EPA Human Studies Review Board (HSRB)
October 11-12, 2023 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A.)
Date and Time: Wednesday, October 11-12, 2023, 1:00 to 4:00 p.m. EDT.
Location: Via Zoom
Purpose: The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subjects research.
HSRB Website: https://www.epa.gov/osa/human-studies-review-board

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Wednesday, October 11, 2023:

A. Meeting Topics and Charge Questions

Topic: Flyvholm, MA, Hall, BM, Agner, T, Tiedemann, E, Greenhill, P, Vanderveken, W, Freeberg, FE and T Menné. (1997). Threshold for Occluded Formaldehyde Patch Test in Formaldehyde-Sensitive Patients. Contact Dermatitis. 36: 26-33.

Charge to the Board – Science: Is the research described in the published study "Flyvholm, MA, Hall, BM, Agner, T, Tiedemann, E, Greenhill, P, Vanderveken, W, Freeberg, FE and T Menné. (1997). Threshold for Occluded Formaldehyde Patch Test in Formaldehyde-Sensitive Patients. Contact Dermatitis. 36: 26-33" scientifically sound, providing reliable data for consideration as part of endpoint selection and derivation of a point of departure for elicitation of dermal sensitization from dermal exposure?

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, DFO, EPA HSRB, OSAPE

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

HSRB members
Lisa Corey, Ph.D., Co-Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (National Institute of Standards and Technology) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) 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) Ann Um (AMSTAT Consulting)

David Williams, Ph.D. (Oregon State University)
EPA staff members
Michelle Arling (EPA, Office of Pesticide Programs (OPP)) Stan Barone (EPA, Office of Chemical Safety and Pollution Prevention (OCSPP)) Deborah Burgin (EPA, OPP) Lexie Burns (EPA, Office of Science Advisor, Policy and Engagement (OSAPE)) Andrew Byro (EPA, OPP) Madison Clark (EAP, OSAPE) Jeff Dawson (EPA, OCSPP) Elizabeth Donovan (EPA, OPP) Judy Facey (EPA, OPP) Ann Huang (EPA, Office of Pollution Prevention and Toxics (OPPT)) Monique Perron (EPA, OPP) Colleen Rossmeisl (EPA, OPP) Monique Tadeo (EPA, Program in Human Research Ethics and Oversight (PHERO)) Tom Tracy (EPA, OSAPE) Kimberly Wilson (EPA, OPP) Kendall Ziner (EPA, OCSPP)
Members of the public, representatives of research sponsor, and research team:
James Damewood (Dupont Chemical) Sorina Eftim (ICF, Contractor Support) Katy Goyak (Celanese) Angelina Guiducci (ICF, Contractor Support) Afroditi Katsigiannakis (ICF, Contractor Support) Sahar Osman-Sypher (American Chemistry Council (ACC)) Emily Pak (ICF, Contractor Support) Jessica Ryman-Rasmussen (ACC)

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 and discuss "Threshold for Occluded Formaldehyde Patch Test in Formaldehyde-Sensitive Patients. Contact Dermatitis" by Flyvholm et al., 1997. He noted that minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of October 11, 2023.

D. Introduction of EPA Staff

Michelle Arling, J.D., OPP

Ms. Michelle Arling invited EPA staff on the call to introduce themselves.

E. Updates from EPA HSRB Review Official

Monique Tadeo, HSRB Review Official, PHERO

Ms. Monique Tadeo noted that there were no updates to share.

F. Updated from EPA HSRB and Meeting Process

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

Dr. Lisa Corey welcomed the Board and reviewed the agenda for the meeting.

G. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Michelle Arling noted that EPA had no significant updates since the last HSRB meeting. EPA is working on a formaldehyde inhalation risk assessment. HSRB feedback from the current meeting will influence the dermal exposure risk assessment. Ms. Arling shared that there is a skin applied repellent study protocol that includes a conventional and biopesticide ingredient slated for discussion in January 2024.

H. EPA Science Review Highlights

Colleen Rossmeisl, D.V.M., OPP

Dr. Colleen Rossmeisl's presentation focused on the two human dermal sensitization assessments for formaldehyde presented to the HSRB. Slide 1 listed the outline for the presentation, which included a review of dermal sensitization and formaldehyde, allergic contact dermatitis (ACD), and an introduction of the two studies (Flyvholm et al. 1997 and Fischer et al. 1995). Slide 3 introduced the purpose of the presentation and provided background information. The Office of Pesticide Programs (OPP) and the Office of Pollution, Prevention, and Toxics (OPPT) are evaluating formaldehyde exposure risks under their respective statutes. Additionally, EPA is consulting with the HSRB on the scientific and ethical conduct for two intentional human exposure studies (Flyvholm et al. 1997 and Fischer et al. 1995) which examine elicitation thresholds from formaldehyde dermal exposure.

Slide 4 provided an overview of the differences between OPP and OPPT. OPP works under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), whereas OPPT works under the Toxic Substances Control Act (TSCA). Dr. Rossmeisl read the differences between OPP and OPPT listed in the slide. Slide 5 discussed the rationale behind considering dermal sensitization endpoints for formaldehyde. It was noted that formaldehyde is a known dermal sensitizer. In addition, dermal irritant effects are reversible. In contrast, after chemical sensitization is induced in an individual, it may last a lifetime. Dr. Rossmeisl indicated that the adverse outcome pathway for dermal sensitization has been well defined and provided a reference article in the slide. Slide 6 highlighted EPA and the quantification of dermal sensitization. In 2004, EPA discussed the use of quantitative dermal sensitization endpoints in FIFRA scientific advisory panels (SAP) on

hexavalent chromium. In 2017, the HSRB supported the quantitative use of the presented studies in establishing a point of departure (POD) for methylisothiazolinone (MIT).

Slide 7 included a table that explained various regulatory agencies' stances on formaldehyde dermal sensitization. Slide 8 described dermal sensitization and allergic contact dermatitis (ACD), which can be characterized by two phases: induction/sensitization and elicitation/challenge. These two phases are induction/sensitization, i.e., exposure of sufficient magnitude and/or duration resulting in dermal sensitization, and elicitation/challenge, i.e., responses from subsequent exposures to the allergen. Slide 9 presented a diagram explaining contact hypersensitivity. Induction and elicitation were both described.

Slide 10 presented other data considered by EPA for dermal sensitization by formaldehyde, e.g., animal and *in vitro* data. Slide 11 provided background information on Flyvholm et al. 1997 and Fischer et al. 1995. It was noted that both studies include healthy formaldehyde-sensitive subjects. Both studies were identified from an OPPT systematic literature search. Slide 12 described the systematic literature search methodology. EPA focused on a subset of studies where testing was completed in formaldehyde sensitive individuals at concentrations less than 1% to determine a "minimum elicitation threshold". Slide 13 acknowledged five additional intentional human exposure studies that were initially identified that tested formaldehyde concentrations below 1%. These studies were not included in the overall data set to support quantitative determination of POD because they had limited or no data on quantitative analytical methods, did not provide information to estimate skin loading, participant information or conducted single dose testing or the dose was not relevant to the lower range of sensitization/elicitation.

Slide 14 displayed a graphical representation of results extracted from Flyvholm et al. 1997 and Fischer et al. 1995. The graph showed formaldehyde loading versus percent positive response rate that can be used for risk assessment purposes. Slide 15 discussed the two types of dermatological skin testing. Patch tests are a standard for clinical allergy testing used to determine an individual's sensitivity to a chemical. Researchers typically apply the material to a small defined area of the skin for a short period of time (24 to 48 hours). The tests may be occluded (i.e., applied to skin that is covered) or non-occluded (i.e., applied to skin that is not covered). There is also a repeat open application test (ROAT). The test article is repeatedly applied to a defined area of the skin in sensitized individuals over a longer time period (i.e., weeks). These tests are normally non-occluded tests and may be considered a more realistic exposure pattern.

Slide 16 presented images of patch tests and ROAT from Lundov, Zachariae, and Johansen (2011). Slide 17 presented the criteria for a positive patch test reading based on the International Contact Dermatitis Research Group (ICDRG) guidelines. Slide 18 showcased images of a range of positive reactions across different chemical concentrations.

Slide 19 and 20 described the study from Flyvholm et al. from 1997. It was noted that OPP made

multiple attempts to request additional data and documentation of the ethical conduct of the study, but no additional information was received. Slide 21 presented information on the study subjects and overall methodology. A total of 14 women and six men with previous positive patch tests to formaldehyde participated in the study. A total of 12 women and eight men with negative patch tests to formaldehyde and other test materials acted as controls. Slide 22 and 23 discussed occluded and non-occluded patch tests in the study. The concentration of the formaldehyde in the solutions for the occluded and non-occluded patch tests was analyzed by an iodine titration method response. Free formaldehyde and total formaldehyde for ROAT was analyzed by a High-Performance Liquid Chromatography method.

Slide 24 restated the International Contact Dermatitis Research Group (ICDRG) criteria for a positive patch test reaction. Slide 25 presented a table of the occluded patch test results, displaying dose-response observations. Slide 26 and 27 displayed Figure 1 and 2 from the study, which both visualized the occluded patch test results. Dr. Rossmeisl indicated that more individuals reacted as the dose increased. Slide 28 discussed the non-occluded patch testing and ROAT results. For both testing types, no positive reactions based on the established criteria were observed. For the ROAT, few follicular papules were observed in five of 20 patients. Variability in doses was attributed to subjects applying varying amounts of cream. Slide 29 noted that EPA attempted to obtain the raw data but were unsuccessful. No additional statistical analyses were feasible for the study based on the lack of reported raw data.

Slide 30 and 31 discussed strengths and limitations of the study. Notable study strengths include an adequate number of male and female participants, participation of individuals with previously confirmed sensitivity to formaldehyde, information on degree of response provided. In addition, the experimental design examined dose-response relationships of elicitation threshold for formaldehyde, and a no observed adverse effect level (NOAEL)/lowest observed adverse effect level (LOAEL) could be identified. Lastly, skin loading in the study aligned with potential skin loading from expected uses. Limitations include limited information on the test substance (e.g., purity or source of formaldehyde or presence of stabilizers), reading day not reported for individual results, and concentrations reported as measured/confirmed but it is unclear if nominal or measured concentrations are used in the study.

Slide 32 presented EPA's overall conclusions of the study. Based on the occluded patch tests, the LOAEL was 250 ppm (0.025% or 7.5 µg/cm^2), and the NOAEL was 50 ppm (0.005% or 1.5 µg/cm^2). EPA concluded that the study was well-conducted and provides quantitative information for deriving a minimum elicitation threshold for formaldehyde and stated that it can be considered as part of endpoint selection and POD derivation. Lastly, slide 33 restated the charge question.

I. Board Questions of Clarification

Dr. Lisa Corey asked if there were any questions of clarification.

- **Thomas Lewandowski**: What was the concentration of methanol when used as a

stabilizer? It was quite low, but for skin sensitization studies, the vehicle can be significant in enhancing dermal penetration of formaldehyde and thus the potential for a positive response.

  - **Colleen Rossmeisl:** We do not know the methanol concentration because it was not reported in the study. Formaldehyde is the only reported concentration. Other studies cite it as formalin instead of formaldehyde. This study only talks about formaldehyde. We know that methanol is a common stabilizer.
  - **Thomas Lewandowski:** Do we know the concentration used for stabilization purposes?
  - **Colleen Rossmeisl:** The typical concentration is about 37% in formalin. That cannot be applied to this study because they did not state if they used formalin.

- **Srikumaran Melethil**: Were the results from occluded and non-occluded tests expected? There was not much effect with the non-occluded test. Were there any evaporation issues with formaldehyde that could have resulted in less test reaction?
  - **Colleen Rossmeisl**: That could be a concern. The study discussed whether evaporation could have impacted the non-occluded test.
- **Sinziana Seicean-Boose**: My question is related to the rating criteria used by the study based on the ICDRG. Since 2015, a weak positive reaction is considered infiltration papule. But if infiltration papules are developing, it is a strong positive reaction. This is quite different than the study's dermal assessment of formaldehyde. We considered number four was redness and infiltration in the area. How will this be taken into consideration?
  - **Colleen Rossmeisl**: Are you citing the variation in the strength of the reaction?
  - **Sinziana Seicean-Boose**: The rating criteria described in this study are different than the ICDRG criteria. The 2015 ICDRG criteria would include the third and fourth dermal assessment based on how it was presented by this study. It includes the papular follicular reaction to the test area together with infiltration and skinning. Therefore, we are missing some positive reactions. The study states it is using the ICDRG criteria, but it is not. I wanted to ensure EPA is aware of this, and if so, how will it be dealt with?
  - **Colleen Rossmeisl**: I do not think EPA was aware of an updated ICDRG criteria and it can be considered when looking at the results.
- **Weiying Jiang**: I would like to hear your opinion on the test materials. Based on the materials and methods section, the occluded patch testing mixture includes the formaldehyde solutions with a range of nominal concentrations. This includes the 1% aqueous formaldehyde solution and formaldehyde releaser. I do not see the mixing proportions, so the exact formaldehyde concentrations are unknown. I would like to hear your thoughts on this and whether additional information is available.
  - **Colleen Rossmeisl**: EPA read the methods and materials section several times. I believe they were testing formaldehyde in the concentrations they specified in the

patch testing. When they discussed the occluded patch testing with other materials, that was part of their effort to test if participants were sensitive to other materials used in the ROAT. The formaldehyde releaser, paraben mix, and rubber were all used in the ROAT. The authors stated they tested those materials with occluded patch testing. EPA interpreted this to mean that was not part of the series dilution. I do not think they were all combined in the patch test.

- **Weiying Jiang**: In the methods and materials section, the authors stated that in addition to the above-mentioned formaldehyde solutions, occluded patch testing was made with formaldehyde 1% aqueous solution, paraben mix dermal 115, and rubber. It seems to me that everything was mixed which will dilute the original concentrations in the testing solution. I am not sure if the concentration will be similar to the nominal concentration in the original test solutions.
- **Colleen Rossmeisl**: Are you suggesting the authors combined the dilution series with something else? For example, when the authors state they tested 500 ppm, it was diluted with other materials.
- **Weiying Jiang**: Yes, that is my concern. If you add something else or mix everything together, the original concentration will change.
- **Colleen Rossmeisl**: Our interpretation is that this was not occurring. There were separate tests for the other materials and the dilution series.

- **Thomas Lewandowski**: The authors tested and excluded participants who reacted to the formaldehyde doner for the ROAT test. However, during the ROAT, they tested participants with the formaldehyde doner chemical. I did not understand the logic behind this decision and wanted to hear EPA's thoughts.
  - **Colleen Rossmeisl:** I was not sure why the authors stated that they excluded participants who tested positive to formaldehyde from the ROAT test.
  - **Thomas Lewandowski**: Yes. If you exclude people who are sensitive, you will not have anyone reacting, which is exactly what happened.
  - **Colleen Rossmeisl:** Yes. I have to reread that section because I also had questions about this.

J. EPA Ethics Review Highlights

Michelle Arling, J.D., OPP

Ms. Michelle Arling presented EPA's ethics review of Flyvholm et al., 1997. She started by thanking the HSRB for their feedback and participation. Slide 2 listed the outline of the presentation.

Slide 3 reviewed the study subject selection. Forty individuals participated and twenty were formaldehyde sensitive. Additionally, sixteen formaldehyde sensitive individuals declined to participate. The formaldehyde sensitive individuals were clinic patients and had a positive patch test for formaldehyde and no negative patch test to certain chemicals. Also, these individuals had no dermatitis or took medication that could interfere with testing. Control subjects were healthy

volunteers with negative patch tests to formaldehyde, parabens, Germall 115, and rubber. Slide 4 reviewed the consent process. Subjects received oral and written information; all subjects gave written consent to participate. Ms. Arling noted that EPA attempted to retrieve additional data from the study authors regarding the consent and ethical review process and the raw data. Two authors said that due to the age of the study, there is no available ethical information or raw data. Slide 5 highlighted risk and risk minimization. Formaldehyde is a known skin irritant, and exposure could cause irritation or dermatitis. The study took measures to minimize risks, including conducting the study at a dermatology clinic under the supervision of medical professionals, using concentrations in line with commonly applied diagnostic patch testing, and excluding subjects who had known sensitivities to other test substances.

Slide 6 discussed the respect for the subjects. It was noted that 16 individuals withdrew prior to enrollment, and all study participants were kept anonymous. Slide 7 focused on the independent ethics review conducted on the study. The research was approved by the Ethical Committee of the Copenhagen Municipality. Slide 8 listed the substantive acceptance standards under which EPA reviews certain human studies conducting this type of research. Slide 9 reviewed the prevailing ethical standards at the time the study was conducted. The research was conducted in the early 1990s and thus, the Declaration of Helsinki was the prevailing ethical standard.

Slide 10 highlighted the findings from the study. All subjects were adults and there was no indication that female subjects were pregnant or nursing. It was also noted that there is no evidence that the research was fundamentally unethical or deficient relevant to the ethical standards at the time of study publication. Slide 11 concluded that the research was not fundamentally unethical based on the available information. Slide 12 presented the charge question.

K. Board Questions of Clarification

Dr. Corey asked if the HSRB had questions of clarification. There were none.

L. Public Comment

Mr. Tom Tracy invited Dr. Jessica Rayman-Rasmussen to begin her public comment.

On slide 1, Dr. Rayman-Rasmussen introduced herself as a senior director of chemical manager at the American Chemistry Council. Dr. Rayman-Rasmussen discussed scientific and risk assessment considerations for the two studies. One slide 2, Dr. Rayman-Rasmussen discussed the skin sensitization endpoint, which involves an induction and elicitation phase. This endpoint has not historically been used as the basis for a reference dose. Thresholds for skin sensitization can be impacted by several variables. It was noted that both Flyvholm et al. 1997 and Fischer et al. 1995 involve the elicitation response in sensitive individuals compared to non-sensitized controls.

Slide 3 reviewed Flyvholm et al. 1997. This is an elicitation study where subjects were both sensitized and controlled. Dr. Rayman-Rasmussen said the ROAT portion of the study was not

relevant. The test was performed under occluded and nonoccluded conditions with a leave-on cosmetic product. Fifteen microliters of formaldehyde in varying concentrations were applied to the skin. Participants were instructed not to wash the area formaldehyde was applied on their skin. Nonetheless, no positive reaction was observed in sensitized or controlled exposed to up to 10,000 ppm formaldehyde applied to a 1 cm^2 area. Positive reactions were observed in the occluded conditions in sensitized individuals only.

Slide 4 reviewed Fischer et al. 1995. This is an elicitation study that utilized formaldehyde sensitized individuals as well as people with eczema and controls. A TRUE proallergen N-hydroxymethylsuccinimide (HMS) patch was used to mimic formaldehyde release on the skin over an extended time. The exposure duration was 48 hours and results were evaluated at 72 and 96 hours. It was noted that comparison of reactions to TRUE HMS patches and aqueous formaldehyde was difficult. Ultimately, Dr. Rayman-Rasmussen concluded that this study has low utility and should not be pooled with Flyvholm et al. 1997 during analysis.

On slide 5, Dr. Rayman-Rasmussen presented concluding thoughts on the use of the two studies in risk assessments. She noted that neither study, alone nor in combination, is useful for deriving a reference dose.

- **Albert J. Allen**: What is the amount of time typically used to demonstrate a sensitization response in a sensitized individual?
    - **Jessica Rayman-Rasmussen**: It depends on the duration of exposure. The second slide lists variables that influence elicitation which includes duration of contact. An important question is as follows: for the conditions of use, are the duration and conditions of exposure at which elicitation occurs of a sensitization reaction in the study relevant?
    - **Albert J. Allen**: The problem is if exposure length is too short, you may get a negative response early. If you give the body a longer time to respond, you may get a positive response. This is a safety study.
    - **Jessica Rayman-Rasmussen**: You could have conditions of use that are very short responses in which a person might never elicit because the duration of exposure and condition of use is not long enough.
    - **Albert J. Allen**: Do you know of scenarios where a sensitized individual may be exposed to formaldehyde on their skin in an occluded way in the real world? I am not convinced that what you are saying will always be relevant.
    - **Jessica Rayman-Rasmussen**: There could be a person working with formaldehyde and it gets under their glove. This person will remove their gloves and wash the area before leaving work. However, in the study participants were encouraged not to wash the exposed area in the study.
    - **Albert J. Allen**: Taking a conservative approach in terms of what might constitute exposure and is safe for a sensitized individual is important. You could argue that there are cases where what you are saying is true, but there is potential

for cases where it is not.

- **Lisa Corey**: We could bring this back up during discussion. I agree with what you are saying AJ. The study conducts something similar to standard allergy testing as opposed to mimicking real world exposures.

Dr. Corey asked if there were additional questions for Dr. Rayman-Rasmussen. There were none.

M. Charge to the Board – Science:

David Williams, Ph.D., Science Review
Weiying Jiang, Ph.D., Science Review
Sinziana Seicean-Boose, Ph.D., Statistical Review

Dr. Corey reviewed the remaining schedule and ensured all members of the Board were present after a break. Dr. Corey then introduced Dr. Weiying Jiang and Dr. David Williams for the Science Review.

Dr. Williams shared the Science Review document with his comments and comments from Dr. Jiang for the Board. Dr. Williams noted Dr. Thomas Lewandowski's involvement and knowledge in the area of study. Dr. Williams gave a short review of treatment groups, study summary, and study design. He clarified the selection process for participants sensitive to formaldehyde for the study and recognized that EPA would principally examine the data from the occluded patch test for determining a POD. Dr. Williams questioned the decision to exclude the 100-ppm dose concentration with the occluded patch experiment as it was not skipped for the non-occluded experiment. Including a 100-ppm group would allow for a more accurate distinction between the NOAEL and LOAEL. He mentioned Dr. Jiang's issues with concentration levels in the study, and that there will be time for further discussion. Dr. Williams highlighted that in Table 3, the units were incorrect by a factor of one thousand— reported in micrograms instead of milligrams. Dr. Lewandowski and Dr. Williams both reviewed the calculations to confirm this mistake.

Dr. Williams then introduced key questions raised by this article. This included whether it was standard to perform multiple treatments simultaneously. Dr. Lewandowski raised the issue of the skin excitation response, asking what the interval is between testing for occlusion and sensitivity. Dr. Williams noted the lack of clarity for what the responses were over time, including when specific observations were performed. In general, he felt the materials and methods section lacked clarity. Dr. Williams recognized that one individual responded at 250 ppm, which set the LOAEL. He expressed concern that if this is not a true response, one individual is dictating a LOAEL, introducing uncertainty. They also used 300 ppm in the ROAT. In general, the study was underpowered, with low participation rates. He then highlighted issues with the non-occluded patch tests, including uncertainty around the rate of release from the ROAT-cream and variability in application with only five individuals. He recognized that this section is not of consequence because only the occluded patch test data will be considered by EPA. Dr. Williams noted the large proportion of women as participants and recruits, and that the authors do not expand on this gender ratio. He noted the EU regulatory concentration levels for formaldehyde in cosmetics and other products the general public is exposed to on a regular basis.

Dr. Williams questioned the applicability of data from a sensitive group in analysis for a general population induction versus elicitation. He concluded that EPA could use parts of the occluded patch data for consideration as a weight of evidence (WoE) for arriving at a POD. He then invited Dr. Jiang and Dr. Lewandowski to provide their input. Dr. Jiang thanked Dr. Williams and noted the lack of clarity in the Test Materials section. He recommended clarifications on the actual formaldehyde concentrations used in the test materials for accuracy and to arrive at a threshold. Dr. Thomas Lewandowski recognized the overall standard methodology, and that excited skin syndrome is noted as a challenge, but this study randomized the location of the different doses.

Dr. Lewandowski then addressed the female to male ratio and explained that allergy and atopy is higher in the female population, mimicking the general population of interest. Dr. Lewandowski also questioned the use of elicitation, particularly the study's reliance on a single individual. He introduced previous work addressing chromium and nickel that aggregated data from multiple studies through the same dose metric. Dr. Corey asked the Board if they had questions for the speakers. Dr. Albert J. Allen provided supplemental literature supporting Dr. Lewandowski's statement about women and the prevalence of allergy and atopy. Dr. Corey concluded the Science Review and introduced Dr. Sinziana Seicean-Boose for the Statistical Review.

Dr. Sinziana Seicean-Boose summarized the study's focus and specified the data of interest for EPA. She noted the lack of statistical analysis in the study and agreed with the ICF statistical review provided by EPA. She presented the basic descriptive statistics, including information on participants. Dr. Seicean-Boose read Tables 1, 2, and 3 of the study, explaining the descriptive statistics. The authors report no differences in the degree of sensitivity to formaldehyde between participants and non-participants. Dr. Seicean-Boose highlighted that no statistical support and analysis for this claim is provided. Furthermore, the authors report a relationship between the degree of patch-test reactivity and formaldehyde concentration without statistical support. She questioned the 250-ppm formaldehyde threshold concentration in sensitive individuals as it lacked analysis. She also noted the lack of information on the control group and questioned why EPA would use this study considering the lack of evidence related to the general population. Dr. Seicean-Boose clarified that a more appropriate study design for statistical analysis would be a case control study with a ratio of one to one. She expressed concern over the study design, particularly the small sample size. For instance, a proportional odds model would need additional participants. She also commented on the lack of information comparing general population demographics and those of the study participants. Addressing the time frame, because of the study design and aims, there should be further statistical complexity. Dr. Seicean-Boose concluded from a statistical perspective for dermal sensitization, this study does not provide reliable data to be considered for a POD and the lack of data did not allow for further conclusions. Dr. Seicean-Boose indicated that EPA could use the raw data from the experiments for a meta-analysis.

- **Albert J. Allen:** Your concern is about using this for dermal sensitization for a POD, what about dermal elicitation?

  - **Sinziana Seicean-Boose:** I am supposed to review the statistical part, and every conclusion that was triggered by the study was not derived from any type of statistical analysis. It is hard for me to say with not enough sample size, and only the descriptive analysis of the participants and results, it is hard to trigger any conclusion from my perspective, did that answer anything?
    - **Albert J. Allen:** I think so, yes.
  - **Julia Sharp:** Can I comment? Because of the limited data and the lack of a dose response model, which is required to develop a POD, I would say that I have similar concerns to Dr. Seicean-Boose. We cannot use the data to establish a POD, however if the EPA is using the data in support of a POD through a meta-analysis, where they are using the means and standard deviations from this and other studies to help with creating the POD, not themselves establishing a POD, which would be fine. But because the dose response model was not possible, which was a requirement to establish a POD, I have concerns with that as well.
    - **Albert J. Allen:** But that would be for a POD for the elicitation response, not the sensitization, correct?
    - **Julia Sharp:** Correct, this was an elicitation study.
    - **Sinziana Seicean-Boose:** I fully agree, I actually think that if the intention is a comprehensive meta-analysis, with a lot of patience and creativity using the results as raw data, something good may be available. And as I mentioned before, it would be up to the EPA even to fix the problem with formaldehyde dermal assessment related to the ICDRG scoring scale by including the third grade, the popular follicular reaction, in the test area as a positive reaction. But again, without raw data, it all depends on the quality of the studies which are actually focused on this need.
- **David Williams:** Maybe this is the way I read the charge, "providing reliable data for consideration as *part of* endpoint selection and derivation." So first of all, although there are problems with the study and there has been an excellent job by the statistical evaluation, I still think they are scientifically sound and provide reliable data and can just be used as part of an endpoint selection. I was just assuming this was going to be used in a WoE approach like we did for airborne formaldehyde. If I were to provide a classification as far as low, medium, or high, it would be medium at best, but I think it could be included in a WoE and as Dr. Lewandowski has done before with the metals.
  - **Lisa Corey:** That is a good point, and as a reminder, when we put together our recommendations, all of our recommendations are in there and we specifically call to them in response to our charge. So, our concerns, although they may not be in the body of the response, will be in the document that goes to EPA.
- **Thomas Lewandowski:** I saw in Dr. Seicean-Boose's view about this study being controversial, however I do think this study is fine for what it is - a dermal patch testing study. There is nothing unusual about that. What is unusual about this is using this kind

of patch testing study to set a regulatory limit. So, I think that is where the unease is coming from, this is not the kind of study that we typically see. Unlike the inhalation study David mentioned, which was a pretty standard tox. study, this is different. But I think we can use it; it is a different kind of study. Patch testing is normally done on smaller numbers of people because it is a lot to ask people to get their patch tested. So, it is what it is. And having a low level of confidence in the final threshold concentration because of the low number of participants is problematic, so I agree that some kind of meta-analysis seems appropriate and that is consistent with the idea of not using this study alone, which as pointed out from the charge question, seems that was not EPA's intention.

- **Lisa Corey:** That is great, and I think that comes back to our public comment from Jessica, which highlights the tension between the aims of this study and the potential use by EPA, and that those are not as aligned as we would like.
- **Albert J. Allen:** Related to the questions about the population used and the structure of the study in terms of the delayed testing, it is worth remembering that formaldehyde contact dermatitis is a delayed response allergic contact dermatitis. In another section of the article, I mentioned on the ratio of men and women, this review from Nature disease primers, one of the points they make is this is often is delayed recognition in the occupational setting. As someone who has worked for days in a gross anatomy lab wearing gloves and smelling formaldehyde, this is not something you can wash off at the end of the day, it permeates your hands and clothing for hours afterwards. This is a situation where occluded exposure is a real risk, and the highest risk is for those individuals who are sensitized by previous exposure. And so, I think the elicitation group, the population they looked at, is such an important group of individuals. The other thing is we do not know who is likely to be sensitized until after exposure. It is roughly 8% I believe, but those individuals are not easy to identify. So, I think a general population is not the population of interest, it is those who are sensitized and at greatest risk.

Dr. Seicean-Boose agreed with Dr. Allen and other colleagues. Dr. Seicean-Boose noted the point about formaldehyde exposure length is pertinent and supported by the dermatology association in terms of dermal sensitization. She acknowledged that the study's focus on formaldehyde sensitizations is a positive feature, however a case-control study is normally used with rarer occurrences such as sensitizations. She emphasized the main issue with the study: that the conclusions made could not be confirmed through statistical analyses. Additionally, as noted by ICF, the existing data does not allow for statistical analysis. Dr. Seicean-Boose concluded the lack of statistical analysis and small sample size made it difficult to recommend the study use.

Dr. Corey asked EPA to expand on how they were planning to use the study in terms of POD determination and derivation. Dr. Rossmeisl personally seconded Dr. Allen's comments on formaldehyde exposure characterization. Dr. Rossmeisl specified a previous study based on a

ROAT-test that had been considered by others. Thus, this would be one study considered as it has the most depth for a human sensitization study. Dr. Rossmeisl acknowledged the difficulty in finding *in vitro* studies and other supplementary human studies. She then asked for clarity on the requirement of a dose response for setting a POD. Dr. Sharp responded that in previous reviews of studies, a dose response model analysis was conducted to formulate a proposed POD. Dr. Sharp then defined POD, which demonstrated that a dose response is core to a POD. Additionally, ICF concluded in its analysis that it is not possible to formulate a dose response model due to low statistical power. Dr. Sharp expressed concern about utilizing this study's data because of the statistical limitations. Dr. Monique Perron addressed these concerns, clarifying that though statistical modeling is helpful, EPA does not require all scenarios to be simulated because the point of the POD is to be health protective from a regulatory perspective. Dr. Perron acknowledged that there is not a study for all exposure scenarios, thus EPA is looking for information related to health protective levels. Additionally, EPA applies an intraspecies uncertainty factor in risk assessment because of concerns about more sensitive populations. Dr. Perron clarified that EPA is examining different lines of evidence, thus does not exclude solely because of lack of statistical analysis. Dr. Sharp said Dr. Perron did answer her questions.

Dr. Corey asked if there were other questions and, seeing none, summarized the consensus. Dr. Corey summarized that though there were several concerns, the article contained useful information. Dr. Corey noted that concerns will always be included, as will the additional EPA resources. Dr. Corey presented the potential drafted HSRB Response. Dr. Corey asked the Board if they would be comfortable noting that the article could be used in the context of more publications through a WoE for endpoint selection towards deriving a POD. Dr. George Milliken supported the qualified statement Dr. Corey drafted after previously expressing concerns. She read the revised Response and asked if there were any questions or additions. None were provided. She then brought the HSRB Response to a vote and noted Dr. Lewandowski's absence. Dr. Corey confirmed with Mr. Tom Tracy that she could vote on Dr Lewandowski's behalf at his request. The HSRB approved the response to the Science Charge Question.

N. Charge to the Board – Ethics:

Philip Day, Ph.D., Ethics Review

Dr. Corey introduced the Ethics review and introduced Dr. Philip Day. Dr. Day thanked the HSRB and introduced the charge question for the ethics review. He summarized the subjects enrolled, noting a lack of sex parity and additional females both groups. Dr. Day explained the inclusion and exclusion criteria. He noted the lack of information on how the control participants were recruited, which is normally part of an ethical analysis. The participants provided written consent, however the process of obtaining informed consent is not elaborated on. He noted that although this information is lacking, it does not necessarily mean the study is deficient ethically. Risks were adequately minimized, and Dr. Day acknowledged that privacy of participants was protected in the article and in general through deidentification. He noted that participants were recruited from a care setting, which could have implications for the care relationship and

participation, but this did not appear to be the case. He stated that based on his review of the materials provided, there is no evidence that the study was conducted unethically. Dr. Day summarized that though specific and important information is lacking, there is no evidence that the study was conducted unethically relative to the standards at the time, and no study procedures would invalidate participant's ability to give informed consent.

Dr. Corey thanked Dr. Day and opened the meeting to HSRB for questions. Seeing none, Dr. Corey presented the proposed charge questions and HSRB Response for ethics. HSRB members voted, approving the material. Dr. Corey thanked the HSRB.

O. Adjournment

Mr. Tom Tracy thanked the HSRB, and the meeting concluded.

The meeting adjourned at 3:46 p.m. EDT.

Thursday, October 12, 2023:

A. Meeting Topics and Charge Questions

Topic: Fischer, T; Andersen, K; Bengtsson, U; Frosch, P; Gunnarsson, Y; Kreilgård, B; Menné, T; Shaw, S; Svensson, L; Wilkinson, J. (1995). Clinical Standardization of the TRUE Test™ Formaldehyde Patch. In Exogenous Dermatology: Advances in Skin-Related Allergology, Bioengineering, Pharmacology and Toxicology. Current Problems in Dermatology, Edited by Surber C and Elsner P. Volume 22:24-30. Basel: S Karger, AG.
DOI: https://doi.org/10.1159/isbn.978-3-318-03459-2

Charge to the Board – Science: Is the research described in the published study "Fischer, T; Andersen, K; Bengtsson, U; Frosch, P; Gunnarsson, Y; Kreilgård, B; Menné, T; Shaw, S; Svensson, L; Wilkinson, J. (1995). Clinical Standardization of the TRUE Test™ Formaldehyde Patch. In Exogenous Dermatology: Advances in Skin-Related Allergology, Bioengineering, Pharmacology and Toxicology. Current Problems in Dermatology" scientifically sound, providing reliable data for consideration as part of endpoint selection and derivation of a point of departure for elicitation of dermal sensitization from dermal exposure?

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?

P. Convene Meeting and Introduction of Members

Tom Tracy, DFO, EPA HSRB, OSAPE

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

HSRB members
Lisa Corey, Ph.D., Co-Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (National Institute of Standards and Technology) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Chad Cross, Ph.D. (University of Nevada – Las Vegas) Philip Day, Ph.D. (University of Massachusetts, Chan Medical School) Nicole Deming, J.D., M.A. (Case Western Reserve University, School of Medicine) Weiying Jiang, Ph.D. (California Environmental Protection Agency)

Thomas Lewandowski, Ph.D. (Gradient) Srikumaran Melethil, Ph.D., J.D. (University of Missouri – Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Seicean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) Ann Um, Ed.D. (AMSTAT Consulting) David Williams, Ph.D. (Oregon State University)
EPA staff members
Michelle Arling (EPA, Office of Pesticide Programs (OPP)) Stan Barone (EPA, Office of Chemical Safety and Pollution Prevention (OCSPP)) Lexie Burns (EPA, Office of Science Advisor, Policy and Engagement (OSAPE)) Andrew Byro (EPA, OPP) Madison Clark (EAP, OSAPE) Jeff Dawson (EPA, OCSPP) Elizabeth Donovan (EPA, OPP) Judy Facey (EPA, OPP) Ann Huang (EPA, Office of Pollution Prevention and Toxics (OPPT)) Tim McMahon (EPA, retired) Monique Perron (EPA, OPP) Colleen Rossmeisl (EPA, OPP) Monique Tadeo (EPA, Program in Human Research Ethics and Oversight (PHERO)) Tom Tracy (EPA, OSAPE) Kendall Ziner (EPA, OCSPP)
Members of the public, representatives of research sponsor, and research team:
James Damewood (Dupont Chemical) Sorina Eftim (ICF, Contractor Support) Katy Goyak (Celanese) Angelina Guiducci (ICF, Contractor Support) Afroditi Katsigiannakis (ICF, Contractor Support) Adrian Krygsman (Troy Corp) Sahar Osman-Sypher (American Chemistry Council (ACC)) Emily Pak (ICF, Contractor Support) Jessica Ryman-Rasmussen (ACC) Clint Woods (Hexion)

Q. Meeting Administrative Procedures

Tom Tracy, DFO, HSRB, OSAPE

Mr. Tom Tracy reviewed the Zoom platform tools and stated the purpose of the meeting was to review and discuss "Clinical Standardization of the TRUE Test™ Formaldehyde Patch" by Fischer et al. 1995. He noted that minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of October 12, 2023.

R. Opening Remarks and Meeting Process

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

Dr. Julia Sharp welcomed everyone to the EPA HSRB meeting after attendees from the HSRB and EPA introduced themselves, briefly introduced the study under discussion and laid out the meeting process and guidelines.

S. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Michelle Arling thanked the board for reviewing the study presented today. There were no noted updates from OPP.

T. EPA Science Review Highlights

Colleen Rossmeisl, D.V.M., OPP

Dr. Colleen Rossmeisl thanked the committee and introduced the study from Fischer et al. 1995 while sharing the slides. Slide 2 introduced the purpose of the study. Dr. Rossmeisl stated that OPP made multiple attempts to request the raw data and documentation of the ethical conduct of the study and did not receive responses from the study personnel. The purpose of the study was to present clinical data used in the development of the TRUE Test™. The study consisted of five different test groups. Five different groups were utilized to determine levels at which irritation versus sensitivity occur, as well as assess reactions in patients sensitive and not sensitive to formaldehyde. Groups 2 and 4 used a series of test concentrations with the TRUE Test™ system and compared it to Finn chamber aqueous formaldehyde patch tests. For this study EPA primarily focused on Group 2 testing. Group 4 also tested a dilution series; however, very limited information was provided in the results section and was therefore of limited utility.

Slide 3 introduced the study. There were 25 study participants in group 2 that had all previously had a positive test patch for formaldehyde. The individuals in the study used both TRUE test™ patch system and formaldehyde patch test exposure.

Slide 4 described the TRUE Test™ patch system. Patches were formulated from the HMS in the vehicle polyvidon (PVP). The Study authors stated that succinimide shows no skin irritation with topical and intradermal testing in guinea pigs, no allergic potential in guinea pig maximization tests and no adverse effects in humans with clinical use in the treatment of nephrolithiasis and epilepsy. Formaldehyde concentrations equivalent to negative, 10, 20, 30, 40, 80, 100, 120, 150, 190, 260, 330, 570 and 1,120 µg/cm^2. Concentration of the formaldehyde in solutions reported as analyzed by colorimetric methods.

Slide 5 provided a description of the study methods. A control patch test system used Finn chambers and formaldehyde aqueous solutions. Fifteen microliters of 1% formaldehyde in water dilutions were prepared and applied in Finn chambers. Formaldehyde concentrations were tested

at negative, 0.015, 0.032, 0.063, 0.13, 0.25, 0.5 and 1.0% (equivalent to 4.5, 9.6, 19, 39, 75, 150 and 300 µg/cm^2). There was no information provided on how sample concentrations were verified but they were referenced as prepared by Chemotechnique Diagnostics AB, Malmo, Sweden.

Slide 6 detailed how the patch tests were conducted. The patch test series were applied on the upper back, varying left and right application at random. The test strips remained on participants backs for 48 hours and evaluated after 72 or 96 hours. The test was evaluated according to the ranking scale recommended by the international Contact Dermatitis Research Group (ICDRG). Slide 7 displayed a table for the criteria for a positive reaction according to the ICDRG.

Slide 8 displayed a table of the results from the Fischer et al. 1995 study, where a greater number of individuals showed a positive reaction to higher test concentrations. Slide 9 displayed a scatter plot of the results from the Finn patch and TRUE test™ results, showing a similar trend in dose-response. Slide 10 detailed that EPA's attempts to obtain the raw data from the study authors were unsuccessful. EPA in conjunction with statistic contractors at ICF, reviewed and attempted to reproduce the statistical analyses in the study. There were no additional statistical analyses that were feasible for the study based on the lack of reported raw data.

Slide 11 describes the strengths of the study. Strengths of the study included an adequate number of participants in the study, individuals with previously confirmed sensitivity to formaldehyde participated, information on degree of response was, and the experimental design to examine dose-response relationship for elicitation threshold for formaldehyde was identified. A Lowest Observable Adverse Effect Level (LOAEL) could be identified as well. Lastly, skin loading in Fischer et al. 1995 aligns with potential skin loading from expected uses (e.g., FIFRA registered uses at 370 ppm formaldehyde, with loading estimates of 3.8 µg/cm^2).

Slide 12 described the limitations of the study. Some limitations of the study include scarce information available on the test substance, including the purity or source of formaldehyde or if stabilizers were present (such as methanol). There was no information on confirmation of formaldehyde test concentrations used in Finn chamber system other than reference to preparing lab. Lastly, there was separate and historical information cited for succinimide, but the data was not provided.

Slide 13 contained the overall conclusions for the Fischer et al. 19995 study. Based on the concentrations tested in the occluded patch test, the LOAEL based on aqueous formaldehyde exposure through the occluded Finn chamber system was 0.015% or 4.5 µg/cm^2. A No Observed Adverse Effect Level (NOAEL) was not obtained. The study was well-conducted and provides quantitative information for deriving a minimum elicitation threshold for formaldehyde such that it can be considered as part of endpoint selection and point of departure derivation. Slide 14 detailed the charge question.

Dr. Sharp asked if there were any clarifying questions for the charge question.

U. Board Questions of Clarification

- **Thomas Lewandowski**: Where in the article did you see that the test patch placement was randomized?
    - **Colleen Rossmeisl**: It was briefly described that test patch placements were randomized in one sentence in the article.
- **Srikumaran Melethil:** Do you have preliminary information about this study? The study did not provide much detail and it was difficult to follow the results and numbers within the paper. For example, in Table 3 when the numbers were 0.03 and 0.01 for the Finn Chamber study where there were only five respondents, there was a much higher than the number of volunteers responding. Would you be able to explain Table 3 to me?
    - **Colleen Rossmeisl:** Table 3 is hard to understand so we reproduced it in the Data Evaluation Record (DER). How the data is presented is based off the low dose and going up. If someone reacted at the lower dose the researchers assumed that that participant would be assumed to react at a higher dose.
    - **Thomas Lewandowski:** The table represents the minimum dose at which a participant responds, not at all doses that they respond at. This is an unusual way of representing the data, and the table provided by EPA in the DER is more likely than what you would expect to see.
    - **Colleen Rossmeisl:** We have seen data presented as just the minimum with the assumption that the participants reacted at all other higher doses in previous papers.
    - **Thomas Lewandowski:** This is more normal in the dermatology world not as normal in the toxicology world.
    - **Srikumaran Melethil:** Did they include 25 subjects in each study or were there only a total of 25 study subjects? A three-dimensional graph would have been helpful to depict this. I am going to think about this to see if I can figure it out.
- **Srikumaran Melethil:** How was the assessment done? Did the volunteers assess the outcome or was there an independent reviewer? Who evaluated the reaction and what was being evaluated? Was it the intensity of the dermatitis? For example, two plus symbols represent a strong positive reaction, erythema infiltration, papules and vesicles. This seems more like an objective test where someone who is familiar with the symptoms, not a volunteer, is evaluating the reaction.
    - **Colleen Rossmeisl:** There is an assumption that someone with clinical training assessed the outcome of dermatitis.
    - **Thomas Lewandowski:** In the Dermtox world there are standard scoring rubrics where they show pictures of different grades of a reaction. I believe in this scenario it would have been the researchers who scored the results.
- **George Milliken**: How much time did this set of studies take? The study discussed on October 11, 2023, seemed to take 18 or more months, and I did not see anything about time in this study.

- **Colleen Rossmeisl**: The span of time was not provided in the study.
- **Thomas Lewandowski**: To clarify your question, Dr. Milliken. The study discussed on October 11, 2023, took 18 months to enroll, and the exposures were brief. That is the case with this current study.
- **George Milliken**: The study discussed on October 11, 2023, took longer to enroll study subjects. To me that was not a negative point for the study.
- **Julia Sharp**: Are you thinking of seasonal effects?
- **George Milliken**: Yes, things change over time. Where did these people live, what did they do every day. I would assume they did the same things over time.
- **Julia Sharp**: The exposure was short, but a participant in January could potentially look different than a participant in October. I am not sure for formaldehyde exposure is for dermatology, but other allergens could be present at different seasons.
- **Albert J. Allen**: This is a type four hypersensitivity reaction. They tested people in the clinic and when the people tested had a positive patch test they were approached by people in the clinic to join the study and then the formaldehyde testing was complete over the next day or two. This would be read by the investigators when they ask them to come back so they could look at the patch test. As far as seasonality is concerned, there may be some elements in this study. Keep in mind that what is being looked at in this study is where you have some potential chemical interaction with tissue that causes the t-cell response that then is the nature of the reaction you are looking at. It is not just dependent on your current allergic state.

Dr. Sharp asked for additional clarifying questions. There were none. She then asked Ms. Arling to talk about the ethics review highlights.

V. EPA Ethics Review Highlights

Michelle Arling, J.D., OPP

Ms. Michelle Arling presented the EPA Ethics Review Highlights for this study and thanked the board. Slide 1 introduced the topic of the presentation and slide 2 outlined its agenda. Slide 3 described the participant demographic information and eligibility criteria for the participant selection process. Group one had a total of nine healthy individuals, three males and six females. Group two had 25 formaldehyde-sensitive individuals, group three has 120 contact dermatitis individuals, group four had 24 formaldehyde-sensitive individuals, and group five had 255 contract dermatitis individuals (159 females, and 96 males). The eligibility criteria were detailed as “healthy volunteers without known sensitivity to formaldehyde, consecutive patients with contact dermatitis, and patients with previous patch tests to formaldehyde.” Slide 4 described the informed consent process, noting that all subjects gave written consent to participate. Ms. Arling stated that EPA reached out to researchers and no information about the consent form or process was available. Slide 5 described the risk and risk minimization in the study. Risks included

known skin irritant, and exposure may cause irritation or dermatitis. Risk minimizations included that the study was conducted at a dermatology clinic under the supervision of medical professional, the concentrations used in the study were in line with the concentration of formaldehyde used in diagnostic patch testing (1-2%, or 10,000-20,000 ppm), and other substances did not show dermal irritation or allergic reactions in animal studies.

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 research was approved by the relevant ethical committees based on where the research was conducted. There were no records related to this research available. Slide 8 presented the substantive ethics standards for the study, 40 CFR §26.1703 and 40 CFR §26.1704. 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 was conducted when the 1989 Declaration of Helsinki was in use, 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 adults, there was no evidence that female subjects were pregnant or nursing. There was no evidence that research was fundamentally unethical or deficient to ethical standards in place when the research was conducted. The subjects consented to participate, doses were in line with doses used in clinical patch testing to identify allergies and to allow measurable results without causing adverse effects. The research had a clear purpose and was overseen by medical professionals. The subject's confidentiality was maintained, and the research was overseen by the independent ethics board.

Slide 11 listed the conclusions of the study's ethical review. The available information indicated the research was not fundamentally unethical, it was not deficient relative to the ethical standards prevailing at the time the research was conducted, and the research was not conducted in a way that placed participants at increased risk of harm or impaired their informed consent. Slide 12 presented the charge questions to the Board.

W. Board Questions of Clarification

- **Thomas Lewandowski:** On slide 2 "subject selection" a quote on eligibility was displayed that was a little misleading regarding the different participant groups. Some of the participants did have sensitivity to formaldehyde.
    - **Michelle Arling:** I will update that in the review, so it is clearer.

Dr. Sharp asked for additional clarifying questions. There were none.

X. Public Comment

Dr. Corey asked Mr. Tracy if there were any public commenters. Mr. Tracy confirmed there were two registered public comments.

Mr. Clint Woods presented slides titled "U.S. EPA Human Studies Review Board Teleconference Public Comments- Science Charge." Slide 2 provided context from other authoritative reviews like the EPA formaldehyde TSCA Scooping plan, the European Chemicals Agency, and a study by Lynch et al from 2022. Slide 3 described industrial hygiene programs. The slide described PPE currently used by companies to protect employees against formaldehyde exposure in different activities. Slide 4 provided background on robust existing regulatory programs that address exposure to chemical agents. Section 9 of TSCA (15 U.S. Code § 2608), OSHA regulatory stands, and other federal regulatory programs with dermal protections were displayed. Slide 5 presented the scope of TSCA risk evaluation and risk management and key exemptions based on statute, products, or sectors. Slide 6 presented the TSCA peer review standards and encouraged coordination withing the EPA. Slide 7 concluded on TSCA's differencing standards for Section 26(h) of TSCA and 40 CFR § 702.33. There are different ways that TCA and FIFA evaluate risk. Mr. Woods recommended that the board should help to ensure its advice is designed to satisfy the scientific requirements under TSCA or if it is a narrower question related to the scientific soundness or ethics related to the studies reviewed.

Dr. Sharp asked if there were any clarifying questions on Mr. Woods presentation. There were none. The meeting continued with the second public comment by Mr. Adrian Krygsman.

Mr. Adrian Krygsman presented slides titled "HSRB October 2023 Meeting Public Comments". Slide 2 provided a description of what Troy Corporation is. Slide 3 presented dermal effects and their role in the assessment of formaldehyde in pesticidal formulations. The slide stated that EPA's risk assessment included a handler risk assessment for occupational and residential uses. Residential concerns were raised recently for do-it-yourself (DIY) paints and cleaning products such as laundry detergents. For Occupational handlers, the primary concern was inhalation risk due to cancer effects using the IRIS unit risk. Slide 4 presented the relevance of dermal and sensitizing effects under EPA's registration review. Mr. Krygsman reminded the HSRB of their charges. Lastly, in the evaluation of these compounds like formaldehyde Mr. Krygsman stated that he hoped there would be a scientific advisory panel in the risk assessment of these chemicals.

Dr. Sharp asked whether there were any questions or comments. There were none.

Y. Charge to the Board – Science:

Thomas Lewandowski, Ph.D., Science Review
Srikumaran Melethil, Ph.D., Science Review
Chad Cross, Ph.D., Statistical Review

Dr. Thomas Lewandowski presented the science review of Fischer et al., 1995. This study aimed to compare two different test methodologies. He noted that formaldehyde is a reactive chemical. Dr. Lewandowski then described patch testing. One concern regarding formaldehyde patch testing is that it can degrade during the manufacturing and distribution process, thus impacting the chemical concentration on the patch test. This paper utilized a formaldehyde doner which

releases formaldehyde when it comes into contact with moisture on the skin. Fischer et al., 1995 investigated whether this methodology is an appropriate alternative formulation for patch testing. Since multiple doses were analyzed, this allows for a potential dose response relationship.

Five different groups were studied. One group contained healthy individuals with no skin disease or formaldehyde sensitivity. Two groups were formaldehyde sensitive based upon prior patch testing. The last two groups contained individuals with eczema. A challenge of this study is that data is not reported for every group. Group two had the best reported data which contained 25 formaldehyde sensitive subjects. These individuals were given the TRUE test and the Finn chamber test. Dr. Lewandowski reminded the HSRB that $\mu g/cm^2$ is the typical dose metric used when testing skin sensitization. He indicated that EPA focused on group two as the group of subjects that had the most available data to understand a dose-response relationship.

Both the TRUE test and Finn chamber test system showed similar results. The lowest dose that gave a positive elicitation response for the TRUE test was 10 $\mu g/cm^2$. For the Finn chamber test, it was 4.5 $\mu g/cm^2$. It was noted that one subject showed this response, meaning the LOAEL was based on a single individual. Dr. Lewandowski also discussed how in the TRUE test, six of the formaldehyde sensitive subjects showed no reaction. For the Finn chamber test, a similar situation occurred with three of the formaldehyde sensitized participants.

Dr. Lewandowski displayed the dose response graph form EPA. He noted that although there is a strong dose response, a small number of individuals participated. He also stated that the study may provide some useful data related to formaldehyde elicitation reactions among sensitized individuals. Standard patch test methodology was used; however, the study was not designed to determine a threshold and not all the data was reported. Therefore, this study could be used in a supportive fashion with other studies that were specifically designed to create a dose response. Nonetheless, this study would not be a good basis for developing a point of departure (POD) on its own.

The strength of the reactions is unknown in the study. EPA stated they tried to obtain additional information but were unable to do so. This may be of concern when using this data. Dr. Lewandowski then asked if the Agency plans to use the TRUE test or Finn chamber test results. He also questioned the difference between positive sensitization reactions and irritant reactions shown in Table 2. Additionally, he asked if any quantitative dose response analysis had been conducted with the data from the dose response curve. There was a dismissal of the fact that the authors only used descriptive methods. It was also unclear how much time passed between the initial evaluation of group two and subsequent testing. Dr. Lewandowski also noted that excited skin syndrome may have impacted the results.

It was noted that this study focused on formaldehyde sensitized individuals as opposed to the general population which EPA typically focuses on in risk assessment. If EPA wants to focus on sensitized individuals, then they should carry that throughout the different components of a risk assessment. Dr. Lewandowski thanked EPA for their development of Table 4 and Figure 1 in the

Data Evaluation Record (DER). He also reminded the HSRB and EPA that this study is old and there may be more recent data to rely on.

Dr. Julia Sharp asked if there were questions from the HSRB.

- **Lisa Corey:** That was a great presentation. Can EPA address the questions mentioned in the presentation?
    - **Thomas Lewandowski:** Is EPA more interested in the TRUE test or Finn chamber result?
    - **Colleen Rossmeisl:** Originally EPA was focused on the Finn chamber result because it was more consistent with other standard tests. However, we realized the TRUE test patches gave consistent results. As a result, we would consider all the data together. The Finn chamber is the most sensitive endpoint which is why it is called out in the DER, but both will be considered. The TRUE test moved forward after this study, so it is a valid way to test dermal sensitivity.
    - **Thomas Lewandowski:** I do not know if this particular formaldehyde doner formulation is commonly used. That would be helpful to know.
- **Thomas Lewandowski:** Do you have any thoughts about dose response analysis? This seems like the classic NOAEL versus the benchmark dose approach. If EPA takes this approach, does it make sense to do some sort of benchmark dose analysis to look at more robust endpoints?
    - **Colleen Rossmeisl:** We have not yet entered that part of the analysis. We were waiting until we brought these studies to the HSRB. That is something we will consider and work through as we move forward.
- **Srikumaran Melethil:** What is the difference between a positive and irritant reaction?
    - **Colleen Rossmeisl:** This is in the guidelines for interpreting patch tests for sensitization. This is one of the things they are concerned about. The goal of this exercise is to establish where they should set the dose at for the TRUE test to elicit a response without having an irritation response show up. EPA did not focus on this part of the analysis very much.
    - **Thomas Lewandowski:** A huge challenge in sensitization testing is to rule out an irritation response. Usually, the dose that provokes elicitation should be below a dose that provokes irritation.
    - **Srikumaran Melethil:** Do you have any documentation on what an irritant reaction is or something that distinguishes the two reactions? It could go into the final document.
    - **Colleen Rossmeisl:** Somewhere but I do not have it with me. Good suggestion.
- **Thomas Lewandowski:** What are EPA's thoughts regarding the potential for patch testing to mimic and reliably predict exposures in the real world?
    - **Colleen Rossmeisl:** I do not know if we have information to differentiate if something like that was happening here, but we can take it into consideration

when interpreting patch testing.

- **Thomas Lewandowski:** EPA mentioned there were additional studies. The HSRB reviews each study individually. Are there additional studies the HSRB will review in the future?
    - **Colleen Rossmeisl:** Yes. I thought there would be more recent studies with multiple test concentrations. I would have preferred to have more recent studies.
- **Albert J. Allen:** I suspect there are individual photographs but all I could find was that video.
    - **Julia Sharp:** Great, thank you.
- **Srikumaran Melethil:** I have been listening to the public comments. At the end I am assuming EPA will present numbers on. e.g., workplace concentrations of formaldehyde. I am hearing a caution from the public comments that EPA needs to be careful when exposure standards are published.
    - **Julia Sharp:** Our task is to respond to the charge question taking into consideration our review and the public comments. In my draft response to the charge question I include that cautionary framework. We can come back to that when the response to the charge question is presented.

Dr. Chad Cross presented the statistical review of Fischer et al., 1995. There is no available raw data, so the results are qualitative. Group sample sizes are quite different. In some groups, male to female ratio is provided and in other groups it is not. Table 1 provides results across tabulation of TRUE test versus aqueous preparations. If this is based on group two, the 0.01 mg/cm^2 dose result for the TRUE patch tests are surprising because they are not listed as a dose in the experimental design section on page 26. It is only reported for group three. The lowest dose provided for the TRUE test for group two was 0.02 mg/cm^2 in the experimental design statement, however a dose of 0.01 mg/cm^2 is shown in Table 1. There may have been an error in the experimental design paragraph, but it leads to many questions about the accuracy of the data.

There is very little information provided that would allow for further analysis, as stated in the ICF document. No statistical analyses are feasible. Unfortunately, absence of the data does not allow us to verify the 0.01 mg/cm^2 question mentioned above. Based on the presumed alignment of the TRUE test patches and aqueous preparations, the science review suggested a LOAEL of 0.015%. The basis for this assessment is interesting and the absence of raw data is important. The EPA could consider using frequency data to discuss the similarities between the two tests. EPA should remember that the lower end of the dose response distribution may be missing because we do not know where the 0.01 came from.

EPA acknowledged that the study did not fully meet all the screening criteria. In particular, it did not meet criteria 11, which focuses on comparison of treatment groups to acceptable controls, or criteria 13, which focuses on adequate data on the chemical testing. After acknowledging the limitations, EPA concluded the study is appropriate for quantitative use and can be considered as part of endpoint selection and POD derivation. Dr. Cross questioned EPA's concluding

statement. EPA should provide additional justification for the usefulness of their reanalysis of the data given the analytical non-feasibility statement in their own statistical statement by ICF.

- **Julia Sharp:** Can EPA comment on the Table 1 comment? Did EPA notice this error in the document?
    - **Colleen Rossmeisl:** I did not catch this. There is also a negative test in the table which also was not mentioned in the methods section. We had assumed the table was correct.
- **Thomas Lewandowski:** I did not notice that mistake either. Thank you, Chad, for highlighting this. In Table 1 there are no results for 0.02 mg/cm^2. Is that a typo that got shifted over? Although the correlation between is not significantly impacted, it leads to questions around the quality and reliability of the study. I find this concerning.
    - **Chad Cross:** You can do very simple things by sorting columns and rows to lower and upper and reviewing the kappa agreement on that diagonal to understand the agreement between the two methods. If the numbers are presumed correct the relationship is strong. But if numbers are lost due to the unknown 0.01 mg/cm^2 value, the relationship between the two tests is influenced. I do not know if it is a critical limitation, but it is something to consider. Without the raw data, there is no way to verify this.
    - **Thomas Lewandowski:** I wonder if the 0.01 mg/cm^2 value is an artifact from another table and the other values should be in other places in the table.
    - **Julia Sharp:** Are the units the same as they are in the text?
    - **Chad Cross:** Yes.
    - **Colleen Rossmeisl:** I want to clarify at the very beginning of the study the authors mention the 0.01 mg/cm^2 test concentration when they list them all out.
    - **Chad Cross:** They listed it as a concentration and provide it as a group three which is the only place it is shown.
    - **Colleen Rossmeisl:** Yes, that is true. I see what you are saying.
    - **Thomas Lewandowski:** The study tested multiple things.
    - **Chad Cross:** This was a very comprehensive set of testing, and they were asked to put together a book chapter. The authors tried to put everything in the paper they thought was useful, but they are missing some experimental design information.
    - **George Milliken:** I am guessing they do not want 0.01 mg/cm^2 and instead only want 0.02 mg/cm^2. But we do not know.

Dr. Sharp asked for additional questions on the statistical review. There were none. She then shared the charge question and draft response and invited HSRB feedback.

- **Julia Sharp**: Should we edit the phrase "scientifically sound?"
    - **George Milliken**: That is okay. I am wondering about the use of "reliable." Was that removed?

- **Julia Sharp**: Yes, I have removed that.
- **Thomas Lewandowski**: Table 1 relates to the TRUE test which is important if EPA wants to use the data from this test. The fact that there is a mistake overall makes us question the study overall. However, the place where the mistake was found is most important. And it does not necessarily impact the formaldehyde Finn chamber results. It is concerning.
- **Julia Sharp**: The first portion of the sentence in the charge question response discusses the intent of the research. The response states that it is scientifically sound to compare the two test methods. Do we agree with that?
- **George Milliken**: I have no issues.
- **Thomas Lewandowski**: That is fine with me.
- **Julia Sharp**: The second part focuses on the data from the study, particularly from group two, could be used to corroborate results of studies that were specifically designed to identify a threshold. From dermal exposure. One potential edit could be to add in the Finn test after group two if we are not confident about the TRUE test.
- **Thomas Lewandowski**: I think that makes sense.
- **Julia Sharp**: The second sentence now reads: the data from the study, in particular the Finn test used in group two, could be used to corroborate results.
- **Lisa Corey**: I like that one.
- **Thomas Lewandowski**: I am okay with that too.

Dr. Sharp asked for additional comments.

- **Julia Sharp**: Sri, you mentioned concerns with the public comments. Have I addressed your thoughts here?
  - **Srikumaran Melethil**: When a public comment is made about the legal standards and best available science, the anticipation is that this may be challenged in court. In my previous life I have seen litigation brought on exposure standards. I think the public comments should be used as a caution. My main point is that EPA should keep those comments in mind in an anticipatory manner.
  - **Julia Sharp**: Thank you. The statement after the comma discusses limitations that EPA should consider. We could add more cautions to that list.
  - **Srikumaran Melethil**: To condense it, we could recommend that the best available science is used. That will address many of the comments that were made, including those made last month.
  - **Albert J. Allen:** As I listened to the public comments, the takeaway was that the HSRB should not worry about contact dermatitis. However, the EPA is thinking about and considering this as an issue. I do not think the HSRB has enough information or is in a position to weigh in on this. We have been asked to evaluate these individual studies. I understand where some of the discussion comes from in

these public comments, but I am not convinced there should not be dermal standards. I think we should focus on the charge question and respond to it.

- **Srikumaran Melethil**: I appreciate that. We are the science board. The EPA depends on us for science matters. This includes not only the science, but also how it relates to regulatory requirements. The question is whether the study meets the best scientific standards that have been presented by public speakers. I agree that we need to focus on the quality of science, but we should let EPA know these concerns. One public commenter noted that EPA has not come up with peer review standards. Those are trigger words for me in the future.
- **Julia Sharp**: Thank you. In the science review, there is a comment about using the best available science. Do we want to strengthen that comment?
- **Thomas Lewandowski**: The public comments takeaway was that EPA's approach to develop an elicitation-based limit for formaldehyde is not standard. The charge question asks if the study is suitable. There is tension between the bigger picture of whether this is something that should be done from a scientific standpoint and the specific charge question. In the past, the HSRB has commented beyond the specific charge question to capture concerns about how the study will be used. However, I get the sense that there is a regulatory policy question that is beyond the scope of what we are asked to comment on.
- **Albert J. Allen:** I agree that we have commented beyond the scope of the charge question before. However, this was after taking a detailed look at the issue. I do not think we are currently in a position to comment on this policy topic. None of us have examined data and thus do not have the necessary background or expertise to provide comments.
- **Julia Sharp:** Can EPA weigh in?
- **Michelle Arling:** Thanks Julia. Monique, can you give an overview of where this review fits in EPA's overall development and public engagement process?
- **Monique Perron:** I really appreciate this conversation because sometimes we get ahead of ourselves. This is one step in a larger process around formaldehyde. We are looking at acute inhalation, the oral aspect, chronic inhalation, and many other pieces that will be brought together in one comprehensive review. For this case, we are coming to the HSRB to ensure that this study can be utilized in the larger picture, given that it included intentional exposure to humans. EPA will take into account all these discussions as well as the public comments. Additionally, there will be a public comment period when the draft risk assessment is released to the public.
- **David Williams:** A public commenter asked about coordination between different agencies. I think EPA is correct to put emphasis on inhalation exposure because of the regulatory activities. Coordination with the Food and Drug Administration (FDA) would be appropriate here since formaldehyde is present in

cosmetics, making dermal exposure very important. The European Union has a limit of 2,000 ppm in cosmetics. Is EPA coordinating with FDA with respect to regulatory practices?

- **Monique Perron:** EPA coordinates with other agencies. EPA has coordinated with the United States Department of Agriculture on pesticides. Additionally, other agencies will provide public comments with additional information. EPA also collaborates internationally as needed. This happens during and after the risk assessment is completed.

Dr. Sharp asked the HSRB to vote on the response to the charge question. A consensus was reached.

Z. Charge to the Board – Ethics:

Joseph Tuminello, Ph.D., Ethics Review

Dr. Joseph Tuminello shared the two charge questions to the Board for the Ethics Review. Dr. Tuminello noted that little information is shared regarding subject selection. Informed consent was obtained from the participants, and studies were approved by ethical committees but did not provide further information. Based on the information provided in the publication patient confidentiality was maintained. There is no evidence to indicate deficiency relative to the ethical standards at the time, the 1989 Declaration of Helsinki. Dr. Tuminello presented the draft charge responses.

Dr. Sharp asked if there were questions for the Ethics review questions. There were none. Dr. Sharp shared an updated draft charge responses and asked for comments on the responses to the charge questions as they are currently written. There were no comments or questions. The Board then voted on the responses to the charge questions, and a consensus was reached.

Dr. Sharp stated that the reviews have been placed into a report format and requested any updates be made before the next meeting on November 16th to approve the report.

- **Lisa Corey:** Dave, I see you left a comment in the chat "Does FDA have a current regulatory concentration for formaldehyde in cosmetics? If so, it seems to me that EPA should coordinate with FDA as cosmetic exposure is entirely dermal and, in many cases, chronic. It would not make sense for EPA to set a regulatory level lower than what is permitted in cosmetics." Is that something you wanted a response to now or should it be placed in our final document?
    - **David Williams:** I do not think it is necessary to include this in the report. It is more of an advisory thing. It seemed to me cosmetic exposures to formaldehyde are what EPA should be focusing on, and EPA should coordinate with the FDA on creating guidelines.
    - **Julia Sharp:** Should we include that as an overall recommendation to EPA?
    - **David Williams:** Before we include it in the report, I would like to do some research and look into what the FDA says about it. Let us hold off on including it

in the report.

Dr. Sharp thanked the attendees and reminded them that the next meeting will take place on November 16, 2023.

AA. Adjournment

Mr. Tom Tracy thanked the HSRB.

The meeting adjourned at 3:35 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 Sacramento, CA
Thomas Lewandowski, Ph.D.	Principal	Gradient Seattle, WA
Srikumaran Melethil, Ph.D., J.D.	Professor Emeritus	University of Missouri-Kansas City Kansas City, MO
George Milliken, Ph.D.	President	Milliken Consultants Manhattan, KS
Sinziana Seicean-Boose, M.D., Ph.D., M.P.H.	Assistant Professor	Case Western Reserve University Cleveland, OH
Joseph Tuminello, Ph.D.	Assistant Professor	McNeese State University Lake Charles, LA
Eun Um, Ed.D.	President and CEO	AMSTAT Consulting San Jose, CA
David Williams, Ph.D.	Distinguished Professor	Oregon State University Corvallis, OR

Attachment B: Federal Register Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10408-01-ORD]

Human Studies Review Board (HSRB) Meetings—2023

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of public meeting.

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

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

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

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

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

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

SUPPLEMENTARY INFORMATION:

Background

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

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

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

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

How May I Participate in this Meeting?

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

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