EPA Human Studies Review Board (HSRB)
April 3, 2025 Meeting Minutes

Committee Members: See Appendix A: HSRB Current Committee Membership.
Date and Time: Thursday, April 3, 1:00 to 5:00 p.m. EST
Location: Via Zoom
Purpose: The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subject research.
HSRB Website: https://www.epa.gov/osa/human-studies-review-board

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Thursday, April 3, 2025

A. Meeting Topics and Charge Questions

Topic: "Evaluation of Topically Applied Insect Repellent Products Containing Oil of Lemon Eucalyptus (Citriodiol) Against Mosquitoes in the Field." March 22, 2024. Sponsored by Citrefine International Ltd. Moorfield Rd. Yeadon, Leeds. LS19 7BN U.K. MRID 523504. Protocol version 0.1 as amended March 11, 2024. IRB approved March 7, 2024. 117 p.

Charge to the Board – Science: Is the protocol "*Evaluation of Topically Applied Insect Repellent Products Containing Oil of Lemon Eucalyptus (Citriodiol) Against Mosquitoes in the Field*" likely to generate scientifically reliable data, useful for estimating the amount of time each of the products tested repels mosquitoes?

Charge to the Board – Ethics: If amended to address the EPA's and the HSRB's recommendations, is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

B. Convene Meeting and Introduction of Members

Emily Sokol, designated federal official (DFO), EPA HSRB, Office of Science Advisor, Policy, and Engagement (OSAPE)

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

HSRB members
Julia Sharp, Ph.D., Co-Chair (National Institute of Standards and Technology) Philip Day, Ph.D., Co-Chair (University of Massachusetts, Chan Medical School) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Gretchen Bruce, DABT (Intertox, Inc.) Chad Cross, PhD, MFT, PStat® (University of Nevada, Las Vegas) Nicole Deming, J.D., M.A. (Case Western Reserve University, School of Medicine) Richard Feinn, Ph.D., M.A. (Qinnipiac University) Thomas Gillam-Shaffer, MPH (Michigan Public Health Institute/State of Michigan Partnership) Weiying Jiang, Ph.D. (California Environmental Protection Agency) Thomas Lewandowski, Ph.D. (Gradient) Srikumaran Melethil, Ph.D., J.D., (University of Missouri-Kansas City) George Milliken, Ph.D. (Milliken Associates, Inc.) Joseph Tuminello, Ph.D. (McNeese State University) David Williams, Ph.D. (Oregon State University)
EPA staff members
Emily Sokol (EPA, OSAPE) Tom Tracy (EPA, OSAPE)

Michelle Arling (EPA, Office of Pesticide Programs [OPP]) Stephanie Cooke (EPA, Program in Human Research Ethics and Oversight [PHERO])) James Nguyen (EPA, OPP) Monique Perron (EPA, OPP) Shweta Sharma (EPA, OPP) Geoffrey Sinclair (EPA, OPP) Monique Tadeo (EPA, PHERO) Philip Villanueva (EPA, OPP)
Members of the public, representatives of research sponsor, and research team
Sarah Dewhirst (ARCTEC, Public Commenter) Genevieve Faherty (Citrefine International Limited) Ali Goldstone (ICF, Contractor Support) Josh Hunnicutt (SC Johnson) Afroditi Katsigiannakis (ICF, Contractor Support) Dana Lateulere (The Acta Group) Katie Lenae (ICF, Contractor Support) Kimberly Nemeth (Proctor & Gamble) Emily Pak (ICF, Contractor Support) Kristine Styer (Woodstream Corporation) Kendall Torres (SC Johnson) Daniel Usry (SC Johnson) Alicia Werner (Citrefine International Limited) Angelina Winnett (ICF, Contractor Support)

C. Meeting Administrative Procedures

Emily Sokol, DFO, EPA HSRB, OSAPE

Ms. Sokol reviewed the Zoom platform tools and features and stated that the purpose of the meeting was to review and discuss the paper sponsored by Citrefine International Ltd., (2024) "*Evaluation of Topically Applied Insect Repellent Products Containing Oil of Lemon Eucalyptus (Citriodiol) Against Mosquitoes in the Field*." Ms. Sokol noted that the minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of April 3, 2025.

D. Introduction of EPA Staff

Michelle Arling, J.D., OPP

Ms. Michelle Arling introduced herself and the members of the EPA OPP staff to the Board.

E. Updates from EPA HSRB Review Official

Monique E. Tadeo, HSRB Review Official, PHERO

Ms. Monique Tadeo introduced herself to the Board and noted there were no updates to share with the meeting participants. Ms. Tadeo asked Ms. Stephanie Cooke to introduce herself to the

HSRB Board members.

F. Opening Remarks and Meeting Process

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

Dr. Philip Day welcomed the Board and reviewed the meeting's logistical procedures. Dr. Day stated that the purpose for this meeting was to discuss the Citrefine International Ltd., (2024) protocol. He stated that the meeting would begin with presentations from the EPA followed by public comments submitted and an HSRB discussion of the science and ethics review.

G. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Arling noted that there were no topics scheduled for the Board to discuss over the summer, and that there were no current updates to present to the Board.

H. EPA Science Review Highlights

Shweta Sharma, Ph.D., OPP

Dr. Shweta Sharma introduced herself to the Board and reviewed the outline for the presentation. She stated that the presentation would cover the Board's review of the scientific aspect of the study protocol for the field study of the topically applied mosquito repellent. The study protocol, sponsored by Citrefine International Ltd., is designed in accordance with Office of Chemical Safety and Pollution Prevention 810.3700 Guideline and efficacy standard rule for efficacy testing of invertebrate pests.

Dr. Sharma then presented slide 3, which displayed the protocol summary. The objective of the proposed study is to test the residual longevity of skin-applied repellent formulations against mosquitoes in the field using a sample size of 13 treated human subjects. Additionally, the study is in line with the EPA Product Performance Test Guidelines, and the products are tested in three genera of mosquitoes (*Culex, Aedes,* and *Anopheles*).

She then displayed the definitions for endpoints and measures on slide 4. Complete protection time (CPT) is the time from application of a repellent until efficacy failure as it is defined in each study. For example, the time from application until the first efficacy failure even confirmed within 30 minutes by a second similar event. First Confirmed Landing (FCL) is one confirmed landing followed by second landing within 30 minutes.

Dr. Sharma provided a summary of the relevant EPA Guidelines on slide 5. A landing is the act of flying or jumping insect or other arthropod alighting on human skin without probing or biting. Attractiveness testing landing pressure is completed before the test. Subjects expose their untreated forearms to the target insects in a test cage to establish their attractiveness. The landing pressure during attractiveness testing is five mosquito landings in 1 minute or less. Field testing landing pressure of the target species is at least one mosquito landing within 1 minute or five

landings within 5 minutes or less. The EPA recognizes that the existing guideline mentions at least one mosquito landing within 1 minute, but the Agency recommends that there are five landings in 5 minutes or less as the current guideline for an efficacy study. Dr. Sharma noted that the Agency is working on updating the guidelines.

She displayed a summary of the EPA Guidelines pertaining to the protocol on slide 6. The EPA's rule "Pesticide Product Performance Data Requirements for Products Claiming Efficacy Against Curtain Invertebrate Pests" specifies that testing in three genera (*Culex, Aedex,* and *Anopheles*) is required. The testing must also include one of the following *Culex* species: *Culex pipiens*, *Culex quinquefasciatus*, or *Culex tarsalis*. The study must also include one of the following *Anopheles* species: *Anopheles albimanus*, *Anopheles freeborni, Anopheles gambiae, Anopheles hermsi, Anopheles punctipennis, Anopheles quadrimaculatus, Anopheles stephensi*. Additionally, the study must include one of the following *Aedes species*: *Aedes aegypti* or *Aedes albopictus*.

Dr. Sharma presented a summary of the protocol submitted to the EPA. The objective is to test residual longevity of two skin applied repellent formulations against mosquitoes in the field using a sample size of 13 treated subjects. The sample size is recommended by the EPA power analyzers, and the study is in line with the EPA's Product Performance Test Guidelines. This product is tested against natural populations of mosquito species of public health importance within the genre across two field sites in the United States. Additionally, the product has already been registered with the Agency (EPA Reg No. 84878-2). In 2002, the EPA issued an unconditional registration of lemon eucalyptus citadel oil for use in dermally applied repellents. The Agency approved a 40 percent oil spray formational and a 30 percent lotion formulation at the same time.

Product No. 84878-2 contains 30 percent Oil of Lemon Eucalyptus (OLE) as a pump spray formulation in aerosol format. This product is registered with the EPA by Citrefine International Ltd. in 2008 as a pump spray formulation and is intended to be sold in an aerosol format. The second product contains 10-15 percent OLE and is a liquid emulsion formulation also to be sold in an aerosol format that closely resembles the formulation currently sold in Europe. Also, the toxicity profile of product 84878-2 is based on toxicity profile of p-menthane-3,8-diol (PMD), a key component of OLE and was previously reviewed by the EPA in 2023. The Agency concluded that there were no risks of concern from the use of PMD in insect repellent products when applied to human skin. In addition, the 2018 HSRB report stated that PMD has a relatively inodorous toxicology profile when applied topically with no relevant toxicity concerns. Dr. Sharma stated that the Agency is not concerned about the risks of exposure to human subjects exposed to the products containing OLE as an active ingredient. Therefore, a quantitative risk assessment calculation, which is Mode of Exposure (MOE) in this case, is not required as no toxic endpoint of concern is identified through the dermal route of exposure at or below the limit dose of 1000 mg/kg/day.

Dr. Sharma displayed a list of pre-test activities on slide 8, which included the recruitment process, informed consent, inclusion and exclusion criteria, and withdrawal criteria.

She then discussed the pre-test laboratory activities on slide 9. Dr. Sharma stated that the attractiveness test is conducted using arm-in-cage method with pathogen-free mosquitoes that have never had a blood meal. If the subject fails to receive five landings in 1 minute, the test is repeated two more times with a new batch of mosquitoes. Additionally, if the subject still fails to achieve the threshold of landing rate, he/she is disqualified from participating in the study. In the aspirator training, subjects who prove to be attractive to mosquitoes are trained to use aspirators for capturing mosquitoes before they probe or bite. The training is conducted in a screened free-flight cage. Furthermore, subjects are paired with a partner and instructed to dress in long sleeved shirts and pants, gloves, and disposable head nets. The pairs will practice for no longer than 1 hour until they skillfully aspirate mosquitoes from their partner's leg. If proficiency is not achieved after 1 hour, the subject is disqualified and unable to participate in the study. Finally, Dr. Sharma discussed the measurement of skin surface area for the test. The skin surface of the left and right lower leg of each test subject is calculated by multiplying the length from knee to ankle and the average circumference of the leg. The leg circumference is measured from two equidistant points. The amount of product applied to each subject is adjusted to their lower legs' surface area.

Dr. Sharma described the field site qualifications on slide 10. Two field sites are selected based on the presence of target mosquito species and absence of mosquito-borne pathogens within 25 miles of the proposed sites in the 4 weeks preceding field test initiation. The potential sites are monitored for 4 weeks prior to test initiation using DC Gravid Traps, CDC Light Traps baited with carbon dioxide, and/or BGS traps to document mosquito diversity, abundance, and activity. The temporal distribution of mosquito species is assessed using BGS traps equipped with counters as a way to assess mosquito activity during the day closer to the test days. The study director also coordinates with the local health department and mosquito control districts at least weekly for 2 months before field testing begins to confirm the absence of reported mosquito-borne disease cases in humans within 25 miles of planned test site, and again 1 week before each test day is conducted.

Mosquitoes captured during site monitoring are screened for detection of pathogens using polymerase chain reaction technique. *Culex* is tested for West Nile Virus, St. Louis Encephalitis Virus and Eastern Equine Encephalitis Virus (EEEV). *Aedes* mosquitoes are tested for EEEV and Zika Virus. Additionally, *Aedes* are also tested for Chikungunya and/or Dengue if there is an identified threat. The products are tested at two field sites against mosquito species of public health relevance within the genera *Aedes, Anopheles,* and *Culex.*

Dr. Sharma detailed the experimental design on slide 12 and presented an image of a three-by-three Latin square. The experimental design is a Latin square design, and nine collection stations are set up at the field site with minimum distance of 3 meters between each station. Paired test subjects are randomly assigned to the collection stations. Dr. Sharma detailed the randomization of the tests. 20 subjects are randomly selected from a pool of 30 participants. Of the 20 randomly selected subjects, 13 are randomly assigned as treated subjects, two as controls, and the

remaining five as alternates on the day of efficacy testing. By order of arrival, the first seven males and first seven females to arrive to the test facility, plus the eighth male or female, are assigned as test subjects on repellency testing day. The remaining subjects who arrive later are assigned as alternates. Each product is tested at both field sites on two separate days, 1 day per site. Application of treatment to either the left or right leg of treated subjects is also randomized. Additionally, the treated subjects are paired and randomly assigned to the nine collection stations. The two controls are not paired together, but rather each control subject is randomly paired with one staff member. Likewise, the unpaired treated subjects are randomly paired with a staff member. Study staff perform counts but do not expose their own legs.

She then described the field test on slide 14. For the compliance check, subjects are contacted within 48-72 hours prior to test day for verification of their health and compliance with test conditions. The subjects are reminded to not use insect repellents and scented soaps, shampoo, deodorant, perfumes, or cosmetics, to not drink alcohol, smoke, chew tobacco, or engage in vigorous exercise for 24 hours immediately preceding the study, and to wash only with hot water and the unscented soap provided at the attractiveness test meeting. In addition, subjects are asked to arrive at the test facility approximately 3 hours ahead of the efficacy test initiation to allow time for registration, randomization, product application, and travel to the test site. Upon arrival at the test facility on the day of testing, subjects are checked for eligibility and for their compliance with test conditions. Subjects are also be reminded that they can withdraw at any time and request that their data not be used without affecting their compensation.

Prior to product application, the lower leg of treated and control subjects is washed with unscented soap and water and rinsed with a water solution of 70 percent isopropyl alcohol. Dr. Sharma noted that the amount of product needed to be applied is calculated by dividing the area of the lower leg by 600 cm^2 and multiplying the result by 1 gram for a target dose of 1.67 mg/cm^2. A beaker is then weighed, and its weight recorded. The previously calculated and recorded individual dose per subject is weighed by spraying an aliquot of the repellent into the beaker and placing the beaker on a balance. Next, the product is applied evenly over the lower leg from the ankle to the knee using a single gloved finger to ensure uniform coverage. After application, the spatula/beaker is reweighed until it contains less than 0.05 grams of product. The excess product is weighed and recorded as disposed of in the product accountability log. Finally, the weight of the glove before and after testing is recorded. Dr. Sharma continued to detail the exposure delay and sequence of exposure. Exposure delay is proposed to be 1 hour from product application. Human landing collection 5-minute exposure periods will begin 1 hour after product application.

She finished the description of the field test on slides 16 and 17. The mosquito landing pressure is determined before the treated subjects expose their legs. First, control subjects expose their lower leg for 5 minutes or until five landings occur, whichever occurs first. The control subject can then cover the lower leg. Untreated control subjects monitor landing pressure throughout the test. On slide 17, Dr. Sharma specified that once both control subjects have received five

landings, treated subjects expose their treated skin for a 5-minute period at 30-minute intervals. This sequence of exposures is repeated for each control and treated subject until he/she experiences FCL or reaches the end of the test day, whatever happens first. The time of the landings on control and treated subjects, and when the threshold number of five landings occur on control subjects are recorded under the supervision of a staff member. Mosquitoes landing on test subjects are collected for taxonomical identification and pathogen screening.

Dr. Sharma described the stopping criteria for field testing on slides 18 and 19. On slide 18, she detailed the criteria for skipping exposure periods and ending testing. Low landing pressure is defined as fewer than five landings on either of the two controls in a 5-minute exposure period. The test stops if there is insufficient landing pressure on controls. If there are four non-consecutive exposure periods with low-landing pressure or due to bad weather, the test day is stopped, and testing is re-arranged. Additionally, if there are three consecutive exposure periods with low-landing pressure or due to bad weather, the test day is stopped, and testing is re-arranged. Testing ends when more than half of the test subjects experience the first confirmed landing. A median CPT (mCPT) is established if there is time to treatment failure data for half the subjects. At this point, testing ends. On slide 19 Dr. Sharma described the criteria for use of right censored data and end testing. Participants that withdraw during the test day have their data included in the statistical analysis as right censored data. Furthermore, withdrawn subjects whose data are right censored is not replaced. If three or more participants on an individual test day withdraw before they record treatment failure, the study director makes the decision as to whether to continue testing and include these right-censored values in the analysis or end the test day and attempt to repeat at a later date. Should this occur, the data is reported but not included in statistical analysis.

She detailed the assessment of CPT on slide 20. A minimum of three consecutive exposure periods should occur before subjects experience an FCL. If an FCL occurs within the first three exposure periods, the CPT is counted as 0 hours. If a single landing on a test subject during an exposure period is followed by a missed exposure period (due to bad weather) then the first landing is treated as a confirmed landing. Additionally, if a confirmed landing occurs during an exposure preceded by a period of low landings or by a missed exposure period due to bad weather, then CPT is recorded as the earliest time point in that preceding period.

Dr. Sharma described the statistical analysis used in the field test on slide 21. The sample size of 13 treated subjects is employed according to the EPA recommendations for sample size. The mCPT from a sample of 13 subjects is calculated using the Kaplan-Meier survival analysis. The 95 percent confidence interval (CI) of the estimated mCPT is calculated with the log-log transformation applied to survival function and Kaplan-Meier survival curves are presented in the study report.

Slide 22 details the compliance of testing with current scientific standards. The protocol complies with the requirements of Good Laboratory Practices as set forth in 40 Code of Federal Regulations (CFR) Section 160. Testing is conducted in conformity with OPPT's 810.3700

Guideline for Testing of Insect Repellents Applied to Human Skin and the Efficacy standard rule for efficacy testing of invertebrate pests.

Dr. Sharma detailed the EPA's assessment, comments, and recommendations for the test:

1) A more detailed plan for site monitoring is recommended.
2) Location of proposed field sites should be included and the distance between sites needs to be ensured to greater than the flight distance of mosquito species encountered at the site(s).
3) Samples of raw data sheets for recording mosquito attractiveness data should be appended to the study protocol.
4) A sample of data sheets for difference in weight of finger cots before and after product application should be appended to the study protocol.
5) The proposed label should be appended to the study protocol for review of label efficacy claims to be supported with data.
6) The criterion for determining proficiency/competence in the use of aspirators for catching landing mosquitoes should be established and included in the protocol.
7) Mosquito rearing procedure and maintenance condition for the laboratory experiment needs to be explained.
8) Specific procedures regarding the mosquitoes used in the laboratory should be described in the protocol.
9) The applicant needs to explain how stratified selection will be performed while still maintaining randomness.
10) Testing in three genera (*Culex, Aedes, and Anopheles*) of mosquitoes is required.
11) The applicant should consider the adequacy of replacing subjects into testing who withdraw thus to minimize right censoring and avoid reducing sample size.
12) The specific concentration of active ingredient should be reported in the study protocol.
13) The endpoint and the definition of CPT is inconsistent and incorrect.
14) The protocol needs to be amended to include the formula to convert from weight to volume.
15) The number of trained technicians applying the test substances to subject's legs needs to be disclosed.
16) Transportation of the subjects to the field site and product application before the start of the study needs to be explained in detail.
17) The protocol should include results from Tier I mammalian toxicity data for each product formulation.
18) The MOE calculation for each proposed formulation must be addressed in the protocol.
19) Explanation is needed to clarify what happens to the partner of one treated subject who gets FCL or withdraws before end of testing.
20) Explanation is needed to clarify whether the first hour after product application will be counted as repellent efficacy time.

Dr. Sharma ended the presentation with the charge question. She asked the Board for questions.

I. Board Questions of Clarification

- **Srikumaran Melethil:** Looking at this from a consumer perspective, if I apply a repellent, I do not want mosquitoes to land on or bite me. How does this protocol meet that real life situation?
    - **Michelle Arling:** Can you clarify your question?
    - **Srikumaran Melethil:** If you have a mosquito repellent, the goal is that no mosquitoes land on you or that less mosquitoes land on you. How do the details presented in the protocol address the issue of mosquitoes landing on you?
    - **Michelle Arling:** The protocol talks about the purpose of this research into repellents and how the research should be conducted to investigate how long the repellent will last.
- **Srikumaran Melethil:** In reading the science component of this protocol, there are 13 treated and two controls, why is there such a big difference in those numbers? How does this protocol replicate in realistic conditions in a meaningful way?
    - **Shweta Sharma:** Are you concerned about the sample size of 13?
    - **Srikumaran Melethil:** No, my question is how does the control work?
    - **Michelle Arling:** The purpose of the control subjects is to make sure that there is adequate landing pressure, so we can verify that there are active mosquitoes foraging in the field at the time the research is conducted.
    - **Srikumaran Melethil:** And that has no bearing? Is the effectiveness of the repellent not an endpoint of this?
    - **Philip Day:** That is the trial endpoint of the test. The purpose of the study is to see what the CPT of this formulation is. You can see that in Section 3.1 of the protocol. Did you have a specific question about the science review portion of the meeting?
    - **Srikumaran Melethil:** No, thank you.
- **David Williams:** On page 11 of the EPA science review, it states that the range is greater than or equal to 15 km; therefore, the distance between field sites should not be less than 15 km. I think it was meant to say less than or equal to 15 km because if it is greater than 15 km, then having the protocol say less than 15 km does not make sense.
    - **Julia Sharp:** This is on slide 24.
    - **Shweta Sharma:** The fields site should not be less than 15 km.
    - **David Williams**: The justification you have does not make sense if it is greater than 15 km. If it is less than 15 km, then the justification would make sense.
    - **Shweta Sharma:** We are asking registrants to have locations that are greater than 15 km apart.
    - **David Williams:** You are saying that it should not be less than 15 km?
    - **Shweta Sharma:** Yes, it should not be less than 15 km.

- **David Williams:** The publication said the field range could be much larger than 15 km, so the justification does not hold. On page 28 under endpoints and measure's part b it states that there are two alternative subjects. Should that list five alternative subjects?
    - **Julia Sharp:** We are currently just asking for clarifying questions to the EPA. This statement can be brought up during the review comments and recommendations section of the discussion.
- **Weiying Jiang:** In a slide, you mentioned that quantitative risk assessment is not needed. The Board reviewed a very similar protocol last year that contained OLE as the active ingredient, and from that review, the MOE and risk assessment were conducted. What is the rationale for not needing a risk assessment for this protocol currently under review?
    - **Monique Perron:** The Agency's recommendation is that an MOE and risk assessment should not occur because in our risk assessments, we do not have points of departure. We support a qualitative assessment for the OLE.
    - **Weiying Jiang:** Is it because this is a biopesticide and is currently going through the biopesticide registration process rather than the traditional process?
    - **Monique Perron:** That was based off the toxicological database that we have available that demonstrated that there are no adverse effects at relevant doses for human health risk assessment.
- **Thomas Gillam-Shaffer:** Is the control group roughly equal to the two sample collection sites exposed groups? Is that why the experiment is designed that way? How many participants are exposed at each sample collection site?
    - **Michelle Arling:** At each site there will be 13 treated participants and two control participants to monitor landing pressure.
- **Gretchen Bruce:** Regarding the distance between sites, what is the rationale of the distance between sites as opposed to the distance between the treated subjects, which is only a few meters. Why does the distance between sites need to be 15 km or more?
    - **Shweta Sharma:** All species of mosquitoes have a flight distance of about 15 km. Having the distance between the two sites be at least 15 km is to make sure that the same mosquitoes do not fly between the two sites.
    - **Gretchen Bruce**: Is it not a concern if the mosquitoes fly within a site between the subjects?
    - **Philip Day:** Once a mosquito lands, it would be aspirated and destroyed per the protocol.

J. EPA Ethics Review Highlights

Michelle Arling, J.D., OPP

Ms. Arling shared the Ethics Review entitled "*Evaluation of Topically Applied Insect Repellent Products Containing Oil of Lemon Eucalyptus (Citriodiol) Against Mosquitoes in the Field: Ethics Review.*" She thanked the HSRB Board members for their preparation work. On slide 2, "Value to Society," Ms. Arling reaffirmed that the study supports registration of products and

tells users the estimated protection time of the repellent, particularly for labeling. Then, on slide 3, Ms. Arling discussed the recruitment process, including United States testing location selection and recruitment advertising methods. Ms. Arling explained the use of Facebook, Google, and flyers for advertising and providing basic information about the study such as length and number of visits. She then shared the protocol's enrollment approach. Ms. Arling explained that recruitment continues until at least 30 individuals who meet criteria to consent and participate are identified. She specified that all requirements except the attractiveness test and aspirator proficiency must be met to be considered. Of the 30 participants for each product and each site, 20 are needed to have 13 test subjects, two untreated controls, and five alternatives. She then shared the protocol's discussion of demographics on slide 5 and stated that efforts are made to recruit a demographic that is reflective of the population of repellent product users. Ms. Arling acknowledged the limitation of facilitating the testing in English and thus recruiting English speakers only. The study director may continue recruitment until a broader, reflective sample is identified or proceed with the 30-subject pool and stratify the selection to align with protocol as closely as possible.

Slide 6 covers the inclusion and exclusion criteria required by the study. Ms. Arling explained the rationale for including those able to stand outside for periods of time and good general health, particularly due to heat. The good health requirement is discussed in more detail in the protocol and includes good cardio and respiratory health. For the exclusion criteria, Ms. Arling emphasized the importance of participant's nonparticipation in other studies for at least 3 months after an interventional study.

Ms. Arling addressed the attractiveness and aspirator use training, specifying that these criteria cannot be met until subjects agree and consent, as they require field testing. The subject gets three times to test whether they are attractive to mosquitoes through arm-in-cage testing. Additionally, she noted that aspirator use training and proof of proficiency is necessary to proceed to participation. Ms. Arling then discussed the consent process outlined on slide 8. She explained that a one-on-one meeting for staff to confirm participants' identifications and discuss the entirety of the consent form occurs. This process, as well as providing participants with a copy of the form, ensures the subject has received all relevant information. Staff remind participants that they can remove consent or ask questions at any time. Finally, Ms. Arling discussed staff asking questions related to a subject's comprehension.

She then transitioned to compensation, presented on slide 9, which is 10 dollars per hour for the consent process. All subjects are paid in cash or given a prepaid card at the end of each visit. Ms. Arling then covered plans in case of an adverse reaction to test materials. The protocol calls for minimizing adverse reactions by excluding subjects with allergies to a variety of relevant products or with known or active skin conditions. She explained that treated areas are washed after each session and that a subject is removed immediately if there are issues, such as a cut, during the process.

Slide 12 covers field trapping, mosquitoes, and vector-borne illnesses. Ms. Arling discussed how

mosquitoes are trapped and tested prior to the study. She also noted the use of protective equipment and aspiration tools for subjects to ensure that non-exposed areas are safe, and mosquitoes are aspirated prior to biting. Ms. Arling then addressed the physical discomfort of mosquito bites, which is managed by excluding those who are allergic or hypersensitive. She also explained that in the case of a bite, study staff provide a topical antihistamine upon request. Ms. Arling discussed the challenges of participants being outdoors. She listed the use of water, snacks, and a cooled, screened sitting area to mitigate the effects of being outside over a long period of time. First-aid staff are on site particularly with special attention to subjects with a history of heat sensitivity or heat stroke. Other risks include pregnancy tests and results as well as COVID-19 risks and loss of confidentiality. The challenge of pregnancy testing and results are mitigated by having same-gender staff provide results in a private area and allowing for self-certification for those not considered capable of childbearing. Ms. Arling covered COVID-19 precautions, which are to follow CDC recommendations for timing and exclusion. While there are no direct benefits to participants, public benefits of the study are new repellent information. Overall, study risks are low and reasonable compared to the benefits of gained knowledge.

Next, Ms. Arling reviewed the steps of the Independent Ethics Review of the protocol. The Western Institutional Review Board (WIRB) reviewed the study, and Ms. Arling discussed their qualifications. She explained that the WIRB are registered with the Office for Human Research Protections and hold federal-wide assurance for the protection of human subjects. As per the Human Studies Rule, documentation was provided to the EPA.

Ms. Arling then highlighted the EPA comments related to the Ethics Review. The EPA recommended expanding to Spanish speakers to provide more fair access to participants. Next, she suggested that first-aid staff conduct a skin check to ensure that there are no conditions that disqualify participants rather than relying on self-report. Additionally, the EPA recommended raising the age limit, as there is a broader user population for repellents. Though the protocol notes they can remove subjects for any reason, the EPA suggested including clear examples and reasoning to prevent confusion. Ms. Arling called for further clarity surrounding compensation, particularly for transportation wait times or other delays. She then highlighted the EPA's concern around user data privacy, and emphasized the need for clear language that participants may withdraw their data at any time and more information on transportation between the field and testing sites. Ms. Arling also discussed the need for additional information in the consent form about female subjects not of childbearing potential to self-certify and ensure it aligns with changes to the protocol.

Ms. Arling then addressed the Ethics Standards and Findings beginning on slide 24. She explained that this protocol is for third-party research that involves intentional human subject exposure. She then identified the relevant standards and acts related to pesticide law such as the 40 CFR 26, Subparts K and L, and the Federal Insecticide, Fungicide, and Rodenticide Act 12(a)(2)(P). In addition to the EPA's Ethics review, an included attachment addresses the CFR standards in a point-by-point evaluation. Ms. Arling identified the requirements needed to

comply with Ethical Standards, and stated that the requirements of Sections 26.1111, 26.1116, 26.1117, 26.1125, and 26.1203 meet the EPA's recommendations.

She concluded the Ethics Review with a summary on slide 27. The EPA found risks for the study "*Evaluation of Topically Applied Insect Repellent Products Containing Oil of Lemon Eucalyptus (Citriodiol) Against Mosquitoes in the Field*" have been minimized and are reasonable compared to the benefits. Ms. Arling stated that with the EPA's comments addressed, there are no deficiencies, and the study will likely meet standards. She then presented the charge questions.

K. Board Questions of Clarification

Dr. Day asked the Board for any questions surrounding the Ethics Review.

- **Thomas Lewandowski:** Regarding the potential for the study director to dismiss anyone, do we normally present examples? And could we provide the sponsors with examples for reasons to dismiss?
    - **Michelle Arling:** Yes, we have in the past. Some of the reasons may be insufficient landing pressure or too many missed testing periods early in testing so that the data would be unreliable, thus it would be unethical to continue testing. But we do not want scenarios included such as if the weather is bad and staff do not want to continue.
    - **Thomas Lewandowski:** Regarding dismissing subjects, this could be related to following instructions and behaviors.
    - **Albert J. Allen:** Some information about removals for safety reasons could be included.
- **Philip Day:** Where is minimum wage mentioned in the protocol or consent form?
    - **Michelle Arling:** I think I mischaracterized this. There are some states with minimum wages lower than $10, and so it was meant to be revised because if there is a higher minimum wage than $10, we would want to match that. It would be under including people to participate.

Dr. Day recognized that often the Board has not asked about changing inclusion criteria such as age to be more mindful of the principles of justice and thanked the EPA for including these suggestions. He then asked for additional questions.

- **George Milliken:** This group of 13 people are the number of participants needed for a given stratum, so if you stratify by male and female you are going to have to have 13 males and 13 females. If you are going to test if there is a sex-related effect on the length of time this product's effect, or similarly for age, you need to have at least 13 people in each one of those strata.
    - **Julia Sharp:** Yes, this is discussed in the Statistics Review.
    - **George Milliken:** Yes, but for the Ethics Review we need to emphasize the requirements per strata because it is not okay to discuss factors like sex without the right number of people participating.

- **Julia Sharp:** Okay, we can also include that in the Ethics Review.

L. Public Comment

Ms. Sokol introduced Dr. Sarah Dewhirst as a public commenter.

Dr. Sarah Dewhirst thanked the Board for their review and explained her interest in the review, as she wrote the protocol. Dr. Dewhirst highlighted two primary risks in conducting the study, which were vector-borne diseases and the timing of mosquito activity. She also noted the presence of vector-borne illnesses typically emerge in the United States in July, and that she wants to work with the EPA to start before this risk rather than only relying on mosquito testing.

Dr. Dewhirst noted that mosquito biting patterns vary throughout the day depending on species, for which the current protocol does not account. She emphasized that during a 10-hour testing day, there are often lulls in the afternoon, leading to inconsistent landing pressure during trials. To address this, she proposed a staggered crossover design with shorter testing windows such as two 5-hour windows that participants switch between the next day. Finally, Dr. Dewhirst suggested intravenous therapy use to help supplement the time points with low landing pressure. Dr. Dewhirst summarized that these suggestions enable the collection of robust data and reduce risks to participants. She requested EPA feedback on these suggestions.

Ms. Sokol thanked Dr. Dewhirst and noted that there were no other public comments.

M. Board Discussion – Science/Statistics

Weiying Jiang, Ph.D., Science Review
Gretchen Bruce, Ph.D., Science Review
Chad Cross, Ph.D., Statistics Review
Richard Feinn, Ph.D., Statistics Review

Dr. Weiying Jiang expressed his appreciation to the EPA for their consideration of his comments. Dr. Jiang and Dr. Gretchen Bruce reviewed the study protocol and concluded that it complies with the U.S. EPA Guideline OPPTS 810.3700. If the recommendations and comments from the EPA and the Board are adequately addressed, the study is expected to generate scientifically reliable data to estimate the amount of time each product tested will repel mosquitoes.

Dr. Jiang described a deviation in the study protocol from the aforementioned Guideline. The study protocol outlines that untreated groups are exposed to mosquitoes for 5 minutes to assess landing pressure. However, the Guideline recommends at least one mosquito landing within 1 minute. Reducing the study protocol time from 5 to1 minute may decrease the health risks for the untreated group (e.g., decreased mosquito bites).

He also addressed Section 6.2 of the study protocol, which states that mosquito attractiveness for all volunteers is assessed using one species only. However, Section 2 (study objectives) lists three target species. The EPA Guideline suggests conducting an attractiveness assessment for all target species. Thus, Dr. Jiang recommended that the study authors conduct an attractiveness

assessment for all three target species or provide justification for testing only one.

Dr. Jiang then asked for clarification on application rates of products noting that Section 6.4 states that the application rate is based on the amount of product. He asked the study authors to clarify whether more OLE will be applied to volunteers exposed to product containing 30 percent.

He highlighted that the application method of the product differs between the study protocol (wiping of the arm with product) and intended market application (aerosol). This is a deviation from the Guideline. However, Dr. Jiang acknowledged the EPA's acceptance of this alternative study application method for aerosol applied products.

Dr. Jiang added that the Guideline recommends the use of positive controls, which the study protocol does not include. However, the EPA clarified that protocols without the use of positive controls are acceptable.

Lastly, Dr. Jiang recommended that the study authors consider data from previously conducted studies of products with similar formulations and percentages of OLE. This may improve the study design and minimize the likelihood of having right-censoring data, which could hinder the development of mCPT values, specifically for the product containing 30 percent OLE. Dr. Bruce requested the study authors clarify the exact concentration of the product containing 10-15 percent OLE.

Dr. Richard Feinn recommended that the study authors provide details on descriptive statistics and additional data summaries included in the analysis. These data help assess the validity and generalizability of the study. Dr. Feinn also requested clarification on the exact concentration of the product containing 10-15 percent OLE. He then emphasized that the differences in the study product application method may produce statistical results not directly related to intended commercial use. The test method protocol should match the product's intended commercial use methodology.

Dr. Feinn addressed subject pairing as described in the protocol's study design. He noted that pairing could have an impact on endpoint leading to non-independent observations. This affects the confidence bounds for product mCPT, leading to a lower than assumed precision. Survival models should also account for clustered data.

He pointed out that the World Health Organization's guidelines suggest a minimum of 20 meters between testing stations. He questioned the 3 meters proposed in the study protocol and discussed the possibility of the diffusion effect. He also recommended balancing study pairs by sex, noting that mosquitoes may be attracted to different sexes differently. He recommended that pairs be balanced in the following way: female/female, male/male, female/male.

Dr. Feinn asked for clarification on the definition of "efficacy." He emphasized that statistical analysis is conducted only for the treated subjects and there needs to be a comparison group to establish efficacy. Dr. Feinn then requested additional justification regarding sample size, adding

that the precision parameter of K=0.6 results in a wide CI. He also requested clarification on the impact and efficiency of performing site-specific models. Assuming that the survival curves are similar, the study authors should include both sites (for the same product) in the Kaplan-Meier analysis to increase precision. Dr. Feinn also suggested including the five alternate subjects when study logistics permit.

He also requested an additional explanation of Latin square implementation. If there is potential that the same pair ordering has an impact on endpoint, which may occur if stations are adjacent, a Williams design is a more suitable option. Potential landing inaccuracy was then discussed and Dr. Feinn questioned who would observe the landing. During each 30-minute interval, study participants are exposed to mosquitoes for 5 minutes. He noted that this 25-minute interval of no risk is included in the calculated landing time, which may inflate the estimate. Lastly, Dr. Feinn asked what happens to a study subject if their partner ends participation before the conclusion of the experiment.

If the comments and recommendations provided by the EPA and the Board are adequately addressed, and assuming an accurate and unbiased estimate of landing time can be calculated, the study is likely to generate scientifically reliable data useful for estimating the amount of time each product tested repels mosquitoes.

Dr. Chad Cross acknowledged Dr. George Milliken's request to add a recommendation to incorporate STATA to analyze male and female data.

- **Julia Sharp:** I appreciate your recommendation about the Latin square and Williams design. Are there additional study design considerations? The public commenter mentioned the study is designed over a 10-hour interval. Would it be possible to gain similar estimates with two 5-hour intervals?
    - **George Milliken:** Table 5 of the protocol labels test pairs as one through seven; however, another point in the protocol uses a, b, c, d, e, f, g. To avoid confusion, the protocol should use consistent labels. I think the Latin square design is okay because it is used in an unusual manner. However, in previous studies the participants never moved from one station.
    - **Richard Feinn**: I believe the reason a 10-hour design was utilized is because it is possible a mCPT will not be reached within 5 hours.
- **Albert J. Allen:** How is varied biting pressure throughout the day addressed? Should tests be conducted in both the morning and evening to achieve a balanced assessment?
    - **Chad Cross:** Different mosquitoes bite at different times of the day and there must be sufficient pressure across all species groups.
- **George Milliken:** It is unclear to me whether the two treatments will be tested separately. Two sites are needed for the 10-15 percent product, and two more are needed for the 30 percent product. The Latin square design does not address this properly. Are subjects paired to reduce the study staff requirement? I believe previous studies reviewed by the Board had one staff member per subject. Two people pairs could cause issues with

the statistical analyses.

- **Julia Sharp:** Can we add this to the statistics review?
- **Chad Cross:** This point will be added as a clarifying recommendation.

Dr. Day read aloud the proposed response to the science charge question:

"*The research proposed in the protocol "Evaluation of Topically Applied Insect Repellent Products Containing Oil of Lemon Eucalyptus (Citriodiol) Against Mosquitoes in the Field" is likely to generate scientifically reliable data useful estimating the amount of time the product tested repels mosquitoes given the comments and recommendations provided by the EPA and HSRB are adequately addressed*."

The Board concurred with this response.

N. Board Discussion - Ethics

Nicole Deming, J.D., Ethics Review

Ms. Nicole Deming noted that the protocol screens out pregnant and nursing women. Ms. Deming assumed that recruitment materials were reviewed by the institutional review board. She disagreed with the protocol's language around justification for only recruiting English speakers because there is no benefit to study participants. Ms. Deming stated that there is an inherent benefit to participants and, thus, recruitment should not be limited to English speakers. She also noted that there is no justification to exclude individuals older than 55 years of age. Ms. Deming felt that the health screening should adequately address a risk benefit analysis. She also could not find a requirement to include specific COVID-19 language in the protocol and suggested generalizing the language if there is no COVID-19 specific requirement.

The protocol states that women may be exempt from the pregnancy test requirement if they are considered to not be of childbearing potential. Women must provide signed eligibility for their exemption but are not required to disclose the reason. The protocol states that the study director can choose to exclude women participants if they believe an individual woman's exemption is incorrect. Ms. Deming found this to be overly broad, problematic, and recommended that the language be revised to address the individual woman's participation, not all women in the study.

The protocol allows study participants to drive their own vehicles on the test day. Ms. Deming asked the study sponsor to clarify reliability and responsibility in the event of an accident. She also asked for clarification regarding what happens if a mosquito captured during the study tests positive for arbovirus. Beyond contacting participants via telephone, she wondered what recommendations and support the study sponsor would provide. She then highlighted that the protocol states a minimum record retention time but not a maximum. If there is no maximum time, the protocol should state this clearly. She also asked for clarification regarding compensation for the study participants. Lastly, she noted the interchangeable use of "sex" and "gender" throughout the protocol and recommended consistency.

- **Philip Day:** What is your response to the charge question?

- **Nicole Deming:** I recommend approval of the protocol assuming the EPA and HSRB comments and recommendations are adequately addressed.

Dr. Day read aloud the proposed response to the ethics charge question:

"The research proposed in the protocol "Evaluation of Topically Applied Insect Repellent Products Containing Oil of Lemon Eucalyptus (Citriodiol) Against Mosquitoes in the Field" is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L, if the recommendations made by the EPA and HSRB are adequately addressed."

The Board concurred with this response.

O. Adjournment

Ms. Sokol thanked the HSRB, and the meeting concluded.

The meeting adjourned at 3:33 p.m. EST.

Attachment A: HSRB Current Committee Membership

Name	Title	Affiliation
Julia Sharp, Ph.D.	Mathematical Statistician	National Institute of Standards and Technology Fort Collins, CO
Philip Day, Ph.D.	Assistant Professor	University of Massachusetts, Chan Medical School Worcester, MA
Albert J. Allen, M.D., Ph.D.	Consulting Specialist	Self-employed
Gretchen Bruce, DABT	Director of Toxicology	Intertox, Inc.
Chad Cross, Ph.D., MFT, PStat®	Professor, Faculty in Residence	University of Nevada Las Vegas, NV
Nicole Deming, J.D., M.A.	Assistant Dean, Faculty Affairs and Human Resources	Case Western Reserve University, School of Medicine Cleveland, OH
Richard Feinn, Ph.D., M.A.	Professor of Basic Sciences, Chairperson of University IRB	Quinnipiac University
Thomas Gillam-Shaffer, MPH	Environmental Health Navigator; Adjunct Professor of Public Health	Michigan Public Health Institute/State of Michigan Partnership
Weiying Jiang, Ph.D.	Staff Toxicologist	California Environmental Protection Agency Sacramento, CA
Thomas Lewandowski, Ph.D.	Principal	Gradient Seattle, WA
Srikumaran Melethil, Ph.D., J.D.	Professor Emeritus	University of Missouri-Kansas City Kansas City, MO
George Milliken, Ph.D.	President	Milliken Consultants Manhattan, KS
Sinziana Seicean-Boose, M.D., Ph.D., M.P.H., LLC	Assistant Professor	Case Western Reserve University Cleveland, OH
Joseph Tuminello, Ph.D.	Assistant Professor	McNeese State University Lake Charles, LA
David Williams, Ph.D.	Distinguished Professor	Oregon State University Corvallis, OR

Attachment B: Federal Register Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-12412-01-ORD]

Human Studies Review Board Meetings—2025

AGENCY: Environmental Protection Agency

ACTION: Notice of public meeting

SUMMARY: The Environmental Protection Agency (EPA), Office of Research and Development (ORD), gives notice of its public meetings of the Human Studies Review Board (HSRB) for 2025. 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 29-31, 2025; and
2. April 3–4, 2025; and
3. July 22–24, 2025; and
4. October 14–16, 2025

Meetings will be held each day from 1 p.m. to 5 p.m. Eastern Time. For each meeting, separate follow-up meetings are planned for the HSRB to finalize reports from the three-day meetings. These follow-up meetings will be held from 1 p.m. to 5 p.m. Eastern Time on the following dates: February 26, 2025; May 1, 2025; August 26, 2025; and November 18, 2025.

ADDRESSES: All of the 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), Emily Sokol, via phone/voicemail at: 202-564-1451; or via email at: *sokol.emily@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. 10. The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of proposed or completed human research submitted by EPA, including research involving intentional exposure of human subjects to any substance to be considered by EPA in connection with an action under FIFRA (7 U.S.C. 136-136y) or section 408 of FFDCA (21 U.S.C. 346a), and research involving intentional exposure of human subjects to pesticides to be

considered by EPA in connection with an action under any statute or regulation administered by EPA.

Meeting access: These meetings will be open to the public. The full agenda with access information and meeting materials will be available 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, Emily Sokol 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 ten days prior to each meeting to give EPA as much time as possible to process your request.

Public Participation

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, Emily Sokol, 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, Emily Sokol, 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 Emily Sokol listed under **FOR FURTHER INFORMATION CONTACT**.

Kathleen Deener, Director, Office of Science Advisor, Policy, and Engagement.