EPA Human Studies Review Board (HSRB)
December 14, 2022 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A)
Date and Time: Wednesday, December 14, 2022, 1:00 to 5:00 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

Table of Contents

EPA Human Studies Review Board (HSRB)
December 14, 2022 Meeting Minutes

Wednesday, December 14, 2022:

A. Meeting Topic and Charge Questions

Topic: Carroll, Scott P., Study Director. (2020) Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions. Unpublished Document. January 5th, 2022. MRID 517706-01.

Charge to the Board – Science: Did the research summarized in "Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions" generate scientifically reliable data, useful for estimating the amount of time the product tested repels ticks?

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

B. Convene Public Meeting and Identification of Board Members

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

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

HSRB members	Lisa Corey, Ph.D., Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (Colorado State University) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Chad Cross, Ph.D. (University of Nevada-Las Vegas) Philip Day, Ph.D. (University of Massachusetts, Chan Medical School) Nicole Deming, J.D., M.A. (Case Western Reserve University, School of Medicine) Weiying Jiang, Ph.D. (California Environmental Protection Agency) Srikumaran Melethil, Ph.D. (University of Missouri-Kansas City) George Milliken, Ph.D. (Milliken Consultants) Sinziana Siecean-Boose, M.D., Ph.D., M.P.H. (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) Eun Um, Ed.D. (AMSTAT Consulting) David Williams, Ph.D. (Oregon State University)
EPA staff members	Michelle Arling (EPA, Office of Pesticide Programs (OPP)) Tom Tracy (EPA, Office of Science Advisor, Policy and Engagement (OSAPE)) Angela Myer (EPA, OPP) Clara Fuentes (EPA, OPP)

	Brandall Ingle (EPA, OPP) James Nguyen (EPA) Frank Antwi (EPA, Office of Pollution Prevention and Toxics) Matt Crowley (EPA, OPP) Shannon Borges (EPA, OPP) Stephanie Watson (Office of Transportation and Air Quality) Robert Mitchell (EPA, OPP) Rebecca Lasko (EPA)
Members of the public, representatives of research sponsor and research team:	Scott Carroll, Ph.D., Carroll-Loye Biological Research Shawn King, M.S., Caroll-Loye Biological Research Dana Lateulere, Bergeson & Campbell Lara Hall, Bergeson & Campbell Jonathan Cohen (ICF, Contractor Support) Afroditi Katsigiannakis (ICF, Contractor Support) Angelina Guiducci (ICF, Contractor Support) Lucas Rocha Melogno (ICF, Contractor Support) Kathryn Van Artsdalen (ICF, Contractor Support)

C. Meeting Administrative Procedures

Tom Tracy, Designated Federal Officer, EPA HSRB, OSAPE

Mr. Tom Tracy reviewed Zoom Meeting platform tools and features and stated the purpose of the meeting was to review the paper by Scott P. Carroll, "Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions." He noted minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of December 14, 2022.

D. Updates on Human Subject Research Program

Monique Tadeo, M.S., CIP, HSRB Official and Director

Ms. Monique Tadeo welcomed everyone to the EPA HSRB meeting and thanked Ms. Michelle Arling for her work and commitment to leading the program.

E. Meeting Process

Lisa Corey, Ph.D., HSRB Chair

Dr. Lisa Corey thanked everyone for attending the meeting and reviewed the agenda.

F. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Michelle Arling explained there were no updates to the research discussed at the previous meeting. She then announced there would be two formaldehyde studies and an acetate study to review in the winter and spring. She thanked the Board for sharing their expertise and time to support OPP's mission.

G. Review and Finalize HSRB Report on Andersen and Molhave Study

Dr. Corey announced there were no comments from EPA regarding the Andersen and Molhave Study.

H. Review and Finalize HSRB Report on Kulle Research

Dr. Corey shared a comment about the lack of any benchmark dose analysis. Dr. Sinziana Seicean-Boose agreed this was a concern and suggested inclusion of an announcement memo. Dr. Chad Cross noted the comment likely was made before the Cohen and O'Neal document was provided, which resolved the issue.

Dr. Julia Sharp recommended keeping the comment "EPA should note that the additional tests (Fisher's Exact Test and Cohen-Armitage test) should be interpreted with caution given the assumption of independence is likely not satisfied." Although the independence assumption may not be valid, Dr. Sharp emphasized it was important to include a note of caution for interpretation. Dr. George Milliken concurred. The Board agreed it was important to note statistically significant differences and trends were unclear.

I. Review and Finalize HSRB Report on Mimikai MIM-006

Dr. Albert J. Allen suggested adding a note stating the regulations and standards to protect human subjects research were specific to EPA 40 CFR subparts K and L, which are similar to the Common Rule.

Dr. David Williams agreed with the updated language referring to geographical regions of the U.S., such as "Southeastern" and "Pacific Northwest," rather than states. He explained there can be many different ecological and geographical environments within a state, especially in the American West, while the same type of environment exists across multiple states. Dr. Cross agreed with this update and perspective.

The Board voted to approve the comments and updates to the report.

J. EPA Science Review Highlights

Angela Myer, Ph.D., OPP Health Effects Division

Dr. Angela Myer described the schedule of the study, noting the date of protocol submission for Institutional Review Board (IRB) approval and several logistical challenges encountered. She stated the study adhered to established guidelines after receiving final protocol approval from the Advarra Institutional Review Board (IRB). She provided a study summary, describing subject selection, randomization characteristics, and study procedures occurring prior to efficacy testing. She explained the study team screened subjects for tick attractiveness, provided training on tick handling prior to testing, and used three tick species for efficacy testing. She displayed a table describing the tick species, where they came from, and their age and maintenance conditions. She explained the authors determined the Complete Protection Time (CPT) for each subject by species. Repellency testing involved 25 study participants interacting with ticks in 15-minute exposure periods during which ticks were positioned on both forearms. One active tick was tested per subject per exposure period. The untreated forearm certified tick activity. Travel of the tick on the forearm determined repulsion scores.

Dr. Myer then described the statistical analysis, which included CPT for each subject and Kaplan-Meier survival analyses using R and mCPT and 95% confidence intervals. She mentioned EPA statisticians

performed additional tests that showed there were significant differences between the species. Though variability could occur, the data suggests repellency failure may occur earlier in some species compared to others. She explained EPA's repellency awareness guidelines indicate CPTs should be calculated from three species. She reported study results for each of the three species, including the estimated median CPT for each of the species, and the finding that among the three species, the lowest CPT of 4 hours was observed for *A. americanum*.

She mentioned the reported protocol deviations, clarifying gender was not considered to influence the outcomes and noting lag time between applications varied more than expected. Dr. Myer emphasized EPA decided none of the deviations would have affected the outcome of the study and reiterated gender is not expected to have an impact. Study recommendations include supporting future statements with appropriate scientific references, noting all deviations in the study report, and describing methodological procedures in detail within the main body of the report.

Dr. Myer then displayed the charge question about the reliability of the data in the study "Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions."

K. Board Questions of Clarification

Lisa Corey, Ph.D., HSRB Chair

Dr. Lisa Corey requested questions from the audience. Dr. Siecean-Boose asked whether the study focused on the time ticks crawled on subjects' arms or the time it takes for ticks to attach to humans, noting it is an important clarification because the time between crawling and attachment is heterogeneous. It could take 4-6 hours for a tick to crawl in order to see attachment, and there is no transmission of disease without attachment.

Dr. Myer responded, stating the overall goal was to assess whether the repellent worked. Dr. Clara Fuentes commented the repellent would impede ticks from traveling beyond the treated area, thereby preventing attachment. Dr. Siecean-Boose said the assessment would seem to be about crawling and attachment prevention. Dr. Myer confirmed the purpose was to assess repellency by preventing crawling. The test protocol did not include allowing ticks attach to subjects.

Dr. Allen asked for clarification about three unreported deviations related to use of two different tick colonies. Ms. Arling confirmed the use of two sources and admitted they did not have the same quality of pathogen screening but indicated this was an ethical issue they would discuss later. Dr. Allen commented it is hard to separate science from ethics.

Dr. Jiang asked whether the repellent tests took hours to complete and what steps were taken to avoid contact with the treated area. Dr. Myer explained participants received consistent reminders about not disturbing the area. Dr. Jiang mentioned an EPA standard operating procedure (SOP) on residential pesticide exposure, which suggests a 4-hour period for a study conducted outdoors, and asked how the authors would reconcile results since the study occurred under laboratory conditions. Dr. Clara Fuentes responded they maintained standard conditions and would use the results for further developments.

Dr. Melethil asked whether the subjects kept their hand at 30 degrees for many hours. Dr. Myer stated this was not the case. Subjects endured exposure for 15-minute periods and had one treated forearm and one untreated forearm. They placed the tick on the untreated forearm and waited to see whether it moved within 3 minutes. If it did, it was transferred to the treated forearm to see if it moved within 3 minutes.

Ms. Arling mentioned there were three phases for the exposure and explained them in detail. Dr. Siecean-Boose then asked about the standard methods followed. Dr. Fuentes clarified the 30-degree method was present in EPA's guidelines and noted it captures a greater surface area compared to other available methods. Dr. Siecean-Boose noted the same tick will have the chance of crawling 3 minutes at a time. Dr. Fuentes mentioned ticks might crawl faster and reduce the exposure time. Dr. Williams asked whether EPA had any input regarding planning positive controls despite some limitations. Dr. Fuentes said they are no longer recommending positive controls.

L. EPA Ethics Review Highlights

Michelle Arling, J.D., OPP

The group transitioned to discussing the ethics review. Ms. Arling reviewed study procedures, including recruitment, eligibility, and subsequent study activities. She indicated recruitment used an IRB-approved script and occurred through Craigslist and listservs at the same time other studies were taking place. She noted although no subjects had participated in previous studies, some candidates expressed interest in participating in multiple studies at the same time, which was allowed. Subjects were eligible to participate if they met study inclusion criteria relating to age and general health status upon verification of identity and age via government-issued identification.

At a consent meeting, participants reviewed the consent form, eligibility criteria, risks of participation, and other study materials. The consent meeting also included a demonstration of test-related procedures. The researcher asked questions to affirm participants' comprehension before obtaining a consent form signature. The demographics data summary indicated a sample size of n=44, from which 31 consented, and 27 participated at least one day.

Ms. Arling summarized test day procedures, including the three tick species and the distribution of male and female participants within each group, per species. Pre-testing procedures included a COVID-19 screening. She described the compensation provided to subjects after completion consent, training, and test day study-related activities. Respect for Subjects steps taken included informing subjects of their freedom to withdraw at any time and maintenance of subjects' confidentiality throughout the study. She listed three Substantive Acceptance Standards (40 CFR §26.1703, 40 CFR §26.1705, FIFRA §12(a)(2)(P)) prohibiting reliance on data involving intentional exposure of pregnant or nursing women or children, reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L, and use of a pesticide in human tests without fully informed, voluntary consent. She confirmed study subjects were 18 years old or older, not pregnant or nursing, and fully informed their consent was voluntary and they could withdraw at any time.

Ms. Arling then summarized IRB activity for the study, affirming the study operated in substantial compliance with the protocol as approved and amended. The study operated under Advarra IRB approval and later also received approval from the California Department of Pesticide and Regulation. EPA reviewed the protocol and submitted written reviews. The study report and appendices satisfied all IRB documentation requirements. Prior to study implementation Advarra IRB approved three study protocol amendments, none which impacted study subjects. There were 11 protocol deviations, and one unreported deviation about lack of documented pathogen-free status for one of the tick species that should have been reported to the IRB through a protocol amendment. There were no reported adverse effects in subjects, and no tick-to-human attachment occurred. She stated how many subjects withdrew and reasons for withdrawal.

Ms. Arling concluded by highlighting several lessons learned. Primary recommendations for consideration in future studies include obtaining IRB approval of all amendments to the study protocol and re-opening recruitment if needed to allow a better balance of male and female participants. She then listed the science and ethics charge questions.

M. Board Questions of Clarification

Lisa Corey, Ph.D., HSRB Chair

After Ms. Arling's presentation, Dr. Allen asked if problems encountered were issues related to deviations, noting the report was difficult to understand. Dr. Milliken indicated the power analysis suggested a minimum of 25 participants per group, but the study only had 25 participants in total. Dr. Corey mentioned discussion of these questions would occur later.

N. Public Comments

Dr. Corey invited members of the public to speak.

- **Scott Carroll**: One point I want to discuss is the importance of certification of pathogens being free from disease. Ticks were sourced from multiple sources for the first time, which was unanticipated. The wording used in the study was not intended to indicate a single source alone would be used, but incorporating the additional species source proved challenging. Our correspondence with Vertex laboratory did not reveal insufficient certification. The EPA suggestion of having full documentation to the greatest extent possible regarding tick pathogen status is something we are very interested in providing. The phrase we have used for the last decade ("certified disease free from the 2010 guidelines") is not something we should use in our consent forms because the ticks tested are not the ones subjects will encounter. Hopefully we can work together to develop more clear and accurate phrasing. We will likely implement our own screening for pathogens in the future because there are many reasons to anticipate certain pathogens will be absent from the Vertex colony. Another important issue is our frustration with drafting reports in a different report style than we have used in the past. Multiple EPA staff have requested we simplify reports by referencing the protocol. In this case, we implemented that for expediency, but I want to communicate that particularly for human subjects studies simplifying the reports is not our preference. Another point I would like to raise touches on sex ratio. Although we are relying on little indication in the literature of gender influence on tick behavior, that is not something on which we wish to rely. Factors influencing my decision to deviate from the subject group we intended to work with include working during the COVID-19 pandemic and strong guidance received from EPA statistical staff for prior studies recommending we work with the same subjects for all three species when working with multiple tick species. I made decisions about sex ratio based on those points.
- **Shawn King**: We have a higher-level question. There are times we find harmonizing recommendations and requirements from EPA's human subjects research review process with requirements for good laboratory practice compliance challenging. For example, in amendment number two, there are several formal protocol documents we reclassified as study documents, such as subject facing documents reviewed and modified by the IRB. They are reported in the final report, but instead of being associated with the protocol they are distributed as individual pages in other parts of the study report. We need clarification about how IRB recommendations

relate to good laboratory compliance. This is a challenge, and we look forward to working with EPA to resolve them.

- **A.J. Allen**: You mentioned good laboratory practices. Are you familiar with good clinical practices?
- **Shawn King**: No, I am not deeply familiar.
- **AJ Allen**: This may be something to further discuss because the pharmaceutical industry uses both good clinical and good laboratory practices. This study has a lot of similarities to clinical studies.

O. Board Discussion

Lisa Corey, Ph.D., HSRB Chair

Dr. Corey opened the floor to board discussion, starting with the science review.

- **Weiying Jiang**: Everyone on the Board has received a draft review of the study report from me. The charge question is, "Did the research generate scientifically reliable data useful for estimating the amount of time the product tested repels ticks?" My general conclusion is the study results are scientifically reliable, and I agree with EPA the study findings are useful. The study complies with the latest EPA guidelines and protocols. I do have a few specific comments. The study report lacks demographic information on subjects. Age, race, and gender were collected, but only gender information is included in the report. Secondly, the study used a nominal application rate at half a gram per 600 square centimeters, but it is unclear how this rate was selected. I am unsure of the purpose of the margin of exposure calculations. Additionally, why were generic surface areas used instead of measured values? Certain tables on page 45 provide conservative estimated exposures for general contacts of products and users. For that purpose, child exposure should be assessed because they have a greater surface area to body weight ratio. I noticed a few deviations from EPA insect test guidance, including the lack of positive or negative controls in the study. EPA guidance now specifies 3 centimeters in 3 minutes as a criterion, so the study report should clarify how this was determined. Also, the study used syringes to apply the product, but the end-use product will be in a spray canister, thus application methods are different.
- **Sri Melethil**: I looked at the charge question from a broader perspective. On page 18, EPA expresses concerns about possible underperformance of the product. We should consider this when we vote. Mean values have large statistical variability, which we need to address. The 3-centimeter value is confusing me because if you look at the picture it is hard to tell if it is 3 or 6 centimeters. Perhaps the sponsor should provide more clarifying details. During the ethics presentation, a question arose as to whether use of two different species might have affected the results. Lastly, there is no survival probability issue, so maybe the y axis should change to CPT or something similar.

Dr. Corey asked for any other comments on the scientific section.

- **A.J. Allen**: Regarding the question about gender, there is not a large enough sample to balance gender. There was limited data suggesting it was not relevant. By not including that data we now forever are taking the approach that gender balance does not apply to these studies until we collect enough data to balance gender. Wemust recognize it was a choice to not balance gender.

Dr. Corey asked Dr. Siecean-Boose, the statistics reviewer, to provide her assessment.

- **Sinziana Siecean-Boose**: The questions I asked before were directly related to my statistics review. The study aims to determine CPT after applying the recommended dose using three tick species. Subject selection and randomization occurred according to EPA protocol. The study used a final sample of 25 subjects for treatment according to the power calculation and used the specific Kaplan-Meier survival analysis to calculate CPT and 95th interval. The Agency used the same statistical methodology recommended in the protocol and found a different confidence interval but the same point estimate, and the difference was due to the transformation methods of different statistical software. The Agency used SAS and study results were similar to those of the study protocol. The standard transformation of the data is recommended according to the Agency's previous method used in simulation of the sample size versus the power analysis for the study. In this study, the proposed statistical methods are a good first step and are appropriate to answer the results question. The protocol generates reliable data. We perhaps need to conduct a statistical sensitivity analysis to obtain additional evidence and reassurance the overall study results are valid. After reviewing study deviations in relation to the collected data and the overall study results, the recommendation for a sensitivity analysis emerged according to the potential confounders and potential sources of error. We talked about gender and this limitation of the study, but from a statistical perspective lack of evidence indicating gender as a predictor in the study report is an important issue. I think it is wise to test for significance under the constant and survival function for each species. The gender ratios used for the different species are different from one another. There is indication that gender may interfere with the results. The study protocol states all ticks will be sourced from one place, but they were sourced from two places. Additionally, there are statistical differences between the CPT values of the different species that should be explored. The study states ticks used were qualified but does not explain how conclusions were made. A sensitivity analysis could explore whether age has any statistical impact on the results.

Dr. Corey opened the discussion to the rest of the group. She noted she would like to focus on the sex ratio and whether it affects the ability to answer the charge question and also on the idea Dr. Melethil mentioned about whether the values presented might be for less time than the median CPT.

- **Sinziana Siecean-Boose**: We can adjust Kaplan-Meier curves and use inverse probability weighting for one covariate, such as gender. It is still possible to use the current sample size.
- **David Williams**: There is an issue regarding acquisition of ticks from Vertex and the implication they were tested for pathogens when actually they were not. EPA knows there was an undisclosed deviation that should have been reported to the IRB before they proceeded. Participants received the false information there was no risk since ticks were certified as disease free, and then the language changed to say there was an exceedingly small risk and no need for concern, and then EPA requested adding a third species. Ultimately, the study should have conducted their own testing. I have a minor concern with saying they are collecting ethnicity in the demographics information. They say they are going to report it, but they never do. There is also the issue regarding no impact of deviation from equal sex representation. The graph showing no statistical deviation between sex of ticks is okay, but the language they use to compare publications about no sex preference by mosquitos is inappropriate because a mosquito is not a tick. Lastly, they use the word "mosquitos "in place of "ticks" throughout the report, due, I imagine, to cutting and pasting from a previous report. They need to correct that, but it is a

minor issue. The big problem I have is with incorrectly reporting the Vertex ticks were pathogen free and telling participants there was no or only extremely small risk.

- **A.J. Allen**: I am going to address the unreported deviation related to testing of ticks for tick-borne vectors in the ethics section. Regarding insufficient ethnicity or gender data, the lack of such information provides less granularity and limits the conclusions we can draw. We need to recognize conclusions simply are not as detailed as they could have been.

Dr. Corey then asked whether the group felt prepared to vote on a response to the charge question. No one disagreed or opposed.

- **Sri Melethil**: Sinziana Siecean-Boose suggested conducting a different statistical analysis. Can we vote on the charge question today without those results?
    - **Sinziana Siecean-Boose**: It is not very hard to conduct the sensitivity analysis. Results will clarify potential problems, such as why and whether it is necessary to adjust for some specific behavior or time of ticks in the laboratory. Viability between different species is obvious in results, so once you conduct a sensitivity analysis and find no significant results, we know the study is statistically sound.
    - **Lisa Corey**: Can we hear from EPA about this? There is a request for an additional sensitivity analysis to determine whether it has any effect on results. Should lack of this additional analysis prevent us from voting on a response to the charge question today?
    - **Michelle Arling**: Tom should answer whether we can vote.
    - **Tom Tracey**: That decision is up to the chairs.
    - **Sinziana Siecean-Boose**: The methods used is a good approach as a first step. To trigger conclusions and complete the statistical part, it is necessary to conduct an additional sensitivity analysis.
    - **Lisa Corey**: Do we need to know results from that additional analysis, or can we include that in the recommendation for EPA to address?
        - **Sinziana Siecean-Boose**: That decision is up to the whole Board.
    - **A.J. Allen**: Could we frame the wording so that it is subject to the recommendations or dependent on evaluation of results based on this additional analysis?
        - **Lisa Corey**: Yes, we have done that in the past. This can be a recommendation for EPA to undertake.
    - **Sinziana Siecean-Boose**: I am very new to this and am simply providing my opinion. The decision lies with the Board.
    - **Sri Melethil**: If this vote makes a recommendation to the EPA, do they have to follow through?
        - **Lisa Corey**: EPA takes recommendations into consideration.
        - **Sri Melethil:** Is it binding?
        - **Michelle Arling:** No.
        - **Sri Melethil**: Okay, then I am concerned because Sinziana Siecean-Boose said it might throw a new light on the data. I would like to make it be contingent instead of a full recommendation.
- **George Milliken**: We could use the Kaplan-Meier model to include gender, but with our small sample sizes we will not have much power in detecting a difference among those two genders. Unless we design a study to detect a difference, we can only talk about representation, not about why we need to have that representation

    - **Chad Cross**: I agree completely. George, we will not have enough data to examine sex differences.
- **Lisa Corey**: We can phrase points of discussion as recommendations to EPA and phrase our response to the charge question as requiring incorporation of our recommendations.

Dr. Corey read the charge questions and proposed the following response. "The research summarized in 'Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions' generated scientifically reliable data that is useful for estimating the amount of time the product tested repels ticks, provided the recommendations provided by the HSRB are considered."

- **A.J. Allen**: Could we add, "provided the recommendations and limitations"? I think the inability to evaluate gender effects is important.
    - **George Milliken**: Do we need to specify they used three species of ticks?
        - **Lisa Corey**: I do not think so. EPA?
        - **Michelle Arling**: That is correct, Lisa.
    - **AJ. Allen**: Usually, we might say "the recommendations and limitations provided by the IRB and the EPA" because they have a substantial list.

Dr. Corey modified the text and read the revised response to the charge question, which was "The research summarized in 'Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions' generated scientifically reliable data that is useful for estimating the amount of time the product tested repels ticks, provided the recommendations and limitations provided by the HSRB and EPA are considered."

- **George Milliken**: I have a problem with placing ticks on children. There is no data on children, but if this is approved, children will be tested. That is a concern of mine.
    - **A.J. Allen**: Under the ethics rules, we are required to conduct these studies only on non-pregnant adults. That is a reasonable approach. Justification for this is the ability to extrapolate results from adult studies to the pediatric population.
    - **Lisa Corey:** We have a recommendation to include a discussion of that following our science review.
    - **George Milliken**: I just know potentially 50 percent of the use of this product will be on children, so someone needs to evaluate the safety.
    - **Lisa Corey**: This is outside of the scope of what we are doing here, but I agree.
    - **A.J. Allen:** I will add additional resources to the chat.
- **Sinziana Siecean-Boose**: What does the committee think about results presented for the CPT analysis? The fact that CPT time is doubled compared to the other two, what would be the reason? Is it something related to the ticks? Does this reflect the fact that we have deviations from the product goal and the deviations may change the results? What does the Board think?
- **Sri Melethil**: These are all wonderful questions. If we approve the charge question, then basically the sponsor can market it. Is that correct? What is the danger to the public if we say yes to the charge question?
    - **Michelle Arling**: Our response to the charge question simply indicates whether the data are ethically and scientifically valid. Following this, EPA will consider this and other data to review and examine the totality of information available before deciding whether the product can be marketed.

- **Lisa Corey**: Does that help?
- **Sri Melethil**; Yes.

Dr. Corey read the updated response to the charge question, which was "The research summarized in 'Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions' generated scientifically reliable data that is useful for estimating the amount of time the product tested repels ticks, provided the recommendations and limitations provided by the HSRB and EPA are considered." She then asked whether everyone was prepared to vote. Everyone on the call approved the response. Dr. Corey then moved the conversation to the ethics review and asked Dr. Allen to provide his review.

- **A.J. Allen**: I distributed a draft of these comments prior to this meeting. We must rely on data that is not involved with exposure to pregnant women, fetuses, and children. We also must rely on research conducted in substantial compliance with all applicable revisions and comply with the federal insect and fungicide act. The youngest subject was 20 years old, so that meets the requirement of not including children. No subjects were pregnant. Pregnancy testing was conducted in private, and results shared with only one person to confirm no one was pregnant. Urine testing involved does have a wait period where a false negative could occur, but there is not much we can do about that. This study was not funded by EPA but all essential elements of consent required in EPA regulations are present. This study's protocol received IRB approval and was subject to further review through additional amendments. EPA and the HSRB reviewed the protocol and provided comments to the sponsor. The sponsor has either addressed them or left comments as to why they did not, and the investigator provided a scientific response to questions brought by the HSRB regarding ethnicity. However, satisfying IRB protocol requirements does not necessarily resolve ethical questions about representativeness of the study population. We have difficulty in evaluating this because there is no data presented on ethnicity. We do have age data, but we do not have data on children or on anyone over 35, which is a limitation of the study. Recruitment was tailored to students at UC Davis through newsletters, which skews enrollment towards younger populations. The review is scientifically acceptable, but there are two limitations regarding compliance with regulations. They are related to information not included in the report on equitable selection of subjects and the significant unreported protocol deviation of use of ticks not screened for tick-borne illness vectors. There were many deviations regarding the use of ticks from Vertex not screened for vectors of tick-borne illnesses, which is not consistent with the protocol and raises concerns about safety risk. Ticks were raised in such a way it is unlikely there would be vectors of tick-borne illnesses present, but we do not have confirmation. I have no reassurance regarding safety because all the illnesses from a tick bite are ones that will have an incubation period of more than a few hours, so a systematic follow-up is needed. Some uncertainty remains because we do not have that data, but this was mitigated because subjects were trained to remove ticks and recognize tick behavior that can lead to attachment behavior. The amount participants were paid is consistent with other studies. The study made a change at the request of subjects to issue only one check at the very last session, which was noted in the protocol deviations. Overall, my recommendation is this study's efficacy was in substantial compliance with the applicable regulations.

Dr. Corey asked Ms. Arling to display the charge question and asked whether there were any questions relating to the ethics discussion. There were none. She then read a proposed response: "Based on its review of the materials provided by EPA and subject to the limitations and recommendations of the EPA

and HSRB, the HSRB concludes that the 'Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions' was conducted in substantial compliance with the applicable requirements of 40 CFR part 26, subparts K and L."

Dr. Corey asked for comments on the proposed response to the charge question. There were none. Everyone on the call voted to approve the response. Dr. Corey stated she would include the approved language in a report and distribute it to the leads for each section.

P. Adjournment

The meeting adjourned at 5:00 p.m., EDT.

Attachment A: HSRB Current Committee Membership

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

Attachment B: Federal Register Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL–9328–01–ORD]

Human Studies Review Board; Notification of Public Meetings

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of public meeting.

SUMMARY: The Environmental Protection Agency (EPA), Office of Research and Development (ORD), gives notice of the 2022 public meetings of the Human Studies Review Board (HSRB). The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of third-party human subjects' research that are submitted to the Office of Pesticide Programs (OPP) to be used for regulatory purposes.

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

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

Meetings will be held each day from 1 p.m. to 5:00 p.m. Eastern Time. For each meeting, separate subsequent follow-up meetings are planned for the HSRB to finalize reports from the three-day meetings. These meetings will be held from 2 p.m. to 4 p.m. Eastern time on the following dates: March 17, 2022; June 16, 2022; September 14, 2022; and December 14, 2022.

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

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

SUPPLEMENTARY INFORMATION:

Background

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

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

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

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

How May I Participate in this Meeting?

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

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

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

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

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

Dated:

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