusion of the 2008 Declaration of Helsinki in the presentation. The report cited the 1996 version of the Declaration. I assume that will be corrected in the written report.
    - **Michelle Arling**: Yes, thank you.

I. Public Comment

Dr. Lisa Corey announced it was time for public comments. Mr. Tom Tracy acknowledged there were multiple public commenters and asked Dr. James Sherman to introduce himself.

Dr. Sherman introduced himself on the first slide of his presentation, titled "Human Odor Detection and Sensory Irritation Data to Establish Exposure Limits to Formaldehyde," Slide 2 explained how sensory nerve stimulation by formaldehyde is not adverse nor different from sensory responses to many other chemicals. Slide 3 described the progression of effects upon exposure to inhaled formaldehyde, noting non-adverse health effects are followed by adverse health effects at approximately 2 ppm. Slide 4 discussed the scarcity of regulatory guidance on the use of sensory irritation results for establishing health protective exposure limits. Slide 5 highlighted that 32 European Union (EU) member countries have adopted a threshold-based mode-of-action (MOA) approach to setting exposure limits for formaldehyde based on sensory irritation with reduced assessment factors. Slide 6 presented the World Health Organization (WHO) indoor air quality guidelines related to formaldehyde. Slide 7 concluded that sensory irritation studies are ethical and quoted the SCOEL. Slide 8 explained that when determining whether available and ongoing sensory irritation studies are ethical, there are only two choices (ethical or unethical). Dr. Sherman noted he agreed with the HSRB that the sensory irritation studies being reviewed are ethical and that these endpoints can serve as sentinel effects and aid in developing exposure limits that protect from adverse effects.

Mr. Tracy asked whether EPA had any questions or comments on Dr. Sherman's presentation. Ms. Arling confirmed there were no comments from EPA. Mr. Tracy then asked for questions from Board members. There were none.

Dr. Debora Kaden introduced herself on the first slide of her presentation, titled "Comments to the HSRB: Mueller et al., 2013 study." She expressed appreciation toward the EPA for its presentation of the study. Slide 2 displayed the elements of a "gold standard" controlled human exposure study. It was noted that subjects and exposures should both be known, confounders should be known and controlled, and the study should be useful for symptoms within the timeframe of the study (i.e., acute, short-term effects). Slide 3 highlighted EPA's evaluation of the study. It was recalled that this study is considered high-quality by EPA and that the IRIS assessment did not rely on these data since no adverse health effects were reported. Slide 4 listed other agencies' use of the study, including the EU SCOEL. Slide 5 highlighted important points taken from the study, emphasizing that the absence of an observed effect does not mean the data should be ignored. EPA could have identified a NOAEL from these data. Additionally, it was stated that using this high-quality study is more scientifically sound than depending on a medium or lower confidence study.

Dr. Corey asked whether there were any questions or comments from EPA. There were none. Dr. Corey then asked whether there were questions from Board members.

- **Thomas Lewandowski**: My understanding is that the Board is being asked to comment

on the acceptability of the study. Some of the public comments are focused on how EPA should use the study. Is that part of the charge question?

- **Michelle Arling**: EPA is not asking the Board to consider how the data should be used. EPA issued specific charge questions that ask for feedback on the conduct of the studies as well as the use of the four intentional human exposure studies and the two observational human exposure studies as part of a weight of evidence.
- **Thomas Lewandowski**: Thank you.

Dr. Corey asked if there were additional registered public commenters. Mr. Tracy confirmed there were none. Dr. Corey then asked whether there were additional public comments. There were none.

J. Board Discussion: Charge to the Board – Science

Weiying Jiang, Ph.D., and Srikumaran Melethil, Ph.D., Science Review

George Milliken, Ph.D., Statistics Review

Mr. Tom Tracy asked the Board members to confirm they were back from the break. Dr. Lisa Corey indicated the reviewers would present their observations first, and then the Board would formulate the response and then vote (i.e., for the science and statistics charge question response and then for the ethics charge question response).

- **Weiying Jiang**: Dr. Srikumaran Melethil and I did the scientific review for the publication. I will present our observations and recommendations. I will not repeat the charge question or provide a summary about the study since those were discussed previously. The study was well designed and provided reliable data. Limitations included that the subjects were only healthy, non-smoking young males, and the study did not include details about their race or health background. The study may not be representative of other population groups that may be more susceptible to formaldehyde exposures.

Dr. Jiang continued reading his notes, including comments and recommendations about the study.

- **Weiying Jiang**: HSRB reviewers recommend EPA discuss possible differences between young male adults and other groups and consider studies that recruited other population groups. Lastly, HSRB reviewers recommend EPA discuss studies that measure objective parameters that are more responsive to exposures. Dr. Melethil, do you have anything to add?
    - **Srikumaran Melethil**: My one concern was about the conclusion on the NOAEL. The authors did not see any results at a concentration of 0.7 ppm. That conclusion needs further review. The other issue I found was the exclusion of women in the study. The reason why that was the case should be explained.
- **Weiying Jiang**: That is all we would like to share.

- **Lisa Corey**: Thank you. Are there any comments from other HSRB members?
    - **AJ Allen**: It is very difficult to go higher in the dose in this type of study. It requires adding another block to every individual, and that affects the power of the study. You are limited to the doses that have been pre-specified in the study design.
    - **Chad Cross**: My comment is regarding the first bullet of the recommendations. There was a comment about contacting the original authors. I think this has been done already by EPA, and the efforts have been exhausted.
    - **Weiying Jiang**: Yes, we noted that. Thank you.
    - **Thomas Lewandowski**: We want to be clear about what we mean regarding the use of this study as a weight-of-evidence analysis but not necessarily in a quantitative way. For example, we heard from EPA that it was not possible to do BMD analysis on the study data. Including this study and others to reach a POD would be ideal. However, it is unclear to me how we could use the study in a non-quantitative way. Could the study reviewers clarify that observation?
    - **Weiying Jiang**: I think using the study results to derive a POD would be hard because most endpoints do not observe adverse effects or show a clear concentration-response relationship. Second, individual data points are not available, which limits further the use of the results for BMD modeling. However, the observations from the study may provide a semi-quantitative support of other studies that can be used to derive a POD. One value about the study is that the authors conducted measurements for both subject responses and the objective measurements. These results provide evidence to show possible biases that cause other responses in other subjects.
    - **Srikumaran Melethil**: As for weight of evidence, meaning that any data are applicable for future studies, this study did not provide large quantitative data. Therefore, it could be used in a qualitative way.
    - **Thomas Lewandowski**: If EPA must look at four different studies, and they plan to use those studies to derive a POD value, then it seems that this review is not opposed to it. The study can be used if other studies as used too.
    - **Srikumaran Melethil**: That is correct; it cannot stand alone.
    - **Chad Cross**: That discussion is similar to one we had about a 1983 study last fall. That study was qualitative but not quantitative. There is a precedent in using qualitative papers.
- **Lisa Corey**: These observations will be considered in the response to the charge question. We should continue with the statistics review.
- **George Milliken**: Statistically, some of the concerns I have are about the random assignment of treatment to subjects. There are better ways to do that. This crossover study is designed to have several treatments applied in a sequence to an experimental unit. One concern I have is that the time between one exposure to the next is only one

day. This is something that is not provided in the study. The process of median split for hypo- and hypersensitive groups is a separate issue. In a previous similar study I reviewed, I noticed there was no age effect, and then I noticed that all subjects were college students and people over 22 were considered adults. Similarly, in this study, artificial grouping was done by using the median split, so there is no guarantee that anybody in the study was hyposensitive or hypersensitive, even if the authors observed statistical differences in their analyses. That type of data analysis detracts from the validity of the study. That said, the analysis using a Student's t-test works well since it was done before and after change. We would have to consider many correlation groupings, but that would be very challenging to do if we had the data. The lack of access to raw data limits us from saying if it is of good quality. Consequently, some of the study conclusions are marginally acceptable because we cannot differentiate hyposensitive from hypersensitive populations.

- **Lisa Corey**: Are there any other HSRB comments on the statistics? We should evaluate whether we want to add the comment about quantitative vs. qualitative use of the study in the response to the charge question.

Dr. Corey read the charge question. Dr. Chad Cross added the charge question in the webinar chat: "Is the research described in "Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males" by Joerg U. Mueller, Thomas Bruckner, and Gerhard Triebig scientifically sound, providing reliable data for use in a weight of evidence to determine a POD for acute inhalation exposures to formaldehyde?" Dr. Weiying Jiang wrote a proposed response in the webinar chat that Dr. Corey read: "*After reviewing the documents provided, HSRB concurs with US EPA to consider this study as a supplemental weight of evidence, but do not recommend using this study in a quantitative way, such as for the determination of PODs for acute inhalation exposures.*"

- **Lisa Corey**: Dr. Melethil, do you have any recommendations?
    - **Srikumaran Melethil**: I agree with the recommendation from Weiying.
    - **George Milliken**: I am not sure that it is completely scientifically sound. For me, it would have a low weight of evidence compared to other studies.
    - **Thomas Lewandowski**: The response could mention the study was "minimally acceptable" in response to the scientific soundness of the study. I want to be cautious saying that a study should be only used qualitatively. Maybe here that is appropriate, but I want to be cautious about characterizing studies as qualitative very frequently.
    - **Srikumaran Melethil**: I would ask for serious revisions or reject the study, which would suggest it is not scientifically sound. We should decide whether it is or not.
    - **George Milliken**: Without the data, we cannot say whether it is scientifically sound.
    - **Srikumaran Melethil**: Then it is not scientifically sound.

- **Lisa Corey**: It is not a perfectly documented study, but we are not always going to have all the pieces of information. And the absence of some of it cannot be a reason to reject the study.
- **Weiying Jiang**: I think it is scientifically sound, but if we are going to use the study to derive a POD, I am not confident in using this study to do that.
- **Lisa Corey**: That makes sense. I would also like to add that if we are moving toward qualitative, could we say it is semi-quantitative?
- **AJ Allen**: I am not comfortable saying this is a marginal study. The data are not available because it is over 10 years old, and there is no requirement in Germany to keep the data. In addition, the institution does not exist anymore. Raw data are not available for 90 to 95% of the published literature from the past decade or two. The argument of the lack of raw data is not enough to reject the study or say that it is a bad study. There are some concerns regarding the hypo- and hypersensitive groups, but it is a well-designed study. The study had been accepted in a peer-reviewed journal. Furthermore, many other scientists are saying this study is particularly useful as opposed to other observational studies. We need to acknowledge the limitations of the study, but we should be careful about rejecting the paper.
- **David Williams**: I am in total agreement with Dr. Allen.
- **George Milliken**: The problem I have is that without going out and recruiting hypersensitive subjects for a study, there is less value in conclusions based on the artificial grouping that took place in this study.
- **Lisa Corey**: I agree, and that is a consistent observation that will be described in the report.
- **AJ Allen**: The conclusions from the authors are theirs. I have disagreed with conclusions from authors of other studies, but their data can still be useful. I think EPA is looking at the evidence beyond the conclusions from the authors.
- **Lisa Corey**: Excellent point. I have incorporated this feedback in the proposed response. The proposed response now reads: *"The research described in 'Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males' by Joerg U. Mueller, Thomas Bruckner, and Gerhard Triebig is minimally acceptable and provides reliable semi-quantitative data for use in a weight of evidence to determine a point of departure for acute inhalation exposures to formaldehyde, given the recommendations by HSRB are considered."* What is the opinion of the Board about this answer?
- **George Milliken**: I am fine with it.
- **David Williams**: The "minimally acceptable" language raises issues. Epidemiological studies have their flaws, but they can represent the population. The Mueller et al. study has defined doses in a controlled environment, but the study population is not representative of the total population. I am reluctant to

minimize the study by using that language.

- **Srikumaran Melethil**: I agree with Dr. Williams. Do we really need that statement? If it already provides reliable data, then the consensus is that it presents useful data.
- **Lisa Corey**: I agree.
- **AJ Allen**: I have concerns about "minimally acceptable" language, as well. I think it could say "semi-quantitative" only. It does not address the "scientifically sound" part of the question, but they are reliable data that can be used for other purposes.
- **Lisa Corey**: A revised response reads: *"The research described in 'Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males' by Joerg U. Mueller, Thomas Bruckner, and Gerhard Triebig provides reliable semi-quantitative data for use in a weight of evidence to determine a point of departure for acute inhalation exposures to formaldehyde, given the recommendations by HSRB are considered."* Any suggestions?

No other suggestions were given.

- **Lisa Corey**: Now we should vote on the charge question response. Dr. Corey read the latest revised response.

Dr. Lewis Brown asked a question in the chat. Ms. Arling responded that EPA did not conduct the study and could not address the question from Dr. Brown. Dr. Corey thanked the Board for voting, which resulted in approval of the revised response.

K. Board Discussion: Charge to the Board – Ethics

AJ Allen, M.D., Ph.D., Ethics Review

Dr. AJ Allen noted this study does not have much to review from an ethical standpoint. There are a few sentences in the article and a mention of the Declaration of Helsinki, as well as the ethics committee approval form. On page 108, it states that after written informed consent was received, 41 healthy, non-smoking, male adults were enrolled. Also on page 108, it is noted that the trial was approved by the ethics committee. It was recalled that the exclusion criteria comprised those with allergy or skin diseases; drug abuse; exposure to formaldehyde in the workplace or at home; diseases of the respiratory tract, metabolism, or heart; and inadequate vision. Dr. Allen explained that ethics committees in Europe function similarly to those in the United States. The ethics committee offered its approval of the study on May 11, 2009, and it was stamped as being received on May 28, 2009. Efforts to obtain additional information were unsuccessful due to the age and nature of the study.

Dr. Allen noted that the Declaration of Helsinki was developed by the World Medical Association (WMA) and first approved in 1964. Since then, it has been amended 10 times, most recently in 2022. The 2008 version of the Declaration would have been applicable at the time the study was conducted. Principle 2 of the Declaration states that it is addressed primarily to

physicians, but the WMA encourages other participants and medical researchers involving human subjects to adopt the principles as well. At least one of the authors in the study was a physician, making him specifically bound by this Declaration.

Principle 6 of the Declaration states that in medical research involving human subjects' wellbeing, the individual research subject must take precedence over all other interests. Principle 10 states that physicians should consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own and other counties. No national or international ethical-legal-regulatory requirements should reduce or eliminate any of the protections for research subjects set forth in the Declaration.

The study was conducted in Germany. This country has a history of experiments conducted by Nazis during the Second World War. As a result of this, German physicians, institutions, and the government are now among the most conscientious in terms of research ethics.

Principle 11 states the duty of physicians who participate in medical research to protect life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of research subjects' personal information. Dr. Allen recalled that subjects were not mentioned in the study report. Principle 12 states that research involving human subjects must conform to generally accepted scientific principles based on current knowledge of the scientific literature and other relevant sources. The study's introduction discusses the scientific literature regarding formaldehyde exposure. Additionally, the public comments discussed the role of the study within the larger research context in terms of EPA guidelines and ongoing work.

Principle 15 discusses the process and legal requirements of submitting a protocol. The researcher must allow the ethics committee to monitor the experiment if they choose. Principle 16 emphasizes that medical research must be conducted only by individuals with appropriate scientific training and qualifications. Principle 18 declares that every medical research study involving human subjects must be perceived by careful assessment and predictable risk to the individuals involved in the research should be compared to foreseeable benefits to the individuals and other communities affected by the condition under investigation. Principle 21 states that medical research involving human subjects may be conducted only if the objectives and benefits outweigh the inherent risks and burdens to the research subjects.

Principle 22 requires participation to be voluntary, and Principle 24 expands on the informed consent process. The study indicated that informed consent was obtained. Principle 30 states that authors, editors, and publishers all have ethical obligations with regards to the publication of the research. Summary results were presented along with supplemental materials, although the raw data are unavailable.

Sources of funding and conflicts of interest should be declared in the publication. Dr. Allen noted there have been several other occasions when publications included the Declaration compliance statement, but there ended up being questions surrounding that compliance. Dr. Allen recalled that EPA stated the documentation standard does not apply for this study since it

was not submitted to the Agency. In terms of standards for the EPA's reliance on the research, the study subjects were all healthy, non-smoking, adult male individuals. No children or pregnant women were involved, which complies with EPA's standards. Written consent was obtained from study subjects and approved by the ethics committee. There is no suggestion that this research was conducted in a fundamentally unethical manner. Dr. Allen stated he believes the study was conducted ethically and in compliance with the Declaration of Helsinki.

Dr. Corey asked for questions or comments from the Board related to the ethics review. There were none. She then asked for suggested edits to the proposed response to the charge question. There were none. The Board then voted on the response, and a consensus was reached.

L. Adjournment

Wednesday, May 17, 2023:

M. Meeting Topic and Charge Questions

Topic: Lang, I., Bruckner, T., and Triebig, G. (2008) Formaldehyde and chemosensory irritation in humans: A controlled human exposure study. Regul Toxicol Pharmacol 50:23–26. DOI:10.1016/j.yrtph.2007.08.012

Charge to the Board – Science: Is the research described in "Formaldehyde and chemosensory irritation in humans: A controlled human exposure study" by Isabelle Lang-Zwosta, Thomas Bruckner, and Gerhard Triebig 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 the conduct of the research was not fundamentally unethical?
- Does available information support a determination that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted or conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

N. Convene Meeting and Introduction of Members

Tom Tracy, DFO, EPA HSRB, OSAPE

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

HSRB members
Lisa Corey, Ph.D., Co-Chair (Intertox, Inc.) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Chad Cross, Ph.D. (University of Nevada – Las Vegas)

HSRB members
Philip Day, Ph.D. (University of Massachusetts, Chan Medical School) Nicole Deming, J.D., M.A. (Case Western Reserve University, School of Medicine) Weiying Jiang, Ph.D. (California Environmental Protection Agency) Thomas Lewandowski, Ph.D. (Gradient) Srikumaran Melethil, Ph.D., J.D. (University of Missouri – Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Seicean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Eun Um, Ed.D. (AMSTAT Consulting) David Williams, Ph.D. (Oregon State University)
EPA staff members
Michelle Arling (EPA, OPP) Deborah Burgin (EPA, OPP) Lexie Burns (EPA, OSAPE) Madison Clark (EPA, OSAPE) Timothy Dole (EPA, OPP) Elizabeth Donovan (EPA, OPP) Judy Facey (EPA, OPP) Timothy McMahon (EPA, OPP) Monique Perron (EPA, OPP) Colleen Rossmeisl (EPA, OPP) Dana Sackett (EPA, OPP) Monique Tadeo (EPA, PHREO) Tom Tracy (EPA, OSAPE) Susanna Wegner (EPA, OPP)
Members of the public, representatives of research sponsor, and research team:
Sorina Eftim (ICF, Contractor Support) Debra Kaden (Ramboll) Afroditi Katsigiannakis (ICF, Contractor Support) Katie Lenae (ICF, Contractor Support)Emily Pak (ICF, Contractor Support) James Sherman (Celanese)

O. Meeting Administrative Procedures

Tom Tracy, DFO, HSRB, OSAPE

Mr. Tom Tracy reviewed the Zoom platform tools and features and stated the purpose of the meeting was to review the paper by Lang et al., *"Formaldehyde and chemosensory irritation in humans: A controlled human exposure study."* He noted minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of May 18, 2023.

P. Opening Remarks

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

Dr. Lisa Corey thanked everyone for the previous discussion on May 16 and explained the format of the EPA HSRB meeting on May 17. She noted the HSRB will review the article by Lang et al., hear from EPA on the science review and ethics review, hear public comments, and hold a discussion with a vote on charge question responses. Dr. Corey then reviewed the procedures and thanked all those attending. She then asked for updates from EPA OPP.

Q. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Michelle Arling confirmed there were no unaddressed questions from the previous day or updates from OPP.

R. EPA Science Review Highlights

Deborah Burgin, Ph.D., DABT, OPP Antimicrobials Division

Dr. Deborah Burgin began the presentation, sharing the first slide, titled *"Use of Human Studies for Derivation of an Acute Inhalation Reference Concentration (RfC) for Formaldehyde."* On Slide 2, she recognized special guest Dr. Isabelle Lang-Zwosta and acknowledged members involved from OPP, OPPT, and ICF. Slide 3 provided an overview of Day 1 and reiterated that OPP and OPPT are evaluating the risks from exposure to formaldehyde under their respective statutes, as well as the role of HSRB in providing recommendations on intentional exposure studies and weight of evidence as well as RfC. She introduced the study by Lang et al. on Slide 4, titled *"Formaldehyde and chemosensory irritation in humans: A controlled human exposure study."* On Slide 5, Ms. Arling provided context for the missing raw data from Lang et al., including attempts made at gaining additional documentation regarding the ethical conduct of the study and how EPA obtained information from a phone conversation with Dr. Lang-Zwosta.

Dr. Burgin on Slide 6 reviewed the purpose of Lang et al. and noted the occupational standards at the time. She then presented the experimental design on Slide 7, including the measured effects of formaldehyde vapor exposure, the recruitment of 21 healthy students (10 female, 11 male), how written informed consent was obtained for all subjects, and the inclusion criteria. Slide 8 listed the exclusion criteria for this study, which included use of contact lenses, smoking, drug abuse, and the potential for pregnancy. Slide 9 continued to introduce the paper's experimental design: two-week exposure sequences were randomized, and ethyl acetate (EA) was chosen as a masking agent due to its similar pungent smell to formaldehyde.

Slide 10 further explained the experimental design, wherein exposure periods were four hours, and Dr. Burgin reviewed a table of the exposure scenarios. Slide 11 introduced the parameters assessed, including conjunctival redness, blinking frequency, nasal resistance and flow, pulmonary function, and reaction times to stimuli. The subjective symptoms and complaints were measured by the SPES questionnaire, which Dr. Burgin recognized was discussed in the

previous meeting. Slide 13 described the order of daily examination, including tools used for preliminary examination, the daily tests, and the post-exposure physical examination and pulmonary function.

Slide 14, titled *"Lang et al. Statistical Analysis"* discussed the role of EPA's contractor, ICF (under Dr. Sorina Eftim), which performed statistical analysis assuming independence between responses at different doses. Dr. Burgin explained that because the raw data were not available and for other reasons, Fisher's exact test was used to test certain scenarios, and a Student t-test was used for mean differences before and after exposure. She explained how discomfort and sensory irritation data were analyzed and that a BMR of 10% extra risk was assumed.

Slide 15 demonstrated the Lang et al. results and noted the chamber exposure concentrations were in line with intended target values. The authors acknowledged that formaldehyde was detected despite measures taken for both controls.

Slide 16 provided sensory irritation results. Blinking frequency and conjunctival redness were demonstrated to be the most significant among the objective symptoms. The SPES total symptoms score significantly increased, as did eye irritation for subjective symptoms. Dr. Burgin noted that the levels at which eye irritation was observed in this study were comparable to those in the literature. BMD modeling results showed the SPES total symptom score results were higher than the maximum dose, which suggested caution for point-of-departure derivation. Slide 17 continued to review the subjective symptoms, particularly that respiratory symptoms significantly increased at 0.3 ppm, 0.5 ppm, and 1.0 ppm. Dr. Burgin summarized that at 0.5 and 1.0 ppm, blinking frequency, conjunctival redness and eye, olfactory, and nasal irritation symptoms significantly increased.

Slide 18 reviewed the strengths of the paper, which included males and females being represented equally, several concentrations being measured to examine concentration response, and results characterizing both the incidence and severity of concentration response, plus there was time dependence of responses based on concentration exposure. Slide 19 provided overall conclusions. Dr. Burgin noted the study was well conducted and provides quantitative information for derivation of an acute RfC value for formaldehyde. It also provided concentration-response data for assessing effects from acute inhalation exposure.

Dr. Burgin then introduced the charge question for the Science Review: *"Is the research described in "Formaldehyde and chemosensory irritation in humans: A controlled human exposure study" by Isabelle Lang-Zwosta, Thomas Bruckner, and Gerhard Triebig scientifically sound, providing reliable data for use in a weight of evidence to determine a point of departure for acute inhalation exposures to formaldehyde?"*

S. Board Questions of Clarification

There were no questions. Lisa Corey passed the meeting on to Michelle Arling for the Ethics Review Highlights.

T. EPA Ethics Review Highlights

Michelle Arling, J.D., OPP

Ms. Michelle Arling presented the ethics review of the 2008 Lang et al. study.. Slide 2 detailed an outline of the presentation, which included the subject selection, consent process, risks and risk minimization, respect for subjects, independent ethics review, substantive acceptance standards, and findings and conclusions.

Slide 3 detailed subject selection. Subjects were recruited through online advertisements at local job offices and postings on bulletin boards at the University of Heidelberg. There were 26 total participants enrolled in the study. Twenty-one participants completed the study (11 were male, and 10 were female). All study participants were between the ages of 19 and 39 years old. The eligibility criteria included: persons who were healthy non-smokers; female subjects who were not pregnant or nursing; no severe allergies/skin diseases; no drug abuse/excessive alcohol consumption; no occupational or residential exposure to formaldehyde; no history of diseases in the respiratory tract, heart, or metabolism; and persons who are not contact lens wearers.

Slide 4 detailed the consent process was conducted through one-on-one meetings as part of the prescreening and physical exam. A consent form noted that participation was voluntary and that subjects could withdraw at any time without penalty. The questions from the subjects were answered prior to them signing the consent form. There was confirmation that subjects understood the material. Subjects also had to wait 24 hours before signing the consent form to ensure they had adequate time to consider their participation. It was also noted that women agreed to use contraception to avoid pregnancy during the study period.

Slide 5 detailed the risks and risk minimization efforts the authors took. Formaldehyde exposure can cause eye, nose, and throat irritation. Individuals with asthma or other breathing problems may be more sensitive to the effects of formaldehyde exposure. Risks were minimized through the selection of formaldehyde levels based on existing standards and data and by enrolling healthy, non-smoking subjects.

Slide 6 detailed the respect for subjects. They were free to withdraw without penalty at any time and were compensated €600 for participation. The data were anonymized, confidentiality was maintained, and subjects were not identified in the research publication. Lastly, withdrawing subjects could request their data be excluded from study results.

Slide 7 provided an overview of the independent ethics review. The research was reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg. The University of Heidelberg currently holds a Federal-Wide Assurance, and the Ethics Committee members are independent in the performance of their duties.

Slide 8 listed the substantive ethical standards. Two were considered: 40 CFR §26.1703, which prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children, and 40 CFR §26.1073, which prohibits EPA's reliance on 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 the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

Slide 9 detailed the prevailing ethical standards during the time the study was conducted. The Declaration of Helsinki (1989) was the prevailing ethical standard at the time. It stated that research must be scientifically sound and conducted by qualified personnel. The research should have a clear purpose and protocol and be reviewed and approved by an independent ethics committee. The importance of the study's objective must outweigh the inherent risks to subjects, and measures to minimize risks must be implemented. The privacy of subjects' personal information must be respected. Lastly, participants should give prior, informed, voluntary consent and have the freedom to withdraw from the study.

Slide 10 listed the findings. All subjects were adults, and pregnant and nursing women were excluded. The research was conducted in a university setting by qualified personnel and was overseen by an independent ethics committee. Risks to subjects were minimized and reasonable relative to the expected benefits of the research. All subjects' privacy was respected, subjects provided written consent to participate, participation was voluntary, and subjects were free to withdraw at any point during the study.

Slide 11 detailed the conclusions. The available information indicated the research was not fundamentally unethical. Similarly, the research was not deficient relative to the ethical standards in the 1989 Declaration of Helsinki, and it was not conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

Slide 12 listed the ethics charge question. The first charge question read: *"Does available information support a determination that the conduct of the research was not fundamentally unethical?"* The second charge question read: *"Does available information support a determination that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted or conducted in a way that placed participants at increased risk of harm or impaired their informed consent?"*

Slide 13 listed the scientific charge question: *"Is the research described in the published study "Formaldehyde and chemosensory irritation in humans: A controlled human exposure study," published in Regulatory Toxicology and Pharmacology 50:23-36, scientifically sound, providing reliable data for use in a weight of evidence to determine a point of departure for acute inhalation exposures to formaldehyde?"*

- **AJ Allen**: In the presentation, you said the Declaration of Helsinki that was used was from 1989, and the study was conducted in 2005. Did you mean the most recent Declaration of Helsinki from 2004?
    - **Michelle Arling**: The study reviewed noted the 1989 standards, so that is why they were referenced in the presentation and not the 2004 standards. I agree with what you stated, though, and if it was started later, it would be under the 2004

Declaration of Helsinki.

- **David Williams**: Can EPA clarify what qualifies as adverse? In the public comments from yesterday, Dr. Sherman presented slides stating that if a study has effects that are adverse, then it is unethical for the results to be used for the risk assessment. In the study discussed today, the endpoints being reviewed are eye irritation, and this tends to be a mild effect, so how do you distinguish between a no observable adverse effect level and an adverse outcome?
    - **Michelle Arling**: Are you asking about the adverse effects relative to the ethical evaluation of the study, or just how we look at these effects when we are evaluating a study to set a POD?
    - **David Williams**: I am asking: If the effects are adverse, does that make the study not suitable for use in a risk assessment?
    - **Michelle Arling**: What was covered in the presentation—and what is EPA's position—is that it is important to look at the study and to look at the potential risks associated with participation in the study and how they stack up against the expected benefits of the research. In this study, the expected impacts of participation were sensory irritation—acute, sensory irritation during the participation in the study. In this study, there were no long-term lasting effects for the participants. Balancing that with a study that gives us more occupational/dose-response data that could inform lots of different evaluations of formaldehyde. We review the study based on this information along with whether the study's risks outweigh the benefits.
- **David Williams**: What was the timing of the peak exposures compared to the timing when the measurements were taken? For example, at the timepoints for 15 minutes, 120 minutes, and 195 minutes, when were the 15-minute peak levels measured compared to those time points?
    - **Deborah Burgin**: I provided the time for the ergometer (exercise bike) but did not provide the time courses for the peaks. The authors made sure that the sum of the peak exposures coincided with the exercise bike, but there was a continuous measurement of formaldehyde in the chamber.
    - **Timothy Dole**: This was similar to the study reviewed yesterday. The authors had their average targets and peak targets. The peak exposure time was at about an hour, and when you combine those together and calculate the TWA, the TWA is a little higher than what was measured. The article says that the peaks were not included in the measurements for HPLC. So, they took the air samples between the peaks. It was assumed that for real-time monitoring, it was measured throughout the 4-hour period, so the measurement should have corresponded a little better to the target. However, it is a little bit less, and we are not exactly sure why. One reason could be that the authors prepared the table to compare the real-time monitoring to the HPLC, so maybe they deleted peak monitoring events

from that to calculate the average, but we are not sure.

- **David Williams**: If the peak levels were measured concurrently with the other measurements, how much of a lag was there from when peak levels were concluded and the measurements were taken?
- **Isabelle Lang-Zwosta**: The participants were on the bicycle right before the peak started. During the peak time, they were on the bicycle and then the blinking frequency test took place. So, after the bicycle, they were getting the slit lamp photography for the eye redness test and then blinking frequency test. The peak coincided with those measurements.

U. Public Comment

Mr. Tom Tracy introduced Dr. James H. Sherman for public comments.

Dr. Sherman presented slides on the subject of sensitive subpopulations in healthy young adults for sensory irritation, and no male/female differential sensitivities were noted. He stated that the study being restricted to young adults, not including sensitive subpopulations, and the use of only males might not be valid reasons to downgrade the designation of the equality of the Mueller study. Dr. Sherman then presented slide 2, which included excerpts from Dr. Pamela Dalton's comments to EPA related to the declines in olfactory and trigeminal sensitivity with age.

Dr. Sherman stated that the sensitive subpopulation consists of adults between the ages of 20 and 30, and they were the best choices for a study that needed a sense of smell and that needed to notify the researchers of a change in smell. He then stated that in toxicology experiments, if there is not a difference between males and females in the studies, then it is okay to use just males to reduce the use of animals. He reiterated that he does not think the use of young, healthy male volunteers was a problem for this study. He also stated EPA needs to define what an adverse effect is. In the study considered today, adverse effects were discussed, but there was no increased risk of harm to the participants in the study. Lastly, he stated that if it is an adverse effect, it is harming human health, and he did not think that chemical sensory studies are measuring adverse effects. He then thanked the HSRB for their time.

Mr. Tracy introduced Dr. Debra Kaden for public comments.

Dr. Kaden presented her slides on the Lang et al. (2008) study. She stated that the controlled human exposure studies are the gold standard of toxicology studies. In these, the subjects and exposures are known, and the confounders are known and controlled for and are useful for symptoms within the time frame of the study. She stated that as with the Mueller study, the Lang study has been judged to be high quality by EPA, the EU SCOEL, and other authoritative bodies including the WHO. The draft EPA assessment does not rely upon it because the authors reported only measures at the highest concentration evaluated (0.5 ppm), with or without a 1 ppm and with or without the masking agent. As such, EPA was unable to find a dose response to produce benchmark modeling. However, it should be noted that the WHO and the EU SCOEL did depend on this study and based various short-term safety values on the eye blink test and

upper respiratory irritation. She then pointed out that these agencies used minimal uncertainty factors. Lasty, she reiterated that although the study did not find a dose response, this alone is not enough to ignore a POD as it has been identified as a high-quality study.

Dr. Lisa Corey asked whether there were any questions from HSRB members and from members of the public. There were none. The group then went on a 15-minute break following these presentations.

V. Board Discussion: Charge to the Board – Science

David Williams, Ph.D., and Thomas Lewandowski, Ph.D., Science Review

Sinziana Seicean-Boose, Ph.D., Statistics Review

Dr. Lisa Corey introduced the HSRB discussion format: science review, statistics, discussion and vote on the charge question, ethics review, and approving the charge question and responses. She then introduced Dr. David Williams and Dr. Thomas Lewandowski, the science reviewers for Lang (2008). Dr. Williams asked the following charge question: *"Is the research described in "Formaldehyde and chemosensory irritation in humans: A controlled human exposure study" by Isabelle Lang-Zwosta, Thomas Bruckner, and Gerhard Triebig scientifically sound, providing reliable data for use in a weight of evidence to determine a point of departure for acute inhalation exposures to formaldehyde?"* He then gave a summary of the study's structure, a double-blind, randomized dose exposure, and listed the ten different dose regimens.

There were five objective endpoints noted: conjunctive redness, blinking frequency, nasal resistance, pulmonary function, and reaction times. The subjective endpoints were the physical and mental state determined by SPES, a questionnaire given before each exposure, and personality factors. Personality effects were measured by the Positive and Negative Affectivity Scale (PANAS) questionnaire to assess individuals' emotions and level of anxiety.

Dr. Williams noted that the study in the chamber employed real-time formaldehyde measurements that were confirmed by dinitrophenylhydrazine and HPLC analysis. This verified that the formaldehyde levels were consistently close to the target levels, although there were background levels of formaldehyde ranging from 0.02 to 0.05 ppm. Dr. Williams noted that the TWA level was not listed in Table 6.

Dr. Williams then summarized key results. Conjunctival redness was a sensitive indicator of irritation from formaldehyde exposure, significantly greater at 0.5 ppm with peaks of 1.0 ppm at 195 minutes. The statistical re-analysis from ICF found significant differences across all concentrations but only at 195 minutes. Similarly, the authors found blinking frequency to be significant at exposure to 0.5 ppm, with peaks of 1.0 ppm at 195 minutes, although the ICF reanalysis did not support this. There was a significant correlation between eye irritation and blinking frequency in the presence of EA. Dr. Williams then noted where the authors failed to see statistically significant effects, including nasal resistance and flow. For subjective reporting, the authors observed increases in eye and nasal irritation, although both were mild and the nasal

effects could not be distinguished from the impact of the masking agent, EA. The authors found respiratory irritation increased significantly at various concentrations, but ICF reanalysis confirmed these findings at only 0.5 ppm. For personality factors, when the authors analyzed the results of subjects with negative affectivity as a covariant, they were no longer significant, particularly at the lower dose ranges.

David Williams summarized that considering these key results, the authors concluded a NOAEL for subjective and objective eye irritation of 0.5 ppm for a continuous 4-hour exposure; a NOAEL for variable exposures was a 4-hour exposure at 0.3 ppm with 0.6 ppm peaks. He compared these results to those of ICF from its reanalysis, which concluded that the BMDs and BMDLs were greater than the highest formaldehyde concentration test. Thus, using this information in POD determination would be problematic.

Dr. Williams then stated the HSRB Response to Charge: *"The HSRB agrees that the study by Lang et al. is scientifically sound and provides reliable data for use in a weight-of-evidence analysis to determine a POD for acute inhalation exposures to formaldehyde."* He noted there may be edits to this response.

Dr. Williams reviewed the HSRB comments for this study, highlighting that calculated BMDs and BMDLs were greater than the highest dose and that deriving a POD solely from this study should be done with caution, although use of the study in weight of evidence is reasonable. He questioned whether blinking rates are a useful measure of effect considering the wide range of inter-individual variation in blinking rates (2-80/minute) and whether EPA should include their opinion in the review summary.

Dr. Williams acknowledged the exclusion criteria were stringent, not representing the general population, and should be noted by EPA particularly in determining an acute POD. He questioned the study's statement that there was no sex difference as they did not provide the data to independently verify it. Additionally, there was no information about ethnicity or age as variables. Dr. Williams asked how it could be known whether participants were exposed to formaldehyde in the community or occupationally in order to be excluded and whether they should have been excluded at all. He also asked whether the recruited population that dropped out of the study had distinct characteristics from those who remained. Dr. Williams also noted that there was no TWA in Table 6 of the EPA review, unlike with the Mueller et al. study. He asked for clarity surrounding the parameter of negative affectivity and its use in exclusion. He asked for EPA's comment about the lack of raw data and how this limits the ability to use this study. Dr. Williams questioned the study's statement that formaldehyde effects reverse quickly, noting that a daily cumulative effect is unclear. He also highlighted the differences between the Mueller et al. study having control of individual data versus the study from Lang et al., which used a group mean, and how this should be evaluated differently. Dr. Williams and Dr. Lewandowski agreed with EPA on the timing of pulmonary function tests and that this should be noted in the analysis. Dr. Williams also noted minor comments on the ICF figures and tables.

Dr. Williams invited Dr. Thomas Lewandowski to clarify their comments. Dr. Lewandowski clarified that the comment surrounding the peak in TWA was answered earlier in the meeting. Regarding the issue of reversibility, he noted the difference between irritation due to trigeminal nerve stimulation versus a corrosive effect and that the former was the focus; thus, reversibility is of interest. Dr. Lewandowski asked for clarity regarding the statement, *"ICF found significant differences across all concentrations but only at 195 minutes,"* acknowledging that the data do not support this statement and that it is confusing. Dr. Williams said he would go over the original ICF documents and revise the wording for clarity. Dr. Lewandowski stated that overall, they requested clarification from EPA and recommendations, but no specific questions needed to be addressed. Dr. Corey thanked both presenters and opened up Board members to questions.

- **Srikumaran Melethil:** What is the scientific value of using masking agents in these studies?
    - **Thomas Lewandowski:** Because the odor threshold for formaldehyde is so low, people would be able to know whether they were being exposed to formaldehyde or not based on the smell alone. EA was used to allow for blind administration as it is easy to detect formaldehyde otherwise. EA may not be the best mask because of its own irritant effects.
        - **Srikumaran Melethil:** I am familiar with the order of EA and not sure whether it serves very well because it is more fruity; thus, I am not sure whether it actually masks. From a policy perspective, these studies cost money, and if there is a study that does not provide useful information, it is important to note that.
    - **Isabelle Lang-Zwosta:** To confirm, I was in the study chamber. EA was effective at masking, although formaldehyde stings more, so you could possibly distinguish between the two but not from the smell.
    - **Thomas Lewandowski:** And it was not masking against the control with no formaldehyde. It is interesting to hear your perspective on this.
    - **Isabelle Lang-Zwosta:** It was interesting that the participants felt there was still irritation, even without formaldehyde.

Dr. Lisa Corey asked whether there were any other questions regarding this topic. There were none. Consequently, Dr. Corey introduced Dr. Sinziana Seicean-Boose for the statistics review.

Dr. Seicean-Boose reviewed the study methods, participants, endpoint collections, and exposure information. She noted that this is a well-designed study with scientific advantages and that she shared the frustration with not having the raw data. Dr. Seicean-Boose then presented the study's statistical approach, wherein data were collected and analyzed using SAS and a p-value of less than 0.05 was considered significant. She noted tests used, including a Wilcoxon-Mann-Whitney U-test to evaluate gender differences, an ANOVA test for concentration-response relations, and other statistical tests. She specified that the statistical observations made focused entirely on EPA's goal of using the study for POD derivation.

Limitations included raw data unavailability, the lack of information such as blinking frequency and reaction design for endpoints, poorly designed endpoints in relation to the observed level cutoff for conjunctival redness, and blinking precedency. Additionally, the formaldehyde analytical concentration was not reported, and the study used digitized data from figures, which could introduce errors. Dr. Seicean-Boose noted the correlation coefficient test was performed without adjustment for multiple comparisons, and sensitivity analysis, if performed, was not reported in the final paper, so it cannot be evaluated. She highlighted the use of two-way ANOVA in contrast to other approaches to better understand the raw data for sensitivity analysis. Dr. Seicean-Boose noted it is important to assess the robustness to dilation of the multi-way ANOVA exemptions, particularly with the independence between volunteers' responses and different doses, which was violated by the control design. She identified a normality assumption of type I error because ANOVA is sensitive to outliers, particularly in a small sample (defined as less than 50). She highlighted an example from page 28, where high variance in individual blinking frequency resulted in a higher chance of outliers. She stated the statistically recommended solution for dilation to the normality assumption was to use a nonparametric Wilcoxon rank-sum test or a transformation to normalize the outcome. Table 7 demonstrates that the analysis was performed without the recommended transformation. She then commented on the study collection and design, wherein the benefit of the design is the focus on the changes within a subject. With a different statistical approach, this study design could represent the state of the art due to each subject acting as its own control. Dr. Seicean-Boose agreed with the review opinion from EPA and ICF that considering the lack of original data, reproducibility is not possible for certain important results. She concluded that while the study lacks state-of-the-art, newer statistical approaches, it provides quality and usable data, and EPA's use of it for weight-of-evidence analysis for the POD for formaldehyde is well justified.

Dr. Corey opened the meeting to questions related to the statistical review.

- **Srikumaran Melethil:** Looking at Figure 2 (page 28) from the study, did you have any concerns about the number of subjects in the study? The F bar is the same concentration without acetate, and K is the same concentration with acetate. Why did this occur? Were there enough total subjects?
    - **Sinziana Seicean-Boose:** This is a good observation. We have a minimum number of subjects, and we must be careful looking at this. The value of the numbers is important. When we look at the robustness to violation of the assumption of the specific tasks which were done. In this situation, the results are not affected by the number of participants. If there is any error introduced, it may be by data cleaning and outliers.
    - **Thomas Lewandowski:** The graph shows the percentage of the group demonstrating moderate redness, but there is also slight redness. So, while informative, Figure 2 does not provide a lot of information. The F bar being higher than the K bar does not cause alarm.

  - **Srikumaran Melethil:** Looking at the results that state they are statistically valid, why are we seeing no effect when acetate is added?
  - **Thomas Lewandowski:** With the acetate, you see a less pronounced fact, that is not a statistically significant effect. Without error bars, it is hard to get a sense of the increase.
  - **Srikumaran Melethil:** If the sample size was large enough, would the results have been the same?
  - **Sinziana Seicean-Boose:** It is hard to say without the raw data whether it would have made a huge difference. This is why it is important to have access to the raw data and double check the results to see whether any error is introduced.
  - **Lisa Corey:** We are also just looking at the senses of the same population; the effect variant is just a couple of people considering these percentage differences.
  - **George Milliken:** These are also the same subjects, so it is not that they are independent samples. Without having the data, we have no way to say there is a difference.
  - **Srikumaran Melethil:** Does EA in any way interfere with the effect of formaldehyde? If the answer is "no," that is how I would frame it.
  - **Lisa Corey:** There was prior information that EA should not be affecting that irritation.
  - **Srikumaran Melethil:** There was a statement that formaldehyde polymerizes. So, when formaldehyde polymerizes, would the sensitivity be different?
  - **Sinziana Seicean-Boose:** Without the raw data, it is impossible to determine what is going on. These limitations have to be taken into consideration when viewing the results of this study.
- **David Williams:** Regarding EA, this was point 4 on the summary of the results. The mild effects could not be distinguished from those with EA. This is not the perfect masking agent for doing low-dose studies, but it does serve some purpose in masking the impact of formaldehyde.
- **Thomas Lewandowski:** The more problematic outcome would be if formaldehyde plus EA were having the effect. Then you would not know how much is due from the EA
- **Sinziana Seicean-Boose:** I agree; this would be more worrying than an additive effect.
- **Thomas Lewandowski:** There is an increase of effect as the amount of formaldehyde is going up. It is unclear how effective EA is at masking. This should be part of the weight-of-evidence in the evaluation. It is clear that there is no perfect study for formaldehyde, and these are human data (which are rare). This group of studies together will be useful for a weight-of-evidence.
- **Lisa Corey:** There is a consensus that this does not seem to be problematic in responding to the charge question.

Dr. Corey presented the response to the charge that had been adapted to contain the previous discussion. The charge response is as follows: "*The HSRB agrees with EPA that the study*

"Formaldehyde and chemosensory irritation in humans: A controlled human exposure study" by Isabelle Lang-Zwosta, Thomas Bruckner, and Gerhard Triebig, is scientifically sound and provides reliable data for use in a weight-of-evidence analysis to determine a point of departure for acute inhalation exposures to formaldehyde, given the recommendations by the HSRB are considered."

There were no suggested edits. Dr. Corey asked members of the Board to vote on the charge question. The members unanimously approved the charge question.

W. Board Discussion: Charge to the Board – Ethics

Philip Day, Ph.D., Ethics Review

Dr. Philip Day thanked Ms. Michelle Arling and Dr. AJ Allen. He presented the ethics charge question on *"Formaldehyde and chemosensory irritation in humans: A controlled human exposure study"* by Lang et al. and associated materials provided by EPA, acknowledging the HSRB has determined that the conduct of the research was not fundamentally unethical. The HSRB has also determined that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted and was not conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

A total of 26 subjects were enrolled in the study; 21 completed it, 11 of whom were males and 10 of whom were females. Recruitment was conducted via online advertisement, through employment offices, and on bulletin boards at the University of Heidelberg. The inclusion and exclusion criteria were thorough and appropriate for this type of study. Participants underwent a thorough screening process to confirm their health status and eligibility. They were provided information about the study, including study-related testing, possible health effects of formaldehyde exposure, the study schedule, and how to behave in the exposure chamber. Finally, potential participants also received an agreement from the principal investigator guaranteeing study confidentiality and data anonymity.

The principal investigator confirmed to EPA that female volunteers took pregnancy tests to confirm they were not pregnant and also confirmed that none of the participants were nursing. These details were not included in the published manuscript.

A total of five subjects withdrew from the study before it was concluded. Three withdrew after one or two study days due to concern about personal risk, one left for personal reasons, and one was withdrawn from the study due to headache and fever, possibly from a respiratory disease. Participants who completed the study activities received €600. Following recruitment procedures, written and informed consent was received after adequate reflection time in accordance with the Declaration of Helsinki. Participants provided written informed consent a week in advance of the study start and 24 hours after the screening. This allowed adequate time to review the provided information and reflect on their decision to participate in the study. While the article does not provide more information about the consent process, EPA ethics review provides further detail (as provided by the study's lead author).

Dr. Day indicated that the consent form, upon brief review, adequately described the purpose of the study, study activities, and screening procedures. The consent form also stated that participation was voluntary, participants could withdraw at any time for any reason, and they could have their data destroyed upon request. The received form was translated from German into English using an online translator, so it is hard to judge the reading level of the original; however, the translated version does contain several instances of technical jargon and unexplained scientific or biological terms.

Risks to subjects included *"possible health effects of formaldehyde, such as irritation of the airways and/or eyes, and the unpleasant odor."* It is also reasonable to infer psychological risks, such as those measured in the study and reported by participants, including anxiety and other "negative affects" captured by the PANAS. Risks to subjects were minimized via the screening procedures, the informed consent process, verification of eligibility via the inclusion and exclusion criteria, and by limiting the formaldehyde exposure to then-current safety levels. Participants were also notified that they could leave the study at any time, and five chose to do so.

Participant privacy and data confidentiality appear to have been protected: No participants are identified in the article, and demographics and/or characteristics are reported only in aggregate.

There is potential benefit to society by establishing *"occurrence of sensory irritation and subjective symptoms"* of formaldehyde exposure for occupational settings, but there was no direct benefit to study participants.

The study was reviewed and approved by the Ethics Committee of the Medical Faculty at the University of Heidelberg. No detail of the review process is provided in the study manuscript.

Dr. Day mentioned that based on his review of the provided documents, including the published article, the provided EPA science and ethics review, and the additional information provided by the study principal investigator to EPA, there is no evidence to suggest this study was conducted unethically. Only healthy, nonsmoking adults were enrolled. No children were enrolled, and there is no indication that pregnant or nursing subjects were enrolled in the study. Risks were adequately minimized through screening procedures and by adopting an accepted threshold of formaldehyde exposure. Informed consent was obtained, and the study was reviewed and approved by an independent ethics committee. While important and specific information is lacking from the article related to the ethical conduct of this study, there is no evidence that it was conducted unethically or deficient relative to the standards of the time. No study procedures would invalidate or impair the participants' informed consent.

Dr. Day's recommendations included the following questions: Does available information support a determination that the conduct of the research was not fundamentally unethical? Does available information support a determination that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted or conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

Dr. Day responded yes to both questions. The available information supports the determination that there is no clear and convincing evidence that the research was conducted unethically or deficient relative to ethical standards at the time the study was performed. Participants were not placed at increased risk, and no study activities impaired their informed consent.

After its review of *"Formaldehyde and chemosensory irritation in humans: A controlled human exposure study"* by Lang, et al. and associated materials provided by EPA, the HSRB has determined that the conduct of the research was not fundamentally unethical. The HSRB has also determined that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted and was not conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

Dr. Day presented the response to the charge question. After its review of *"Formaldehyde and chemosensory irritation in humans: A controlled human exposure study"* by Lang, et al. and associated materials provided by EPA, the HSRB has determined that the conduct of the research was not fundamentally unethical. The HSRB has also determined that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted and was not conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

There were no other points of discussion. Dr. Corey read the conclusions from Dr. Day for the ethical standards and asked whether there were any suggested edits. There were none. Dr. Corey then asked members of the Board to vote on the charge question. The members unanimously approved the charge question.

X. Adjournment

Dr. Corey thanked the reviewers and the Board for an efficient meeting, as well as EPA for its presentation and the members of the public for their attendance. She noted that the discussion on May 18 would focus on reviewing the previous report and getting that finalized, followed by a discussion on the weight of evidence for acute exposure to formaldehyde. Dr. Corey asked whether there were any points of clarification, and there were none.

Mr. Tom Tracy thanked the Board. The meeting adjourned at 3:28 p.m. EDT.

Thursday, May 18, 2023:

Y. Meeting Topic and Charge Questions

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

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

endpoints and the proposed PODs in Table 3.

Z. Convene Meeting and Introduction of Members

Tom Tracy, DFO, EPA HSRB, OSAPE

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

HSRB members
Lisa Corey, Ph.D., Co-Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (National Institute of Standards and Technology) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Chad Cross, Ph.D. (University of Nevada – Las Vegas) Philip Day, Ph.D. (University of Massachusetts, Chan Medical School) Nicole Deming, J.D., M.A. (Case Western Reserve University, School of Medicine) Weiying Jiang, Ph.D. (California Environmental Protection Agency) Thomas Lewandowski, Ph.D. (Gradient) Srikumaran Melethil, Ph.D., J.D. (University of Missouri – Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Seicean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) Eun Um, Ed.D. (AMSTAT Consulting) David Williams, Ph.D. (Oregon State University)
EPA staff members
Michelle Arling (EPA, OPP) Deborah Burgin (EPA, OPP) Lexie Burns (EPA, OSAPE) Madison Clark (EPA, OSAPE) Jeffrey Dawson (EPA, OPP) Timothy Dole (EPA, OPP) Elizabeth Donovan (EPA, OPP) Judy Facey (EPA, OPP) Sarah Gallagher (EPA, OPP) Timothy McMahon (EPA, OPP) Monique Perron (EPA, OPP) Colleen Rossmeisl (EPA, OPP) Dana Sackett (EPA, OPP) Monique Tadeo (EPA, PHREO) Tom Tracy (EPA, OSAPE) Susanna Wegner (EPA, OPP)
Members of the public, representatives of research sponsor, and research team:

HSRB members
Sorina Eftim (ICF, Contractor Support) Stewart Holm (American Forest and Paper Association) Debra Kaden (Ramboll) Afroditi Katsigiannakis (ICF, Contractor Support) Sahar Osman-Sypher (American Chemistry Council (ACC)) Emily Pak (ICF, Contractor Support) Lucas Rocha Melogno (ICF, Contractor Support) James Sherman (Celanese) Clint Woods (Hexion)

AA. Meeting Administrative Procedures

Tom Tracy, DFO, HSRB, OSAPE

Mr. Tom Tracy reviewed the Zoom platform tools and features and stated the purpose of the meeting was to review the EPA Weight of Evidence for Acute and Peak Inhalation Endpoints. He noted that minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of May 18, 2023.

BB. Opening Remarks

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

Dr. Lisa Corey introduced herself and provided her background. Then the HSRB board members introduced themselves. Lastly, Ms. Michelle Arling and Dr. Deborah Burgin from EPA OPP introduced themselves.

Dr. Sharp indicated that a review of the April report draft will be completed during the meeting. She mentioned that after finalizing the report, a weight-of-evidence review would be conducted, followed by comments from EPA, public comments, and a Board discussion. Dr. Sharp reminded the audience to maintain communications clearly and in an orderly manner.

CC. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Arling indicated there were no requests for information after the meeting the day before and suggested moving forward.

DD. Review and Finalize Report on: S. Freestone and P. McFarlane (2001) A Single Oral Dose Study with Acephate Technical in Humans; Report Amendment 2

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

- **Julia Sharp**: First we will review the report that we had initially drafted in April. We have a couple of clarifications that need to be made before finalizing the report. This

study was a non-guideline, double-blind, placebo-controlled, pharmacokinetic, and cholinesterase (ChE) inhibition study. EPA proposed the use of this study to develop physiologically based pharmacokinetic (PBPK) models. We have the charge questions and comments for EPA. There is a comment from the statistics reviewer to add "arguably" in the text.

Dr. Sharp proceeded to read part of the report and provided context before asking for input from Dr. Lewandowski and Dr. Jiang.

- **George Milliken**: I do not understand the use of "arguably" in the text.
- **Michelle Arling**: I think the question is how it is characterized in the report. It would be acceptable to leave "arguably" in the text since EPA analysis showed the statement about *"owing to >20% variability from baseline"* did not apply to all cases in the study.
    - **Julia Sharp**: Would adding "arguably" work?
    - **Michelle Arling**: Yes. There are other options for other explanations.

Dr. Lewandowski and Dr. Jiang agreed that it was acceptable. Dr. Milliken indicated that it was acceptable to him, as well.

- **Chad Cross**: Could we say "presumably" in that statement (i.e., "presumably owing to >20% variability from baseline in some cases.").

Dr. Sharp and Dr. Lewandowski agreed. Dr. Milliken supported the change. Dr. Sharp mentioned fixing punctuation in the report. She read part of the report regarding dose proportionality (page 6) and a comment associated with it. The comment asked whether dose proportionality should be mentioned or not.

- **Julia Sharp**: Is that last comment correct, Ms. Arling?
- **Michelle Arling**: Yes. The intent is not for the use, so it is less important for EPA.
    - **Weiying Jiang**: So, EPA would use the model for dose proportionality, correct?
    - **Julia Sharp**: No. EPA will develop its model and use the data to compare against the model and see how dose proportionality impacts the outcome.
    - **Thomas Lewandowski**: The concern with proportionality was that the data for females may or may not be generalizable. I think what EPA is saying is that the data will be used to test the predictive ability of the model at different doses for males and one dose for females. The fact that there are missing data will limit the generalization for females. This is a limitation of the data, but EPA will not go beyond what the data currently say (i.e., there is only one dose for females). Is that correct, EPA?
    - **Michelle Arling**: Yes. An outside company will develop the model, and we will use the data to validate the model. We will not use the data to develop a model.
    - **Thomas Lewandowski**: The fact that there are no data for dose proportionality for female results then could be acknowledged, but we should not imply the data cannot be used by EPA.

  - **Weiying Jiang**: I agree. The data cannot be used to validate the dose proportionality since there is only one concentration. My question is: How will EPA use this single concentration when validating the model? You cannot tell whether there is dose proportionality or not.
  - **Julia Sharp**: So, will the data for females be used in the PBPK model?
  - **Michelle Arling**: I will confirm with my colleagues.
  - **Thomas Lewandowski**: The first sentence can stay, up to *"1.0mg/kg."* Then the text could mention that EPA should recognize the limitations of the female data when describing its model validation exercise.
  - **Weiying Jiang**: That is correct.
  - **AJ Allen**: EPA is only interested in the raw data, not in the observations from the paper. It will take the set of data and look at it in a population analysis. In those cases, you will not have a range of doses. I do not know whether this limitation will affect their analysis. This is commonly done in the pharmaceutical industry.
  - **Michelle Arling**: I confirmed that EPA will use the model (e.g., input the dose) and then look at the output of this study and see how well the model predicts an output by comparing it against the values from the study.
- **Thomas Lewandowski**: The data are limited for females. The validation can be done for one dose, but the validation will not be as robust for females as it will be for males because of the data limitations.
  - **Weiying Jiang**: That is correct.
  - **Julia Sharp**: I believe the point is made in the recommendations.

Dr. Sharp confirmed the recommendation about female data is already in the report.

- **AJ Allen**: There is a limitation because there were only 10 females versus 40 males, and EPA should have less confidence in how the model works for females because of this limitation.
  - **Thomas Lewandowski**: I think the recommendation is good, and I do not see it necessary to mention it again in the bulleted list above in the report.

Dr. Sharp eliminated the text from the bullet list, added further clarifications in the text in tracked changes, and asked for feedback. Dr. Lewandowski and Dr. Jiang agreed that the edits were good. Dr. Sharp added a sentence to the text box for recommendations, which added clarity about the data limitations from female subjects.

- **AJ Allen**: We should revise the text to say *"conducting"* instead of *"describing"* in the last bullet point of the recommendations.

Dr. Sharp continued revising the report, reading a paragraph that had comments from Ms. Arling about revising the text based on the 2018 risk assessment for acephate and about dose proportionality.

- **Michelle Arling**: If you could make sure that the report reflects the comments and

information provided by EPA, that would be appreciated.

  - **Weiying Jiang**: Yes, we will confirm it does. I wanted to clarify that this range of doses is from the study, not the range of doses that a population would experience.
  - **Michelle Arling**: If there are observations or data from the 2018 risk assessment, please include that reference in the text so EPA can track the recommendations to be considered by EPA. The document is available online.
- **Julia Sharp**: I can send the 2018 risk assessment. Thinking about the dose proportionality statement, would it be appropriate if that is removed from the text?

Dr. Lewandowski and Dr. Jiang agreed it was appropriate.

- **Julia Sharp**: There were issues about the correlations presented in the report. Dr. Nguyen said it is not clear where the HSRB obtained the correlation values and that additional details would be helpful. Dr. Cross, did you have a reference for the values that we could provide to EPA?
- **Chad Cross**: Correlations were not used for power analysis. It is just a back calculation based on the sample sizes. It is acceptable to remove that sentence from the text.

Dr. Sharp continued reading one of the recommendations and a comment from James Nguyen. She then asked Dr. Cross for comments about the second to last recommendation from the HSRB: *"The lack of a clear sample size determination description should be noted in the US EPA science review, along with the potential effect of the 80:20% gender allocation on statistical power."* James Nguyen commented in the document that it is unclear whether the real statistical power of comparisons in the study should be a concern.

- **Chad Cross**: If you look at the document we submitted for review, there were places where sample size was or was not determined. I do not think it is clear why the sample size had an 80/20 ratio of males and females in the study participants. The recommendation is to clarify this issue.

Dr. Julia Sharp added a comment to the report requesting clarification about how the 80:20% gender allocation impacts the PBPK model evaluation. She also added the comment in the text box for recommendations in tracked changes.

- **Srikumaran Melethil**: The charge mentioned the word "validating." We should check on that.
  - **AJ Allen**: We discussed that. EPA will go through the formal process of validation.
  - **Julia Sharp**: Yes. We changed the word to "evaluation" instead of "validation." The word is the same in the charge question, but our response did change. We have already voted on this, so the wording will not change as we finalize the report.
- **Julia Sharp**: We are using a template for the first time, so there are some technical edits

needed for the document. Is there anything else we need to address, Ms. Arling?
    - **Michelle Arling**: No. Thank you for considering the comments from EPA.
- **Julia Sharp**: We will forward the report to Ms. Arling and Mr. Tracy once we finalize these comments. I want to make sure that everyone is satisfied with the document. Can I see a green checkmark if you approve the report, pending minor edits?

The HSRB voted in unanimous agreement.

- **Julia Sharp**: I will turn it over to Dr. Corey, who will lead the discussion on the Weight of Evidence.

EE.EPA Overview of Weight of Evidence

Deborah Burgin, Ph.D., DABT, OPP Antimicrobials Division

Dr. Lisa Corey introduced Dr. Deborah Burgin, who thanked her and shared a presentation, titled *"Use of Human Studies for Derivation of an Acute Inhalation Reference Concentration (RfC) for Formaldehyde."* She then presented Slide 2, which included acknowledgements, thanking Judy Facey, Timothy Dole, and Monique Perron, and introduced Ms. Michelle Arling.

Ms. Arling presented Slide 3, Human Studies Rule Overview, and specified that the group is moving from discussion of specific studies to discussion of weight of evidence. To do this, she reminded everyone of Human Studies Rule outlines the HSRB is required to consult. The EPA Human Studies Rule apply to intentional exposures initiated after April 2006, when the rule went into effect, all proposals for intentional exposure studies initiated after the rule went into effect, and intentional exposure studies conducted prior to the rule with the intent to identify or measure a toxic effect. Ms. Arling specified that the rule does not apply to observational studies and on Slide 4, distinguished between the two study types. She reiterated the HSRB group members should keep these rules and applicability requirements in mind during Dr. Burgin's weight-of-evidence presentation.

Dr. Burgin thanked Ms. Arling and introduced the slide titled "Office of Chemical Safety and Pollution Prevention (OCSPP) Weight of Evidence Assessment – Formaldehyde Acute Inhalation Exposure." She gave an outline of the presentation, covering the definition of risk assessment, an overview of weight of evidence, a summary of data, OPP and OPPT exposure scenarios, and proposed PODs. Dr. Burgin gave definitions commonly used in risk assessment, including control, distinguishing that this does not have to mean zero but instead the background response, endpoint and some examples, lowest observed adverse effect level (LOAEL), NOAEL, and POD. She then presented the weight of evidence under TSCA, which requires (under Sections 4, 5, or 6) that EPA use scientific standards and base those decisions on the best available science and weight of evidence (15 U.S.C. 2625(h) and (i)). Dr. Burgin recognized that although OPP does not have similar regulatory language, it is a risk-based program with a long history of using a weight-of-evidence approach. She explained that weight of evidence is an integrative and interpretive process used by EPA to interpret data from multiple lines of evidence. Analysis may consider the quality of the data and replicability; the strength and

limitations; the effects induced and their severity; as well as the consistency, pattern, range, and interrelationships of effects across studies, species, strains, and sexes. The conditions under which the effects occur, such as route and dose, are also considered. Dr. Burgin noted that generally no single study drives the overall weight-of-evidence judgement, and evaluation is not done by a particular numerical system but, rather, by scientific judgement. She then presented a background slide on weight of evidence, explaining that IRIS recently completed its draft review and characterized chronic noncancer and cancer risks from inhalation exposure. She noted that shorter inhalation duration exposures are not the focus of the IRIS assessment; however, due to FIFRA registered use patterns and TSCA conditions of use, OCSPP needs to develop acute and short-term inhalation PODs.

Dr. Burgin explained that IRIS performed an exhaustive systematic review of the available literature on inhalation of formaldehyde, including short-term exposure. OCSPP will use this review supplemented by an updated search. She noted that several endpoints were considered and explained why sensory irritation was selected as an endpoint by OCSPP and why it is appropriate for evaluation. Dr. Burgin then reviewed the acute exposure durations, including a peak exposure (limited to 15 minutes), an 8-hour exposure, and a 24-hour exposure.

Dr. Burgin explained the Study Selection process, including the OCSPP evaluation of the IRIS-identified studies for POD derivation related to sensory irritation. She specified that when selecting appropriate endpoints and PODs, matching the route of exposure and duration of interest is preferable. OCSPP selected two primary studies and four additional supporting studies. The primary studies are Kulle et al. (1987) and its secondary data set (1993) and Hanrahan et al. (1984). She identified Andersen and Mølhave (1983), Mueller et al. (2013), Lang et al. (2008), and Liu et al. (1991), an observational study, as supporting studies. Dr. Burgin introduced the Kulle et al. study, noting that it was a controlled human exposure study in healthy, non-smoking males (n=10) and females (n=9) and detailing the exposures and endpoints. She noted that HSRB deemed Kulle et al. scientifically sound, providing reliable data for use in a weight-of-evidence analysis. She then reviewed Hanrahan et al., a residential observational study of male (n=24) and female teenagers (n=37) in mobile homes, 20 of whom were smokers. The IRIS-derived benchmark concentration (lower 95% confidence limit) (BMCL) was 0.071 ppm for sensory irritation, and statistically significant concentration-responses were found for burning eyes and eye irritation. Dr. Burgin then reviewed in more detail the supporting studies, starting with Andersen and Mølhave, a controlled human exposure study in healthy male (n=5) and female (n=11) smokers (n=6) and nonsmokers. HSRB determined that the study could be used qualitatively to support a weight-of-evidence analysis. She then reviewed Mueller et al. and Lang et al., their experimental design, concentration ranges, and sensory irritation detail, as well as study quality and use for the weight of evidence. Finally, Dr. Burgin reviewed Liu et al., a residential seasonal observational study divided by summer and winter, as well as by sex and smoking status. The authors performed logistic regression and found significant associations in both summer and winter.

Dr. Burgin reminded members that they need to review three acute exposure durations: peak, 8 hours, and 24 hours. She explained that Kulle et al. was selected as the proposed study for peak POD due to its study design as a controlled human exposure study that continuously measured the concentration of formaldehyde. The results are supported by Andersen and Mølhave, Lang et al., and Mueller et al. Dr. Burgin recognized the study's limitations, including a small sample size, the non-representative young, healthy volunteers, and the high concentrations for lower-end exposure distribution. She then presented the proposed POD for peak exposures at 0.34 ppm from Kulle et al., as well as the results from the other supporting studies that are within a similar range with relevant endpoints. OCSPP did not consider Hanrahan et al. as a candidate for an acute 8-hour exposure because the duration of exposure was longer than the duration of interest.

Dr. Burgin described duration adjustments of inhalation PODs, which are typically applied for human health risk assessment unless there is evidence that the chemical of interest does not follow Haber's law (i.e., the severity of a toxic effect depends on the exposure and duration). She examined results from the formaldehyde inhalation studies, wherein studies at 1–2 ppm or higher demonstrated that sensory irritation effects occur immediately but do not increase in severity, inconsistent with Haber's law. In contrast, lower doses do appear to adhere to Haber's law as OCSPP has determined. Dr. Burgin explained the duration adjusted POD of 0.13 ppm, obtained by multiplying the POD from Kulle et al. by the 3-hour exposure over the 8-hour anticipated occupational exposure. Duration adjustments were performed on Andersen and Mølhave, as well.

Dr. Burgin discussed the 24-hour exposures, wherein OCSPP selected Hanrahan et al. because of the exposures evaluated, assumption of a longer exposure duration, and more diverse, representative population. She also discussed limitations, including short sampling times and uncertainties, as well as other possible co-exposures not measured. Dr. Burgin summarized OCSPP's selections and proposed PODs for all exposure types and their respective studies. She then asked the charge question: *"OCSPP has developed a weight of evidence for acute inhalation endpoints for formaldehyde that considered multiple studies and proposed acute inhalation PODs for 3 durations (15-min peak, 8-hr, and 24-hr PODs). Please comment on the use of the 4 studies reviewed by the HSRB (Kulle et al., 1987; Andersen and Mølhave, 1983; Lang et al., 2008; Mueller et al., 2013) in OCSPP's weight of evidence for acute inhalation endpoints and the proposed PODs in Table 3."*

FF. Board Questions of Clarification

- **Srikumaran Melethil**: What will EPA do if these recommendations are approved by the Board? How will they be used?
    - **Deborah Burgin**: We use the weight-of-evidence determination in our risk assessment for OPPT and OPP, and we look at our registered use patterns to see where the exposures may lie and what we need to be protecting against.
    - **Monique Perron**: I think you explained it well. OPPT and OPP will take the PODs, separately determine any uncertainty factors to apply, and evaluate each

respective use patterns and conditions of use with their anticipated exposure levels. We then ask whether there is a potential of risk for a worker or the general public and whether there should be any changes, such as personal protective equipment (PPE) or reduction in use.

- **David Williams**: Could EPA review why it feels Haber's law does apply for this determination of PODs? In Lang et al., which I reviewed, I do not think taking the 24-hour TWA is justified because I do not think there is a continuous increase over time of the symptoms.
    - **Lisa Corey**: I would also like to hear whether there are other points in addition to Andersen and Mølhave, as the low endpoints that support Haber's law support this endpoint.
    - **Thomas Lewandowski**: I have seen some references for irritation as an endpoint that suggest it is quite different as it behaves over timeframes. More clarification would be helpful.
    - **Deborah Burgin:** Formaldehyde is used as a classic example of an inhalation exposure violating Haber's law at higher doses. At lower doses (below 1 ppm), there is more uncertainty because there are very few time-course studies to confirm whether there is increasing severity and increased incidence of symptoms at lower doses. Andersen and Mølhave is essentially the only time-course study to refer to, and these lower concentrations (0.24 and 0.44 ppm) did appear consistent with Haber's law. Because these both were below 1 ppm, EPA decided to use this as a distinguishing level. To address the concern from Dr. Lewandowski, sensory irritation is mediated by the trigeminal nerve, which is different from olfactory stimulation. Trigeminal nerve stimulation results in effects one cannot control, such as watering eyes from cutting an onion. Considering these chemically triggered sensory impacts on workers, this gives us a good understanding of the impacts. One of my colleagues has noted that the Acute Exposure Guideline Levels (AEGL) committee also sets the same value for 10 minutes, out to eight8 hours for sensory irritation for formaldehyde.
        - **Lisa Corey**: It sounds like the AEGL committee, instead of using a TWA, just selected one value, going against Haber's law. Is that correct?
        - **Deborah Burgin**: The AEGL committee is used for emergency situations without considering permanent damage.
        - **Timothy Dole**: Yes, they decided that when setting the AEGL 1, to prevent minor irritation with the same value, though it is based on a different study examining eye irritation.
        - **Lisa Corey**: So, their determination is that formaldehyde does not follow Haber's law?
        - **Deborah Burgin**: Yes, they determined the effects at 10 minutes are the same at 8 hours.

- **Lisa Corey**: Would the alternative, if there was not a duration adjustment, just be the POD, or would there be another step if there was not a duration adjustment?
- **Monique Perron**: If there is evidence that we should not be using a duration adjustment, we would have to consider this information, and reconsider how well the non-adjusted values were matching up. In addition, they would have to be evaluated for less than 24 hours. Ultimately, we would put together an argument for not using a duration adjustment and use the data. Examining Figure 7 of Andersen and Mølhave, it is clear there is limited evidence to determine that we should not use a duration adjustment.
- **Deborah Burgin:** As you can see in Figure 7, it is clear there is a step-up increase in incidence and severity of discomfort over time at these lower doses.
- **Lisa Corey**: Yes, this also emphasizes our concerns with the study's lack of traditional dose response. Thank you for the clarification.
- **David Williams**: That slide seems to suggest that the response plateaus at 3 hours.

Dr. Corey noted that would be kept open for discussion and asked whether there were any other clarification questions. She then thanked everyone for their input and passed the discussion on to Mr. Tom Tracy for public comment.

GG. Public Comment

Mr. Tom Tracy thanked everyone and began the public comment portion, calling on Dr. James Sherman. Dr. Sherman began his presentation, titled "*Using Human Odor Detection and Sensory Irritation Data to Establish Exposure Limits for Formaldehyde Part 2: Integration of the Evidence in the WoE Evaluation*." He then presented EPA's definition of adverse effect: *"A biochemical change, functional impairment, or pathological lesion that affects the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge."* Dr. Sherman stated that odor detection and sensory irritation are normal physiological responses to environmental stimuli, including formaldehyde at less than or equal to 1 ppm, and do not reduce functioning or ability to respond to additional environmental challenge; as such, they are not adverse effects. At over 2 ppm, although tissue irritation is observed, sensory irritation is not high enough to be considered debilitating. On Slide 3, he stated the weight-of-evidence approach does not adequately consider both incidence and severity in Kulle et al. (1987, 1993). Kulle et al. gave different definitions for effects: none, mild (present but not annoying), moderate (annoying), and severe (debilitating), and he reviewed the data on eye irritation and odor sensation. Dr. Sherman stated that the POD and NOAEL should not be set 3 to 10 times below a level where there are no adverse effects reported. He emphasized that in his opinion and consistent with the EPA definition of "adverse," odor detection and sensory irritation are not adverse, and he believes the WHO Indoor Air Quality Guidelines (IAQG), EU occupational exposure limit, and Occupational Safety and Health Administration (OSHA)

permissible exposure limit (PEL) have set levels above the proposed. Dr. Sherman stated that sensory effects provide a lower bounding on potential risk from adverse health effects that are observed only at higher concentrations and requested that this information be reflected in the weight-of-evidence section of the report. Dr. Sherman presented a list of "asks." The first was to make a clear distinction between adverse health effects, sensory detection, and normal physiological responses. He mentioned that the HSRB should also avoid using "irritation" in isolation to describe effects and instead use "(chemo)sensory irritation" or "tissue irritation" to avoid confusingly lumping these different effects with different etiologies. HSRB should ensure both incidence and severity are accounted for in any modeling or statistical analyses, as both incidence and severity are critical considerations in dose-response analyses and identification of NOECs, NOAECs, and PODs. Dr. Sherman also asked that HSRB not support PODs that are below the generally recognized thresholds for sensory irritation (0.5–0.8 ppm) or RfCs/OELs that are below the generally recognized threshold for sensory detection (0.1 ppm), both of which are sentinel effects that are not adverse health effects and that provide a precautionary lower-bounding on potential risk. He then asked whether there were any questions. There were none.

Mr. Tracy introduced Sahar Osman-Sypher of the ACC's Formaldehyde Panel. Ms. Osman-Sypher indicated that in the National Academy of Sciences (NAS) review of the EPA 2010 Draft IRIS Assessment of Formaldehyde, it did not agree with the EPA's decision to set aside the chamber studies as less relevant to the derivation of RfCs. She mentioned that the review recommended that the concentration-response data from the occupational, chamber, and residential studies be presented on the same graph to support the approach from EPA. She recognized that the Lang and Mueller studies are considered key by authoritative bodies such as WHO and SCOEL. She stated that EPA set aside high-quality chamber studies in their 2022 Draft Assessment in favor of the much less reliable study from Hanrahan et al., wherein exposure was not controlled and there was greater uncertainty. She emphasized NAS's concern with the use of residential studies, including Hanrahan et al. and Liu et al., particularly because of their short exposure times. Ms. Osman-Sypher reminded attendees that the HSRB's October 2022 review of Kulle et al. was critical of the report and its quality. She then emphasized that properly controlled human exposure studies are the gold standard for setting safe limits, as indicated by other regulatory bodies. She concluded that the Lang and Mueller studies should be considered the most reliable for determining a POD, not the lower quality Kulle and Hanrahan studies..

- **George Milliken**: In the Mueller study, they classified people as "hypo-" and "hypersensitive." They examined 41 people, used CO_2 inhalation, and ranked them; those above the median were "hyper," and those below were marked "hypo." This is an artificial distinction because study participants were not obtained because they were actually hypersensitive. The concern is that we are overestimating the amount of formaldehyde in the hypersensitive people because of this divide, and this detracts from the value of the study.

- **Lisa Corey:** That is a good point, and we will bring it back on for our group discussion.

Mr. Tracy then introduced Clint Woods of Hexion, Inc. from Columbus, Ohio. Mr. Woods thanked the HSRB for its work and wanted to discuss the potential use under FIFRA and TSCA. He summarized the HSRB charter and bylaws, including the Federal Advisory Committee Act (5 U.S.C. App.2). and why HSRB was established. Under TSCA, he noted that it is unique because EPA determines whether priority existing chemicals present unreasonable risk under specific uses and included the 2020 Final Scope of the Risk Evaluation for Formaldehyde. Mr. Woods summarized Section 26(h) of TSCA and 40 CFR 702.33 related to uncertainty factors, unreasonable risk exposure, PPE, and critical uses, including noting recent bans. Under TSCA, the Scientific Advisory Committee on Chemicals has a role to provide independent advice and expert consultation with respect to the scientific and technical aspects of issues related to the implementation of TSCA. Mr. Woods highlighted other unique legal requirements for regulation and other guidelines and relevant advisory institutions. He then presented his recommendations, noting that a coordinated, joint hazard characterization for FIFRA, TSCA, and IRIS should include a harmonized approach to peer review. HSRB's review should be integrated with NASEM, as well as potential forthcoming reviews by the Science Advisory Committee on Chemicals, the Science Advisory Board, or the Agricultural Science Committee. HSRB should also provide access to relevant materials on other studies, work by authoritative bodies, public comment on the draft IRIS assessment, TSCA risk evaluation, and NASEM peer review. It should also include statutorily relevant charge questions to ensure independent validation and other scientific standards under TSCA. Finally, he noted that the Board should evaluate alternative approaches, including those that have gone through peer review and been used as the basis for standard-setting in recent years, adopted by authoritative bodies around the world. Mr. Woods thanked everyone for the opportunity and welcomed any questions.

Dr. Debra A. Kaden introduced herself and noted she was being compensated by the American Chemical Society but that her opinions were her own. Dr. Kaden noted some issues with the Hanrahan study and that her written comment has more information. She began with an introduction to the study, noting that eye irritation information was collected at any time, not in conjunction with the formaldehyde concentrations collected on a single day. She emphasized the low response rate and high smoking rate of the study and the wide range of formaldehyde concentrations. Dr. Kaden noted the lack of statistical explanation, including for concentrations under 0.1 ppm, and emphasized the authors did not account for formaldehyde fluctuations. She noted flaws with symptom reporting and asked from where EPA got the values and data they relied upon. Dr. Kaden showed Figure 1 and asked whether information was approximated from it, which would introduce more uncertainty. She asked that if EPA has original data from the study, those should be made available. Dr. Kaden also noted that the authors considered results a statistically significant response and EPA strengthened this statement by calling it a "strong dose-response" despite half of the data points being below 0.16 ppm; thus, the response comes

from approximately 30 people with an unspecified number being smokers. She emphasized that the RfC is extremely low and that it is a very poor study and asked that the Board look at the scientific quality of the study before making any scientific recommendations based on it.

- **Thomas Lewandowski**: For the Figure 1 graph, between 0.1 or 0.2 ppm, half of the points were below that?
    - **Debra Kaden**: Yes, the median for households reported was 0.16 ppm, and because median is half above or below, half of the homes were at the lowest range of the graph. So they are basically deriving a dose-response from half of the data.

Mr. Tracy thanked Dr. Kaden and introduced the last speaker, Mr. Steward E. Holm. Mr. Holm introduced himself as chief scientist of the American Forest and Paper Association and the American Wood Council. He emphasized that Association members do not manufacture formaldehyde but formaldehyde-based resins in their manufacturing processes, noting that it also occurs naturally in wood products as well as boiler emissions. He summarized that duration adjustments are not needed for point-of-contact sensory irritants. Mr. Holm cited the 2007 NAS review of formaldehyde. Critically, he emphasized that the review found that irritation of the eyes and upper respiratory tract is the primary health effect of concern. Additionally, he noted that formaldehyde irritation does not follow Haber's law for extrapolating between short-term and long-term toxicity levels. He cited that generally, concentrations that do not produce short-term sensory irritation also do not produce sensory irritation after repeated exposure and that irritation subsides with exposure duration. He further supported this point with the 2022 Draft IRIS Assessment and the 2016 EU SCOEL. Mr. Holm noted his concern with HSRB's recommendation to reconsider OCSPP's approach to Haber's law, disagreeing with the statement that it is a health protective approach.

Dr. Corey asked whether there were any questions related to these presentations and whether there were any additional comments from the public. She explained the agenda for the rest of the day and started a 15-minute break.

HH. Board Discussion

Chad Cross, Ph.D.

Nicole Deming, J.D.

- **Chad Cross**: Ms. Deming and I will be leading this session. I wanted to highlight the presentation from EPA and the public comments for their excellent observations, which we will not repeat here. We have outlined some basic ideas to initiate discussion. We prepared a summary, submitted a few days ago. However, two of the documents from the weight of evidence were not reviewed until Tuesday (highlighted in the document in blue). The background has been described, so I will not discuss it. However, I want to mention that the HSRB found that the Kulle et al. (1987) study was scientifically sound and conducted ethically. Additionally, the Andersen and Mølhave study evaluated last fall was deemed scientifically sound and limited to providing qualitative information, and

it was conducted ethically. I will not discuss the studies from the last two days. I included additional comments to the original document based on the discussions in the last two days, and they are highlighted in blue.

Dr. Cross proceeded to read the responses to the science and ethics charge questions, highlighted in blue in his document, with the changes based on the discussion during the meetings from May 16, 17, and 18.

- **Chad Cross**: I will highlight a few recommendations and remarks. We limited our review to the four studies listed in the charge document. We do not have comments on the appropriateness of the Hanranhan et al. (1984) study for determining the proposed POD for acute exposure, i.e.,24 hour duration.

Dr. Cross continued reading their observations, which have remarks, comments, and recommendations. He asked whether Ms. Deming had anything to add. She did not have additional comments. Dr. Corey then requested ICF display the charge question.

- **Lisa Corey**: This is a different charge question, so I want to make sure that we focus on what we have been asked to address. Please raise your hand, if you would like to talk.
    - **Thomas Lewandowski**: I think there are two questions embedded in here. First, are the four studies appropriate to establish an acute inhalation assessment? And second, is the POD proposed by EPA appropriate? From my perspective, separating those two questions would be helpful.
    - **Lisa Corey**: I agree. We will not be reviewing the observational studies. Those are outside of the review due today.
    - **Julia Sharp**: I think we should clarify the question from Dr. Lewandowski with EPA. However, today we should focus on the four studies, not the PODs.
    - **Ms. Arling**: Yes, that is correct. We would appreciate your comments on the use of these four chamber studies as part of a weight-of-evidence analysis by EPA, so EPA can use those data to derive PODs.
    - **Lisa Corey**: Thank you.
    - **Thomas Lewandowski**: The charge question asks for comments in the weight-of-evidence analysis done by OCSPP and the proposed PODs, so I am confused.
    - **Michelle Arling**: Let me confirm.
    - **AJ Allen**: The way I interpret the question is how the use of the four studies adds context to the proposed POD.
    - **Thomas Lewandowski**: Thank you, Dr. Allen. I just want to understand how far along the risk assessment our efforts extend.
    - **Chad Cross**: I agree with Dr. Allen. We reviewed this study in the context of PODs as presented, not necessarily in the derivation of PODs per se.
    - **Lisa Corey**: Yes, I would expect a larger peer-review process to address those topics.
    - **Michelle Arling**: There will be larger public engagement and peer review about

PODs later in the process.

- **Srikumaran Melethil**: Do HSRB members have questions to EPA based on things that were mentioned by the public?
    - **Lisa Corey**: Yes, we take public comments, and we do not have to take them into account mandatorily. You can ask a relevant public question to be considered, if you would like to.
    - **Srikumaran Melethil**: There is some concern about not using the best available science, which was one criticism from the public. What is the response from EPA about that? There was reference to the NAS publications, suggesting that EPA should use the best available science.
    - **Michelle Arling**: From our understanding, that was directed to the IRIS program about PODs, not EPA OPP and OPPT.
- **Srikumaran Melethil**: Are we going to discuss PODs?
    - **Lisa Corey**: No, we will not. The farthest we will go is the POD for the four studies we have reviewed.
- **Srikumaran Melethil**: Are the EPA POD numbers on Table 3 higher than needed for safety considerations? Are we setting the levels higher than needed from a safety perspective?
    - **Lisa Corey**: That is outside of what we will be discussing today. We are only looking at the four studies and the PODs that could be derived from them.
- **George Milliken**: I am concerned about the definition of "acute" inhalation. What is acute?
    - **Lisa Corey**: Acute would be equivalent to 24 hours of exposure.
    - **George Milliken**: We have endpoints, but we did not clarify what levels are acute. There may have been two people that had moderate effects. I do not know how we address the weight of evidence without clarifying these definitions.
    - **Lisa Corey**: I tend to read that as acute duration. We can talk about severity separately.
    - **Thomas Lewandowski**: I agree with Dr. Corey. We could start the response to EPA with what we are covering in our response. What is the response from EPA about the ongoing sensory study that was mentioned before?
    - **Michelle Arling**: We do not have comments right now.
- **AJ Allen**: The chamber studies have some advantages relative to an observational study, wherein you do not control the exposure. The chamber does allow controlling exposure to formaldehyde. In the context of the acute period, this is 24 hours or less to be considered acute as opposed to months or years living or working in a particular setting. My biggest question is that those studies have many limitations, and they are not strong in their ability to correlate exposures to different responses. EPA needs to use the chamber studies preferably.
- **Michelle Arling**: I wanted to offer a few clarifications on the charge questions.

  - **Monique Perron**: Acute is a duration of 24 hours or less. It is different from a medical definition. The weight of evidence is taking the data, uncertainties, and strengths of those studies and coupling them with the observational studies. We would like feedback on how these studies can be used to develop or support POD values.
- **Lisa Corey**: Any additional comments?

No additional comments or questions were provided.

- **Lisa Corey**: We are commenting only on the four chamber studies, not the observational studies. The latter would include a discussion beyond what we have been discussing so far. My recommendation at this point is that EPA should clarify the definitions of hypersensitive vs. hyposensitive because of how the study defined those groups (because they are not representative of the overall population).
  - **AJ Allen**: I agree, but I am not sure it is relevant to the work from EPA in terms of weight of evidence. I do think it is a good point brought up by Dr. Milliken.
  - **George Milliken**: I think the real issue is that people considered hypersensitive in the study do not represent those in the entire population. This could result in a very high POD.
  - **Lisa Corey**: I agree. It can easily be misinterpreted, but the study does not suggest that explicitly. I agree that outside of the study it could be misinterpreted.
- **George Milliken**: I am concerned about how the authors analyzed the data.
- **AJ Allen**: Do we want to discuss if the study supports or does not support the Haber effect?
  - **Lisa Corey**: The supporting evidence that does not follow Haber's law is the study by Andersen and Mølhave. Do we think it is appropriate for use?
  - **Thomas Lewandowski**: The limitations must be reviewed carefully, and EPA could provide a defense of using that type of data. The language we currently have in the report could be stronger.
  - **Chad Cross**: We said *"provide clarification concerning the appropriateness of the Haber Law duration adjustments used to develop the exposures…"* I am happy to edit the text to make it stronger.
  - **Thomas Lewandowski**: We could say "justification" instead of "clarification."
  - **Chad Cross**: Sounds good.
- **Lisa Corey**: And we can clarify the 24-hours issue as it is currently being used as justification. Can we review the response?

Dr. Cross shared his screen with the highlighted replies. He also added the study by Liu et al. (1991) in the last sentence of the first paragraph, under "Remarks and Comments." Dr. Sharp added the charge in the chat.

- **Julia Sharp**: I like the yellow highlighted text for the potential response to the charge

question, which I can add to the chat.

- **Lisa Corey**: We should focus on the priority points of which we have a few currently. Should we include more specific recommendations and comments in the written document?
    - **Dr. Sharp**: Would you propose adding to the response to the charge *"provided that comments and recommendations from the HSRB are considered"*
    - **Dr. Corey**: Yes.
- **AJ Allen**: This is a weight of evidence in discussion, but we have not seen all the evidence. To me it is important that EPA obtains information from multiple sources.
    - **Michelle Arling**: Providing detailed recommendations would be helpful. The more specific, the better for us to consider before moving forward. That way, we will incorporate your feedback for the larger risk assessment efforts.
- **George Milliken**: I am concerned that we have not considered what we have heard today from public comments (and not having the ability to go through those comments in detail).
    - **Julia Sharp**: That goes beyond our scope. We should focus only on commenting on these four papers.
    - **George Milliken**: Yes, but they had information about these four papers.
    - **Srikumaran Melethil**: I agree with Dr. Milliken. It may be outside the scope, but we need to incorporate those points (e.g., using the best available science as required by law and setting limits that may not be necessary).
    - **AJ Allen**: I agree. I have two lines of concerns: Does the Haber effect apply? That is relevant to two of the papers because they have contradictory evidence between the two. Secondly, we had a biased look at these studies. We reviewed the chamber studies, which are controlled trials, as opposed to observational studies. The observational studies were not that large. Should we be giving more weight to the observational studies over the chamber studies given the quality of data that are available?
    - **Julia Sharp**: Given the discussion, is there a remark that we could add to the document that Dr. Cross drafted?
    - **Srikumaran Melethil**: EPA could try to respond to public comments in the document.
- **Michelle Arling**: The feedback from Dr. Allen would be helpful in the report. EPA will have an extensive public period that will include the weight of evidence, so there will be an opportunity to respond to public comments. EPA will not respond to them in the context of this meeting.
- **Srikumaran Melethil**: Why are there public comments now if they will not be used?
    - **Dr. Allen**: I think that allows us to include that feedback in our response.
- **David Williams**: I appreciate the cautionary approach to the PODs. I believe we can say that the four studies should be included. The 8-hour POD should be the same, although I

know we are not supposed to discuss it. If Haber's law does not apply between 3 and 8 hours, then the 24-hour value would be the same. EPA could include uncertainty factors as part of its analysis to consider sensitive individuals.

  - **Lisa Corey**: I think we can add that specific comment. It may be difficult to vote on multiple observations. We have a response similar to what Dr. Sharp added in the chat. The additions we have would be appropriate. We could include more specific points in the written document. We would have specific recommendations in the answer to EPA today.
  - **AJ Allen**: That would be a good starting point.

- **Thomas Lewandowski**: When it comes to specific recommendations, there is more discussion or review that must happen. We all agreed that the studies are useful. Regarding specific recommendations, we should clarify what those would be.
- **AJ Allen**: We will have a report to approve. We could add our observations at that point.
  - **Michelle Arling**: Any recommendations you may have would be helpful.
  - **Tom Tracy**: So, could we discuss this in July then? We could expand the group to six people so that in the July meeting, a more robust conversation can take place..

II. Adjournment

Mr. Tom Tracy thanked the Board. The meeting adjourned at 5:01 p.m. EDT

Attachment A: HSRB Current Committee Membership

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

Attachment B: Federal Register Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10408-01-ORD]

Human Studies Review Board (HSRB) Meetings—2023

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of public meeting.

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

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

1. February 15–17, 2023; and
2. April 18–20, 2023; and
3. July 25–27, 2023; and
4. October 11–13, 2023.

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

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

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

SUPPLEMENTARY INFORMATION:

Background

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

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

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

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

How May I Participate in this Meeting?

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

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

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

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

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

Dated:

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