EPA Human Studies Review Board (HSRB)
July 20 and 21, 2021 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A)
Date and Time: Tuesday, July 20, 2021, and Wednesday, July 21, 2021, both 1:00 to 5:30 pm EDT.
Location: Via Zoom Meeting
Purpose: The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subjects research.
HSRB Website: https://www.epa.gov/osa/human-studies-review-board

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EPA Human Studies Review Board (HSRB)
July 20 and 21, 2021 Meeting Minutes

Tuesday, July 20, 2021:

A. Meeting Topic and Charge Questions

Topic: Dwivedi, A. et al. Acute effects of acrolein in human volunteers during controlled exposure. Inhalation Toxicology. Volume 27, Issue 14. pp. 810-821. December 4, 2015.

Charge to the Board - Science: Is the research described in the published article "Acute effects of acrolein in human volunteers during controlled exposure" scientifically sound, providing reliable data?

Discussants: Janice Britt, Ph.D., and Lisa Corey, Ph.D., scientific review
Julia Sharp, Ph.D., statistical review

Charge to the Board - Ethics: Does available information support a determination that the study was conducted in substantial compliance with subpart Q of 40 CFR part 26?

Discussant: Lindsay McNair, M.D., ethics review

B. Convene Public Meeting Day 1

Tom O'Farrell, Ph.D., Designated Federal Officer, EPA Human Studies Review Board (HSRB), Office of the Science Advisor, Policy and Engagement (OSAPE)

Meeting was called to order at 1:00 pm EDT by Dr. Tom O'Farrell, Designated Federal Official (DFO) for the Human Studies Review Board (HSRB). Dr. O'Farrell introduced the meeting, outlined the Federal Advisory Committee Act (FACA) procedures, and took roll of the meeting participants. The following members and observers were present:

HSRB members	Jennifer Cavallari, Sc.D., University of Connecticut (Chair) Alesia Ferguson, Ph.D., North Carolina A&T State University (Vice Chair) Mark Aulisio, Ph.D., Case Western University Janice Britt, Ph.D., ToxStrategies Philip Day, Ph.D., University of Texas Southwestern George Milliken, Ph.D., Milliken Consultants Tom Lewandowski, Ph.D., Gradient Julia Sharp, Ph.D., Colorado State University AJ Allen, M.D., Ph.D., Eli Lilly Company Eun Um, Ed.D., AMSTAT Consulting Lisa Corey, Ph.D., Intertox, Inc. Lindsay McNair, M.D., WIRB-Copernicus
EPA staff members	Michelle Arling (EPA, OPP) Tom Tracy (EPA, OSAPE) Tom O'Farrell (EPA, OSAPE) Shannon Jewell (EPA, OPP) James Nguyen (EPA, OPP) Don Wilbur (EPA, OPP) Dana Vogel (EPA, OPP) Greg Akerman (EPA, OPP) Jeremy Leonard (EPA, OPP)

	Shalu Shelat (EPA, OPP) Anna Lowit (EPA, OPP)
Members of the public, representatives of research sponsor and research team:	Steven Black (ICF, Contractor Support) Kaitlin Geary (ICF, Contractor Support) Leah West (ICF, Contractor Support) Kathryn Van Artsdalen (ICF, Contractor Support)

Dr. Tom O'Farrell also covered Zoom Meeting platform tools and features, as this was the first HSRB meeting using Zoom. The purpose of the meeting was to review the paper by Dwivedi, A. et al. Minutes of the meeting and a report will be prepared and certified within 90 days of July 21, 2021 and will be available on the website.

C. Welcome and Virtual Meeting Operations

Jennifer Cavallari, Sc.D., HSRB Chair

Dr. Jennifer Cavallari welcomed attendees and provided an overview of Zoom. There are reaction buttons on Zoom, which include a raise hand function which would be used when a member would like to speak. To vote in Board decisions, the green check box indicated that members agreed, and the red box indicated that members did not agree. Dr. Cavallari also informed attendees that they could change their name within Zoom themselves, if desired.

D. Brief Update on Research Discussed at Last HSRB Meeting

Michelle Arling, J.D., Office of Pesticide Programs

Ms. Michelle Arling thanked HSRB members for their time. She also provided an overview of the protocols reviewed during the previous meeting on June 17, 2021. At the prior HSRB meeting, members reviewed two protocols from a company on the efficacy on skin applied repellents against mosquitoes and ticks. Since that meeting, HSRB has provided feedback to the study sponsor, who is now working to update their protocols to address HSRB recommendations.

In October 2021, it is anticipated that the EPA will present a completed study from the Antimicrobial Exposure Assessment Task Force (AEATF), which is an immerse, dip, and soak study. The HSRB reviewed the protocol for this research in October 2018. In January 2022, another study is anticipated from the AEATF, which is part of a broader study on aerosol sprayers. This study includes six sub-scenarios, one of which has been completed and will be submitted for EPA's review and discussion at the January 2022 HSRB meeting.

E. EPA Overview

Jeremy Leonard, Ph.D., Office of Pesticide Programs

Dr. Jeremy Leonard discussed that the reason why these acrolein studies are being presented for consideration is that acrolein is undergoing risk assessment to support registration review. Two additional human exposure studies are being presented to support the current inhalation Point of Departure (POD) value. The HSRB can provide feedback on their scientific merits as well as their ethical considerations. Acrolein is used as an aquatic herbicide in irrigation reservoirs and canals, where it moves with the flow of the water and kills weeds on contact. The pesticide can only be sold and used

by certified personnel and is considered a restricted use pesticide. It is not used directly on crops or in residential settings, and therefore no dermal or oral exposures are expected. There is a chance of inhalation exposure for occupational users, and for unaware bystanders entering recently treated areas. Acrolein is highly toxic through all routes of exposure, is very reactive, and is a strong irritant on eyes and skin. Dr. Leonard noted that there does not seem to be fetal or offspring susceptibility. The chemical is moderately absorbed and rapidly excreted.

Acrolein is not often reported in EPA incident monitoring databases. Poison Control does receive more reports than EPA, but these reports are typically less than five per year. The cases reported to Poison Control are most commonly the result of misuse or lack of proper personal protective equipment. Several of the symptoms seen are point of entry effects in the throat, eyes, or nose.

Dr. Leonard described a 1977 study that examined the tissues and chemical effect, which was reviewed in 2007 by the HSRB. The Board found this to be a well-designed study and no unethical conduct was seen. Dr. Leonard noted that the 1977 study and the two proposed human exposure studies to be evaluated by the HSRB are similar. In 1977, there were three trials which included three different levels of exposure: (1) continuous exposure on 53 individuals for 40 minutes at 0-0.6 ppm for the first 40 minutes and 0.6 ppm for the last 5 minutes; (2) discontinuous exposure on 42 individuals for 1.5 minutes at five distinct exposure levels of 0 to 0.6 ppm; and (3) constant exposure on 46 individuals for 60 minutes at 0.3 ppm. The individuals who participated in this study had to complete surveys on their experienced symptoms. Researchers recorded blink and breath frequency. Annoyance was seen to be greater for the discontinuous exposure group than the continuous exposure group. In the constant exposure group, annoyance occurred almost immediately but then plateaued. Eye irritation was the highest symptom recorded. There were also changes in the breathing rate at 0.6 ppm in the continuous exposure group after 40 minutes, and researchers recorded instances of breathing irregularity. The study investigators suggested that all results represented some indication of adaptation. Eye irritation was determined to be the most sensitive endpoint and an inhalation threshold value of 0.09 ppm (0.2 mg/m^3) was selected for the 2008 risk assessment.

Dr. Leonard then covered strengths and weaknesses of the 1977 study. He also mentioned that in 1980, the National Toxicology Program (NTP) found that effects seen in rodents were more severe and occurred at higher acrolein concentrations than in humans, generally at 4 ppm. Another study, conducted around the same time as the human volunteer study, showed that the respiratory rate in mice decreased by 50% at 1.7 ppm. The study authors proposed a threshold limit tolerable to humans between 0.02 ppm and 0.2 ppm.

When identifying critical values, EPA uses a weight of evidence approach with considerations for species, sex, dose, and route. They examine the biological plausibility and the mode-of-action effects of the chemical.

Dr. Leonard then presented the HSRB with the supporting articles for the current POD of 0.09 ppm, and he reviewed strengths and weaknesses of the studies as well as differences between rodent and human studies. The supporting studies showed that the current endpoint is appropriate for assessing acute short-term and longer-term exposures, because there was no real progression of severity of effects over time. Strengths of the studies included the attempt to blind the subjects, clear effect thresholds, a general overlap of age of study subjects and concentrations used, a focus on the most sensitive endpoint, and availability of raw data. Weaknesses, which do not influence the results or the validity, include a smaller number of subjects and a narrow concentration range. Statistical reanalysis conducted by EPA statisticians identified methods that were either unclear or inappropriate given certain assumptions or

conditions, such as the improper use of repeated measures data. Dr. Leonard concluded the introductory presentation by noting that rodent data showed more severe effects that were both systemic and related to the portal entry at both higher concentrations ranging from one to two orders of magnitude greater than the current inhalation POD. Additionally, Dr. Leonard noted that one study derives an end point that is nearly identical to the one that is currently used, and the other shows that acrolein is rapidly acting in humans at a slightly higher concentration, with some level of adaptation appearing to occur over time. Dr. Leonard proposed these studies for qualitative support rather than replacing the current POD.

F. EPA Science Review Highlights

Jeremy Leonard, Ph.D., Office of Pesticide Programs

Dr. Leonard provided an overview of Dwivedi, A. et al. 2015, a study conducted by an institution in Sweden that investigated acute effects of acrolein in a controlled chamber. The study was used to determine thresholds for acute irritation for acrolein by using lower concentrations more representative of potential real-world exposures. The study consisted of 18 subjects, equally divided by sex and ranging from 20-38 years old. Prior to the study, researchers asked the subjects to complete a questionnaire on medical history and behaviors, such as smoking. The pilot study exposed subjects to six different concentrations between 0.02 and 0.3 ppm for 10 minutes and asked the subjects to rate symptoms. The ratings of smell in the pilot changed immediately after entering the chamber but did not change with concentration; despite increases in certain percentiles for throat and eye irritation, no clear effect thresholds could be established. Therefore, for ethical reasons, the main study used an 8-hour Swedish occupational exposure level for the high concentration and half that for the low concentration. Three subjects per group were exposed to either clean air, the low concentration of 0.05 ppm of acrolein, or the high concentration of 0.1 ppm for 2 hours in six different sessions, separated by 1 week. Ethyl acetate (15 ppm) was added alone and to these same concentrations of acrolein to reduce bias by masking the potential influence of the acrolein odor, for a total of six different treatments. The exposures took place in a 20 cubic meter chamber, and the vapors were generated by air injection and were measured by Gas Chromatography with a Flame Ionization Detector (GC/FID). Subjects were asked to rate symptoms using a Visual Analog Scale (VAS), which included irritation and general health. Symptoms were evaluated before, during, and after the exposure. The blink frequency of the left eye was measured and counted at 20-minute intervals. Several respiratory and nasal measurements were taken during, before, and after exposure. Inflammation markers in plasma and exposure were measured before and after the exposure. Researchers found a significant dose-dependent increase in ratings for eye irritation at 120 minutes, which was not altered by ethyl acetate. Scores for smell increased upon immediately entering the exposure chamber and were generally highest for ethyl acetate alone exposures. Throat irritation was not affected at all, and fatigue increased at all time points, regardless of acrolein concentration. There was no effect on nose or respiratory parameters or on inflammation markers. There were no sex-dependent differences seen.

The study had several strengths, including the blinding of subjects and laboratory workers, exposure frequency, clear adverse effect levels, and availability of raw data including nasal and pulmonary data and blink ratings. Weaknesses, which did not change the validity of the results, included a smaller sample size, narrower concentration range, and a younger subject average age relative to the 1977 study on which the current inhalation POD for acrolein is based. Additionally, use of a second detectable compound, ethyl acetate, may have introduced some level of bias (i.e., anticipation of acrolein exposure). The EPA statisticians indicated that a mixed effects model might be more appropriate than

the repeated measures ANOVA that was conducted, since the assumption of equal correlation structure was not met. It was also noted that it was unclear from the study whether there was a significant interaction between acrolein and ethyl acetate, which could influence statistical power, and that it was unclear how the Friedman test used in the study to analyze irritation rating data accounted for missing values. The EPA statisticians completed a re-analysis of the data most relevant to eye irritation using a mixed effects model with sex, time, ethyl acetate, acrolein, and any possible interactions as the main effects. Multiple comparisons were adjusted using a Dunnett's test.

The EPA's statistical reanalysis used a log transformation of continuous blink data to achieve normality and removed non-significant interactions from the full model; the reduced model showed no significant effects at either concentration. The EPA's statistical reanalysis also found that the ranks of the exposure data for eye irritation were normally distributed and there was a significant interaction between acrolein and the time interval. Additionally, the reanalysis confirmed that there is an effect of acrolein at the 8-hour Swedish occupational exposure level and that there was an increase in eye irritation after at least 60 minutes of exposure.

A previous comment from the Board was made on a figure in the article, noting that it did not have error bars which could be misleading because of the time intervals, which showed equal spacing despite different ranges. Dr. Leonard informed the Board that the slopes on the line were not particularly correct and should have been removed from the article. The eye irritation ratings were re-graphed from the raw data and were available in the presentation. Re-graphed results showed that the eye irritation ratings at 60 and 120 minutes were different from the control for the acrolein-only exposure at the highest concentration, while with the ethyl acetate + acrolein exposure, this was true only for the 120-minute timepoint.

The re-analysis by EPA showed acrolein had no effect on eye blink, showing that an apparent increase in eye blink frequency at the highest acrolein concentration during the last 20 minutes compared to the first 20 minutes, as noted in the study, has no toxicological significance. The EPA re-analysis also agreed with the effect reported on eye irritation, while reducing the time for this irritation to occur from the 120 minutes reported in the study to at least 60 minutes. EPA proposed to use this study qualitatively to support the current inhalation POD.

G. Board Questions of Clarification

Jennifer Cavallari, Sc.D., HSRB Chair

Dr. Lisa Corey: There is not much information on the study population demographics, but there was data presented on sex and age. Is anything known regarding eye irritation potential for different races or any other demographic topics when applying this to a larger population?

> **Dr. Jeremy Leonard:** We examined the questionnaire, but there was not much information provided on the demographics, and I am not sure if there will be any racial differences. The subjects in these studies were students, and they might or might not be representative of the general population.

Dr. Lisa Corey: There was not much information presented visually on the last slide for the re-analysis. In the actual paper, results are generally presented graphically. In some of the figures, data seem to be scattered, which is difficult to interpret visually.

> **Dr. Jeremy Leonard:** The authors provided the EPA with the original data for reanalysis, which should contain all the original scores and explain the scatter in the data. In the interest of time, only eye irritation rating data was reanalyzed. Correcting for baseline measurements may also

allow for more consistency to compare results across treatments. Additionally, the exposure concentrations and irritation ratings are relatively low, so higher concentrations could result in more pain or discomfort and generate a greater signal, reducing some of the noise that you're seeing.

Dr. Janice Britt: (1) Did the 1977 study mention demographic information? (2) Will the applicators wear respirators or any kind of protective equipment? (3) Was the eye blink frequency done by manual counting or was a machine used to count?

Dr. Jeremy Leonard: (1) The demographics were not specifically laid out. The only demographic information provided was age, sex, and that they are students on campus. (2) To apply the pesticide, double layered clothing and a full-face respirator are required. Sometimes the cartridges are expired, leading to exposure. (3) A machine was used for eye blink frequency.

Dr. Julia Sharp: Was the treatment order randomized, or did they all follow the same sequence? If they did follow an order, was that accounted for in the EPA re-analysis?

Dr. Leonard: It was not specified, but the authors did say "balanced design." EPA did not find any order when doing the re-analysis. The statisticians will confirm and follow-up with the Board.

Dr. Julia Sharp: In the manuscript, it said that the subjects were grouped three at a time in a chamber. Which subjects were grouped together to account for the pseudo-replication?

Dr. Jeremy Leonard: We do not know that from the original article. The statistics team might be able to look at that.

Dr. George Milliken: On the second paper, they were using SPSS as a software package. SPSS at that time did not include a covariance matrix. SAS can estimate the matrix and there might be a more appropriate software to use.

Dr. AJ Allen: When you go back to the statisticians, investigate to see whether a Balance Latin Square was used for randomization.

Dr. Jennifer Cavallari: They examined inflammatory and pulmonary endpoints, both of which show circadian variation. Was there any indication of the time these were done?

Dr. Jeremy Leonard: There was no indication of the time of day. The raw data had dates but not any time points.

H. EPA Ethics Review of Highlights

Michelle Arling, J.D., Office of Pesticide Programs

Ms. Michelle Arling thanked the HSRB for their time and provided the Board with her ethics review findings. She reached out to the authors and found that none of the authors were still affiliated with the original research institution listed in the article. It was also not possible to retrieve all the supporting files due to Coronavirus Disease 2019 (COVID-19) restrictions. Additional information was provided in Swedish by one author, Dr. Johannsen, which was translated to English using Google Translate.

Subjects were recruited through advertisements at the test location. 18 individuals enrolled (9 females and 9 males). Of the 18 individuals, 8 also participated in the pilot study. The criteria listed to participate included: 20-50 years old, a nonsmoker, no chronic diseases, not pregnant or lactating, and self-reported as healthy. Dr. Johannsen indicated that anyone with relationships or dependency to a member of the study team was also excluded.

The consent process consisted of an individual meeting between the subject and a study team member. The information regarding the study was provided orally and in writing to subjects, who then provided written consent and completed a medical questionnaire and medical exam. The test substance levels

were selected in the pilot study and guided by the Swedish exposure limits. Subjects were informed of the risks and anyone who normally wore contacts were asked to not wear them. Subjects were free to withdraw at any time, though none did. Subjects were compensated $60 for pilot participation and $240 per study visit.

The protocol for this study was reviewed by the Regional Ethical Review Board, an independent ethics body, on February 2, 2012. The protocol was approved on the condition that information was provided on the biobank if any samples were taken. The ethical principles were followed by the Declaration of Helsinki. The Swedish Act concerning the ethical review of research involving humans was in effect at the time of the study, which adds additional steps and criteria for studies.

Ms. Arling found that there is no clear and convicting evidence that the conduct of the research was unethical.

I. Board Questions of Clarification

Jennifer Cavallari, Sc.D., HSRB Chair

There was a call for questions from the Board but there were none.

J. Public Comments

There was a call for public comments, but there were none.

K. Break

The meeting paused for a fifteen-minute break from 2:35 to 2:50 pm EDT.

L. Board Discussion

Jennifer Cavallari, Sc.D., HSRB Chair

The HSRB's scientific review was presented by Board members Dr. Janice Britt and Dr. Lisa Corey. Dr. Britt said the study and additional science review findings were appropriate and met guidelines. She said they noted a few deficiencies regarding the statistical analysis but agree with the overall conclusion and interpretation of the study. They also agreed with EPA's recommendations. Dr. Britt said they had questions about the composition of the reference population. Dr. Corey explained that they were still guessing and making assumptions about the study population demographics. They wanted to apply the study to a much wider population, so she suggested that as EPA looked at a POD, they should evaluate the demographic differences from the study population as the demographics were not clear in the original l977 study and current study. Dr. Corey noted that study populations can be very racially homogenous or heterogenous depending on where they are conducted. Dr. Cavallari summarized that the group agreed that the only outstanding recommendation to review was demographic differences that could lead to susceptibility concerns.

Dr. Julia Sharp presented the Board's statistical review. She noted the same deficiencies in the statistical analysis approach as EPA. Dr. Sharp recommended considering whether the subjects were randomized to the treatment order. Her other recommendation was to evaluate the observational unit grouping based on the date value in the raw data. Dr. Cavallari summarized these points and asked for additional questions and suggestions from the Board. Hearing none, Dr. Cavallari reviewed the charge question on science and posed the following statement: "The research described in the published article 'Acute effects of acrolein in human volunteers during controlled exposure' is scientifically sound and provides

reliable data." Dr. Corey noted that the clause at the end of the statement might not be correct based on the discussion. Dr. George Milliken added that he was concerned about the study's statistical analysis. He said the data seemed scientifically sound and reliable, but he was not sure the analysis was appropriate. For example, the study did not account for three people occupying the chamber at the time and suggested that the chamber rather than the three different individuals would be the more appropriate sample unit, which could affect the degrees of freedom. Dr. Cavallari noted that a final clause could cover this concern. "The research described in the published article 'Acute effects of acrolein in human volunteers during controlled exposure' is scientifically sound and provides reliable data given the recommendations provided by the HSRB and EPA statistical reviewers are considered." Dr. O'Farrell asked if the response as posed is sufficient for Ms. Arling and Dr. Leonard to move forward. Ms. Arling noted that splitting the statement into two sentences could work.

Dr. Cavallari proposed using the following version: "The research described in the published article 'Acute effects of acrolein in human volunteers during controlled exposure' is scientifically sound and provides reliable data given the recommendations provided by the HSRB are considered." Dr. Cavallari called a vote on this statement and the Board agreed unanimously.

The Board then discussed the ethics charge question: "Does available information support a determination that the study was conducted in substantial compliance with subpart Q of 40 CFR part 26?" Dr. Lindsay McNair presented the HSRB's ethics review of the study. She concurred with Ms. Arling's ethics assessment. Dr. McNair summarized that the study did not include pregnant women. It did not specifically exclude nursing women, but there was no indication that any of the participants were nursing. Participants had to be over eighteen, so there was no intentional exposure to children or to pregnant or nursing women. Dr. McNair said informed consent appeared to have been obtained from all study participants and appropriately documented. Participants were compensated for their time. Payment was appropriate and provided after each visit, so the promise of future payment did not impact ongoing consent. Participants were made aware that they were free to withdraw from the study at any time so there did not appear to be any informed consent concerns. Dr. McNair said it appeared that all appropriate ethical standards were followed, and the research was not unethical in any way. The participants were reasonably protected from harm, and there was no information or procedures that impacted voluntary informed consent. The protocol and consent were reviewed and approved by an appropriate local ethics committee as per local requirements and met all regulatory standards. The Board voted unanimously in favor of the following response to the charge question: "The Board believes that the research described in the published article 'Acute effects of acrolein in human volunteers during controlled exposure' was conducted in substantial compliance with the applicable requirements of 40 CFR part 26."

The meeting adjourned at 3:45 pm EDT.

EPA Human Studies Review Board (HSRB)
July 20 and 21, 2021 Meeting Minutes

Wednesday, July 21, 2021:

A. Meeting Topic and Charge Questions

Topic: Claeson, A-S and Lind, N. Human exposure to acrolein: Time-dependence and individual variation in eye irritation. Environmental Toxicology and Pharmacology. Volume 45. pp. 20-27. May 13, 2016.

Charge to the Board - Science: Is the research described in the published article "Human exposure to acrolein: Time dependence and individual variation in eye irritation" scientifically sound, providing reliable data?

Discussants: Alesia Ferguson, Ph.D., and Thomas Lewandowski, Ph.D., scientific review
George Milliken, Ph.D., statistical review

Charge to the Board - Ethics: Does available information support a determination that the study was conducted in substantial compliance with subpart Q of 40 CFR part 26?

Discussant – Philip Day, Ph.D., ethics review

Overall Charge: When considered together, do the studies described in Claeson et al. and Dwivedi et al. provide a scientific weight of evidence in support of the existing short-term to intermediate-term inhalation point of departure of 0.09 ppm based on eye irritation in risk assessments?

B. Convene Public Meeting Day 2

Tom O'Farrell, Ph.D., Designated Federal Officer, EPA Human Studies Review Board (HSRB), Office of the Science Advisor, Policy and Engagement (OSAPE)

Meeting was called to order at 1:00 pm EDT by Dr. Tom O'Farrell, Designated Federal Official (DFO) for the Human Studies Review Board (HSRB). Dr, O'Farrell introduced the meeting, outlined the Federal Advisory Committee Act (FACA) procedures, and took roll of the meeting participants. The following members and observers were present:

HSRB members	Jennifer Cavallari, Sc.D., University of Connecticut (Chair) Alesia Ferguson, Ph.D., NC A&T (Vice Chair) Mark Aulisio, Ph.D., Case Western University Janice Britt, Ph.D., ToxStrategies Philip Day, Ph.D., University of Texas Southwestern George Milliken, Ph.D., Kansas State University Tom Lewandowski, Ph.D., Gradient Julia Sharp, Ph.D., Colorado State University AJ Allen, M.D., Ph.D., Eli Lilly Company Eun Um, Ed.D., AMSTAT Consulting Lisa Corey, Ph.D., Intertox, Inc.
EPA staff members	Michelle Arling (EPA, OPP) Tom Tracy (EPA, OSAPE) Tom O'Farrell (EPA, OSAPE) Shannon Jewell (EPA, OPP) James Nguyen (EPA, OPP) Don Wilbur (EPA, OPP) Dana Vogel (EPA, OPP) David Miller (EPA, OPP)

	Jeremy Leonard (EPA, OPP) Shalu Shelat (EPA, OPP) Phil Villanueva (EPA, OPP) Patricia Engel (EPA, OPP) Brian Van Deusen (EPA, OPP) Taylor Lass (EPA,OSAPE)
Members of the public, representatives of research sponsor and research team:	Steven Black (ICF, Contractor Support) Kaitlin Geary (ICF, Contractor Support) Leah West (ICF, Contractor Support) Kathryn Van Artsdalen (ICF, Contractor Support)

Dr. O'Farrell introduced the meeting and noted that the purpose of the July 21, 2021 meeting was to review the article by Claeson, A-S and Lind, N. Dr. O'Farrell mentioned that supporting documents were on the HSRB website. The meeting minutes and the Board's report would be on the website within 90 days.

C. Welcome and Virtual Meeting Operations

Jennifer Cavallari, Sc.D., HSRB Chair

Dr. Jennifer Cavallari welcomed attendees and provided an overview of Zoom.

D. EPA Answers to Questions from Yesterday's (July 20, 2021) Session

Jeremy Leonard, Ph.D., Office of Pesticide Programs

Dr. Jeremy Leonard provided the HSRB with answers to questions asked during the July 20, 2021 meeting. Dr. Leonard informed the Board that in response to the question if the order of exposure was randomized, the EPA statisticians reconstructed the exposure order for each of the subjects based on the dates provided in the raw data in response. They found that two data points were not included due to one subject missing from the exposure condition, which was contrary to the statement in the article that they followed a balanced design.

The EPA statisticians also examined the duration between exposures. Most of the exposures were separated by at least 7 days, leading to a longer wash out period, and more than half of the intervals were greater than 2 weeks. Given this long wash out period and that eye irritation effects rapidly diminished following exposure, the carryover effects were minimal, if any existed at all. Statisticians also found that doing a re-analysis with the exposure order could be complicated, and the exposure sequence may not matter, as the overall conclusion of the EPA reanalysis would not substantially be altered regardless of whether the exposure sequence followed a balanced design.

Dr. Leonard provided an answer to the question asked: "Was it considered that the subjects were grouped 3 to 4 at a time, and was this available in the raw data?" There was no chamber information provided by the authors and therefore, data analysis did not incorporate it. The EPA statisticians did find, after looking at the data and attempting to reconstruct chamber information by combining date and exposure condition as a new variable, that if this new variable was incorporated as a random effect as a surrogate for exposure chamber, it would not change the overall conclusion of the analysis due to the very low p-value currently estimated; the possibility of deriving a slightly wider 95% confidence interval was acknowledged.

Dr. Leonard completed a literature screen regarding the demographics in response to Dr. Janice Britt's and Dr. Lisa Corey's questions. He found that Asian individuals have greater susceptibility for dry eyes which increases with age. The university also had a large population of students in the graduate and doctoral programs, comprising a large multinational conglomerate. The student blog reported demographics within their programs as 30-40% European, 7% Hispanic, 7-17% African, and 3-6% Australian and North American. Pesticide applicators were seen to be 71% Caucasian and were typically older than 40 years old. If there are any discrepancies, they are likely seen more with age than race in this case. The Hispanic population might be under-represented, and the Asian population might be over-represented in the study. Dr. Corey suggested to note this information, as it was significant enough to acknowledge in documentation.

E. EPA Science Review Highlights

Jeremy Leonard, Ph.D. Office of Pesticide Programs

Dr. Jeremy Leonard provided an overview of the Claeson, A-S and Lind, N 2016 study conducted at a lab in Sweden. The study purpose was to examine time dependence on sensory irritation detection following threshold level of acrolein in humans. The focus was primarily on sensory irritation rather than adverse health effects. There were more subjects than the study from the July 20, 2021, meeting, but there were more females than males in this study. The doses were half of the Swedish occupation threshold limit for 15 minutes and 8 hours (0.3 and 0.1 ppm, respectively), and the filtered air entered on the floor level into a 3 cubic meter chamber and exited at the ceiling. Heptane (4.95 ppm) was used as a carrier gas vehicle and control. In the chamber, the temperature was kept at 21 degrees Celsius, and the humidity was 18%. Since eye irritation was the sole focus of the study, subjects wore masks covering their mouth and nose. All of the subjects participated in the same study conditions that the authors stated was a balanced design, and which involved visiting the laboratory on four separate days to vary and overlap concentration and time.

Before the main study, the subjects completed two questionnaires. The first was a chemical sensitivity scale and the second was a stress questionnaire on how they perceived stress for the past 4 weeks to provide a baseline level for each subject. The influence of time was measured in terms of confidence and magnitude, which were then transformed onto an overall scale of 1-4. Like the VAS used in the July 20, 2021, HSRB meeting study, this study used a BORG 100 CR scale. The eye blinks and tear film breakup time (BUT) were also measured. The blink frequencies (averaged over a period of five minutes) were filmed throughout exposure and were determined by a hand counter before, during, and after exposure; however, there were no quality checks discussed or included. To assess the eye irritation, subjects looked at a specific spot and measured the length of time that the subject could keep their eyes open. This was measured before, during, and after exposure. The study found that the level of confidence increased but did not reach the threshold of "yes" at any concentration. All concentrations had an increased sensitivity over time.

There was a large variability with respondents who reported acrolein as irritating vs. those who did not detect irritation at all, and so the subjects were then divided into two groups: responders (15) and non-responders (11). This division was based on confidence ratings greater than the combined score for confidence and magnitude (i.e., a value > 2.5) at some point during the 15-minute exposure, which had shown the greatest signal among all time periods. The article stated that the responders did not report any additional stress, effective reactions, or behavioral actions compared to the non-responders in the baseline questionnaires they filled out, and these fell within the range of a normal population.

The level of confidence for the responders increased to above the threshold (>2.5) with time for all three acrolein concentrations but not for the control. The perceived intensity also increased for all concentrations for the responders, but it was only significant for the highest concentration and 15-minute exposure. The authors did not provide any data for all subjects combined for blink frequency or BUT assessments, and there was no significant statistical difference between responders and non-responders for these two parameters despite apparent numerical differences. There was a significant difference between responders and non-responders for eye irritation data when evaluating data corrected for false detections, and acrolein was found to be detected above the level of chance at just under 7 minutes at the highest concentration. The raw data was used for the eye irritation ratings data to examine the uncorrected false positives and negatives, using the same criteria as the authors' analysis. For the non-responders, 82-91% reported no sensation at any concentration after exposure had ended. For responders the percentage decreased but remained relatively high at the two lower concentrations, at 60-79% while significantly decreasing to 33% at the highest concentration These results align with the investigators' findings that the highest concentration remained irritating after exposure. Responders also showed a higher number of false positives (i.e., perceived sensitivity in the vehicle control) before and during exposure (18% and 73%, respectively) relative to non-responders (0% and 27%, respectively), indicating that responders do have some inherent tendency for detection when none exists.

Dr. Leonard then provided the strengths and weaknesses of this study. Strengths included the separate heptane control group, the randomized block design with blinded subjects, and the availability of raw data. Weaknesses included the heptane-only exposure for only 30 minutes despite the longest acrolein concentration exposure lasting 60 minutes, the concern that greater number of female subjects might have raised the false detection rate, lack of provided measurements of the chamber concentrations, lack of information on the clean-air masks worn by the subjects, lack of data on durations between visits to labs, and some statistical methods could have been more appropriate.

The EPA statisticians found that there might have been statistical methods that were more fitting to the study. The authors used repeat measures ANOVA for the analysis of all three parameters; however, EPA found that a mixed effects model might be more appropriate to account for points that repeat measures ANOVA might not capture. This can correct for any non-uniform intervals that might be between measurements and it can also account for random effects of subjects and day in the study design. The author's main objective was to determine how time influences acrolein effects on sensory irritation, but it was not clear how time was used. The high variability among responders and non-responders indicates that data may not have been normally distributed, and it is unclear what adjustments were conducted to achieve normality.

The raw data came later in the review process and EPA was only able to develop code for the BUT and blink frequency data. The comparison only included blink frequency data (log transformation of the duration of counts) for the control and high-dose levels and used a generalized mixed model with Poisson distribution. The re-analysis found no significant effect of acrolein on eye blink frequency after removing the non-significant interaction term for time and concentration. The re-analysis did find 4 potential outliers of subjects having either no blinks per minute or greater than 60, and therefore was followed up with a sensitivity analysis. The outliers were found to not influence the results or conclusions. BUT data were not normally distributed and were log transformed. A mixed- effects model showed that there was no interaction or effect of time or concentration on BUT.

In conclusion, the statistical re-analysis agreed with the study's finding of no effect on the eye blink frequency or BUT, with no effect on concentration of either parameter. BUT was not measured in the older 1977 study, but the newer study agrees that blink frequency was seen at a higher concentration.

This study showed a higher eye irritation effect level than the previous 1977 study with similar annoyance responses. There was high variability among the participants, and the sensitivity was almost instant. There was also a shorter exposure time (45 minutes) compared to the previous study at the same concentration at which eye irritation was detected (60 minutes), but the authors note that exposure to this intermediate concentration does indicate that duration of exposure might need to be extended to 90 minutes to be detected. Dr. Leonard proposed the study to qualitatively support the current inhalation POD, as it shows that effects occur rapidly with some level of adaptation over time.

F. Board Questions of Clarification

Jennifer Cavallari, Sc.D., HSRB Chair

Dr. Tom Lewandowski: One of the things that stood out to me was the issue of relative humidity. This study had a relative humidity of 18% and in the study yesterday, the relative humidity was 30%. Was that considered? What was the impact of the n-heptane vehicle?

> **Dr. Jeremy Leonard:** The 2015 study used 30% and this study used 18% for relative humidity. We looked to try to find humidity information for the region but are not sure how that translates to the study. Also, it is unclear how the n-heptane exposure affected the relative humidity. Acrolein is highly water soluble and highly reactive, so a small increase in humidity would likely be insignificant relative to how quickly the acrolein is reacting.

Dr. Tom Lewandowski: The authors stated that the duration should be extended to 90 minutes, which is based on the extrapolation of their data.

> **Dr. Jeremy Leonard:** That suggestion was based on a figure included in the paper.

Dr. Alesia Ferguson: Even if they extend the exposure time, people seem to adapt, and you might not see any results.

> **Dr. Tom Lewandowski:** Yes, I would tend to agree. In EPA's summary, it was stated as a finding. Your issue of adaptation leaves me to be hesitant about that conclusion.

Dr. George Milliken: You fixed a lot of the problems that the authors had with their analyses, and you indicated important points, such as the distribution of the males and females between the responders.

Dr. Jennifer Cavallari: Can you clarify or state how these two studies will be used?

> **Dr. Jeremy Leonard:** The 1977 study used 0.09 ppm, the 2015 study used 0.1 ppm, and 2016 used 0.16 ppm. Those numbers are around the same 0.1 ppm. We will use it as a citation to support the older 1977 for qualitative purposes only.

G. EPA Ethics Review of Highlights

Michelle Arling, J.D., Office of Pesticide Programs

Ms. Michelle Arling provided an overview of the ethics review. She reached out to the author for materials, which were provided. Some materials were translated by the author, but Ms. Arling had to translate others using Google Translate. Participants were recruited through advertisements posted throughout the test location of Umea University. These advertisements provided the overview, time, criteria, and the compensation for the study. Enrollment involved 26 subjects (18 female and 8 male) ranging in age from 20-47 years old. The criteria to enroll in this study included the requirement that subjects were 18-60 years old, nonsmokers, not pregnant or lactating, and self-reported as healthy. No pregnancy testing was conducted by the study team. The consent process consisted of individual meetings between prospective subjects and a study team member, information provided both orally and in writing, and the freedom to withdraw at any point.

Risks were minimized for subjects through the selection of test substance levels, the eligibility criteria,

targeting detection of the sensory irritation rather than health effects, wearing masks during exposure, and wearing glasses for subjects who usually wear contacts. Subjects were free to withdraw, paid for participation, their privacy was protected, and the study team obtained insurance for adverse effects on subjects from the study. The protocol for the study was approved by the Ethics Committee of Umea University on May 12, 2012. The ethics application was reviewed and approved before the research was initiated. All acceptance standards were met.

Ms. Arling found that subjects were all adults. There was no evidence that pregnant or nursing women were enrolled, and all subjects consented in writing and concluded that the available information indicates that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical.

H. Board Questions of Clarification

Jennifer Cavallari, Sc.D., HSRB Chair

Dr. Philip Day: (1) The article does not indicate if participants completed pregnancy tests or if they were nursing. Pregnancy status was self-reported. (2) I do not think the incentive payment was enough to be coercive for the subjects to remain. What was the timing of the payments? Were they held until the end? If the payment was held until the end, it might be more coercive for the subjects to continue and that should be looked into. (3) In the correspondence, students of the investigators were eligible to participate but there is no evidence that they were not students of the investigators.

> **Ms. Michelle Arling:** The review from EPA does cover pregnancy testing. No pregnancy testing was conducted, and the author did affirm that based on self-reporting, no pregnant women were enrolled. EPA is comfortable relying on that information. I believe that people were paid after each visit, but I will confirm in the author's materials. It might not be in the file, but I have the information.

Dr. Alesia Ferguson: Normally, we like to do the pregnancy test, should the subject not know they are pregnant. There was no intent to enroll the pregnant women according, but it might not be the best practice.

> **Ms. Michelle Arling:** Not every study requires pregnancy testing, but it is becoming more common. They were outside of the United States and so they might not use the standard practices. If the Independent Review Board knew their process, then they were likely operating in the accepted standard of their country. A lack of documentation of pregnancy status does not disqualify a study under the human studies rule.

I. Public Comments

There was a call for public comments but there were none.

J. Break

The Board meeting paused for a fifteen-minute break from 2:15-2:30 pm EDT.

K. Board Discussion

Jennifer Cavallari, Sc.D., HSRB Chair

The HSRB's scientific review was presented by Board members Dr. Alesia Ferguson and Dr. Tom Lewandowski. Dr. Ferguson acknowledged EPA's findings, particularly on the study's weaknesses. She added that there was missing data about responders and non-responders. She also wondered if only one

person counted eye blinks or if there was another observer for quality control. Dr. Ferguson noted that the study had more females than males, but thought it was better to oversample a group believed to be more sensitive to the chemical. Although there were some information gaps in the data, Dr. Ferguson believed the results of the study should still be used to support risk assessment recommendations.

Dr. Lewandowski expressed his doubts about the study and said he would be concerned if EPA used the results quantitatively to set exposure limits. He was concerned about the high number of false positives and negatives among the respondents, especially since there was only a minimal response detected. Dr. Lewandowski questioned how robust the results are. He also was concerned about n-heptane being used as the masking agent and the data not being clear in the figures. However, he acknowledged that the results are qualitatively similar, or even quantitatively similar, to other studies. Dr. Lewandowski said he approved of the study given that it would only be used for qualitative support and added that concerns about the study's methods and interpretation should be noted.

Dr. Leonard concurred and said in isolation he would be hesitant to use the study for anything quantitative, possibly even qualitative. Dr. George Milliken agreed, explaining that the study does not carry much weight by itself since it only measured eye irritation. Dr. Milliken's main concern was that the study split subjects into responders and non-responders after data collection. He noted that perhaps the responders all started with high or medium doses, and the non-responders started with low or controlled doses. Dr. Milliken added that most of the authors' conclusions were based on the responder data, which he felt undermined the study. He also expressed concerns about the study's analyses and models. He was disappointed that Figure 4 used simple linear regression to model probability. Dr. Milliken also noted that there was no indication of power analysis regarding how many subjects were needed to achieve statistical significance, which he believed undermined the results.

Dr. Lewandowski shared Dr. Milliken's concern about the post-hoc nature of the analysis. Dr. Lewandowski wondered if there was a statistical analysis that could address the false positive and false negative rate. He noted that there appeared to be some outliers in the data plots and wondered if one or two individuals were driving the results. Dr. Jennifer Cavallari asked if any committee members with statistical expertise recommended a certain type of analysis to address the false positive rate, but neither Dr. Milliken nor Dr. Sharp had suggestions. Dr. Cavallari also asked if there was any attempt to examine outliers or at the distribution of the data points, even if a formal analysis was not performed. Dr. Milliken noted that Figure 3 showed possible outliers. Dr. Cavallari recommended that EPA perform further analysis of the irritation data to look for outlying data and Dr. Leonard said that is possible. Dr. Lewandowski recommended that EPA use this study for qualitative support but highlight the methodical issues Dr. Milliken added that this study should be given less consideration and importance compared to other qualitative studies. Dr. Ferguson asked if the response level from the 1977 Weber study was being used because it was the lowest of the values from the three studies. Dr. Leonard confirmed that this was correct and that they are using it as a citation to support their risk assessment. Dr. Britt asked whether Dr. Leonard had looked at a study by Claeson and Anderson (2017) and Dr. Leonard said that he was aware of the study, but it was not relevant.

Dr. Cavallari asked the Board to deliberate on a response to the following charge question: "Is the research described in the published article 'Human exposure to acrolein: Time dependence and individual variation in eye irritation' scientifically sound, providing reliable data?" Dr. Lewandowski said he had concerns with the phrase "providing reliable data" and Dr. Ferguson agreed. Dr. AJ Allen noted that the actual data was reliable, but that the analysis was the true concern. Dr. Lewandowski suggested mentioning HSRB's recommendations, reservations, and concerns in the charge question response. Ms. Michelle Arling noted that EPA would review the recommendations as it incorporates the

data into a risk assessment. The Board voted on and unanimously approved the following response: "The research described in the published article 'Human exposure to acrolein: Time dependence and individual variation in eye irritation' is scientifically sound and provides reliable data given the recommendations and concerns provided by the HSRB are considered."

Board member Dr. Philip Day reviewed the ethical aspects of the study protocol. He agreed with EPA's ethics assessment and believed that the study was conducted according to appropriate ethical standards. He said the recruitment procedures were conducted ethically and subject selection was equitable. Participants must have been at least 18 years of age to participate. The study did not enroll pregnant individuals and pregnancy was an exclusion criterion. There was no intentional exposure of any human subjects who were pregnant women, nursing women, or children. Dr. Day explained that participants were provided both written and oral information regarding their eligibility, purpose for the study, study procedures, and risks. All subjects provided their written consent to participate. Dr. Day said that risks to subjects were effectively minimized and believed that the overall benefit to society outweighed the possible risks associated with study participation. He noted that participants were also covered by an insurance policy that would cover injuries incurred due to their participation in the study. However, no subjects reported experienced adverse events or side effects beyond what was expected. Dr. Day noted that the study protocol consent form and recruitment materials were reviewed and approved by the ethics committee at Umeå University, which was the study site in accordance with Sweden's regulations for research containing human subjects. Dr. Day summarized that an independent ethics review was conducted, subject selection was equitable, risks to subjects were adequately minimized, informed consent was obtained and documented, and no procedures impaired or impacted informed consent. Dr. Day said that the provided information supports the determination that when the study was conducted, it was compliant with 40 CFR part 26 subparts K and L, and thus compliant with the Subpart Q. The Board was tasked with responding to the ethics question: "Does available information support a determination that the study was conducted in substantial compliance with subpart Q of 40 CFR part 26?" The Board voted on and unanimously approved the following response: "The Board believes that the research described in the published article 'Human exposure to acrolein: Time-dependence and individual variation in eye irritation' was conducted in substantial compliance with the applicable requirements of 40 CFR part 26."

Dr. Cavallari introduced the overall charge question: "When considered together, do the studies described in Claeson *et al*. and Dwivedi *et al.* provide a scientific weight of evidence in support of the existing short-term to intermediate-term inhalation POD of 0.09 ppm based on eye irritation in risk assessments?" Dr. Cavallari noted the Board's concerns about the limitations of the Claeson *et al.* article. Dr. Ferguson noted that the Claeson *et al.* study has a higher threshold value, so it would not affect the protective level already in place. Dr. Lewandowski said he approved of the charge question as long as the Board's concerns were noted. The Board voted on and unanimously approved the following response to the overall charge question: "When considered together, the studies described in Claeson *et al*. and Dwivedi *et al*. provide a scientific weight of evidence in support of the existing short-term to intermediate-term inhalation POD of 0.09 ppm based on eye irritation in risk assessments, provided the recommendations and concerns of the HSRB are considered."

Dr. Tom O'Farrell thanked all attendees and closed the meeting.

The meeting adjourned at 3:20 pm EDT.

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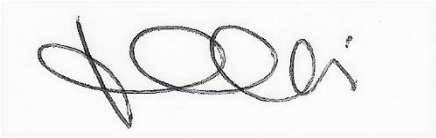
Respectfully submitted:

X Thomas O'Farrell 10/14/2021

Thomas O'Farrell, Ph.D.
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:



Jennifer Cavallari, Sc.D.
Chair
Human Studies Review Board
United States Environmental Protection Agency

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Board members during the course of deliberations within the meeting. Such ideas, suggestions and deliberations do not necessarily reflect definitive consensus advice from the Board members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final report prepared and transmitted to the EPA Science Advisor following the public meeting.

EPA Human Studies Review Board (HSRB)
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Attachment A: HSRB Current Committee Membership

Name	Title	Affiliation
Jennifer Cavallari, ScD, CIH, Chair	Associate Professor	Department of Public Health Sciences University of Connecticut Storrs, CT
Alesia Ferguson, Ph.D., Vice Chair	Associate Professor	Department of Built Environment North Carolina A&T State University Greensboro, NC
Janice Britt, Ph.D.	Managing Scientist	ToxStrategies Tallahassee, FL
George Milliken, Ph.D.	Statistical Consultant	Milliken Consultants Manhattan, KS
Mark Aulisio, Ph.D.	Professor	Case Western Research University Cleveland, OH
Thomas Lewandowski, Ph.D.	Principal	Gradient Seattle, WA
Julia Sharp, Ph.D.	Associate Professor	Colorado State University Fort Collins, CO
Albert J. Allen, M.D., Ph.D.	Senior Medical Fellow	Eli Lilly Indianapolis, IN
Lisa Corey, Ph.D.	Toxicologist	Intertox, Inc. Seattle, WA
Lindsay McNair, M.D.	Chief Medical Officer	WIRB-Copernicus Princeton, NJ
Eun Um, Ed.D.	President and CEO	AMSTAT Consulting Bethesda, MD
Philip Day, Ph.D.	Assistant Professor	University of Texas, Southwestern Dallas, TX

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Attachment B: Federal Registers Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10017-40-ORD]

Human Studies Review Board; Notification of Public Meetings

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA), Office of Research and Development announces the 2021 public meetings dates of the Human Studies Review Board (HSRB) to advise the Agency on the ethical and scientific review of research involving human subjects.

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

1. January 26-28, 2021;
2. April 20-22, 2021;
3. July 20-22, 2021; and
4. October 19-21, 2021.

Meetings will be held each day from 1 p.m. to 5:30 p.m. Eastern Time. Separate, subsequent teleconference meetings are planned for the HSRB to finalize its Reports of the three-day meetings that proceed these dates on March 18, 2021; June 17, 2021; September 16, 2021; and December 14, 2021; all from 2 p.m. to approximately 3:30 p.m. Eastern Time.

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.

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FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact the HSRB Designated Federal Official (DFO), Thomas O'Farrell at the following telephone number: (202) 564-8451 or by email at: ofarrell.thomas@epa.gov.

SUPPLEMENTARY INFORMATION:

Background

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

Meeting access: These meetings will be open to the public. The full agenda with access information and meeting materials will be available seven calendar days prior to the start of each meeting at the HSRB Website: https://www.epa.gov/osa/human-studies-review-board.

For questions on document availability, or if you do not have access to the Internet, consult with the DFO, Thomas O'Farrell, listed under **FOR FURTHER INFORMATION CONTACT.**

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

How May I Participate in this Meeting?

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

1. Oral comments. To pre-register to make oral comments, please contact the DFO, Thomas O'Farrell, listed under **FOR FURTHER INFORMATION CONTACT**. Requests to present oral

comments during the meetings will be accepted up to Noon Eastern Time, seven calendar days prior to each meeting date. To the extent that time permits, interested persons who have not pre-registered may be permitted by the HSRB Chair to present oral comments during the meetings at the designated time on the agenda. Oral comments before the HSRB are generally limited to five minutes per individual or organization. If additional time is available, further public comments may be possible.

2. Written comments. For the Board to have the best opportunity to review and consider your comments as it deliberates, you should submit your comments prior to the meetings via email by Noon Eastern Time, seven calendar days prior to each meeting date. If you submit comments after these dates, those comments will be provided to the HSRB members, but you should recognize that the HSRB members may not have adequate time to consider your comments prior to their discussion. You should submit your comments to the DFO, Thomas O'Farrell 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 Thomas O'Farrell listed under **FOR FURTHER INFORMATION CONTACT**.

Dated:

Jennifer Orme-Zavaleta,
EPA Science Advisor.