EPA Human Studies Review Board (HSRB)
February 14, 2024 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A.)
Date and Time: Wednesday, February 14, 2024, 1:00 to 3:00 p.m. EDT.
Location: Via Zoom
Purpose: The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subjects research.
HSRB Website: https://www.epa.gov/osa/human-studies-review-board

Table of Contents

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Wednesday, February 14, 2024:

A. Meeting Topics and Charge Questions

Topic: "Laboratory efficacy test of an Oil of Lemon Eucalyptus (OLE)- and Picaridin-based skin-applied repellent spray against ticks (Ixodidae) using a human-subject test method," April 7, 2022, as amended, November 11, 2022. Unpublished document prepared by Carroll-Loye Biological Research, 5100 Chiles Road Suite 108, Davis, CA 95618. IRB approved 15 November 2022. 138 pp. MRID 51905311.

Charge to the Board – Science: Is the protocol "Laboratory efficacy test of an Oil of Lemon Eucalyptus (OLE)- and Picaridin-based skin-applied repellent spray against ticks (Ixodidae) using a human-subject test method" likely to generate scientifically reliable data, useful for estimating the amount of time the product tested repels ticks?

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

Tom Tracy, DFO, EPA HSRB, OSAPE

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

HSRB members
Lisa Corey, Ph.D., Co-Chair (Intertox, Inc.) Julia Sharp, Ph.D., Co-Chair (National Institute of Standards and Technology) Albert J. Allen, M.D., Ph.D. (Consulting Specialist) Philip Day, Ph.D. (University of Massachusetts, Chan Medical School) Nicole Deming, J.D., M.A. (Case Western Reserve University, School of Medicine) Weiying Jiang, Ph.D. (California Environmental Protection Agency) Srikumaran Melethil, Ph.D., J.D. (University of Missouri – Kansas City) George Milliken, Ph.D. (Milliken Associates, Inc.) Sinziana Seicean-Boose, M.D., Ph.D., M.P.H., LLC (Case Western Reserve University) Joseph Tuminello, Ph.D. (McNeese State University) David Williams, Ph.D. (Oregon State University)
EPA staff members
Tom Tracy (EPA, OSAPE) Michelle Arling (EPA, Office of Pesticide Programs (OPP)) Monique Tadeo (EPA, Program in Human Research Ethics and Oversight (PHERO)) Lexie Burns (EPA, OSAPE)

Clara Fuentes (EPA, OPP) Emily Sokol (EPA, OSAPE) Shweta Sharma (EPA, OPP) Kevin Ulrich (EPA, Registration Division)
Members of the public, representatives of research sponsor, and research team:
Anastasia Figurskey (North Carolina State University) Angelina Guiducci (ICF, Contractor Support) Afroditi Katsigiannakis (ICF, Contractor Support) Katie Lenae (ICF, Contractor Support)

C. Meeting Administrative Procedures

Tom Tracy, DFO, HSRB, OSAPE

Mr. Tom Tracy reviewed the Zoom platform tools and features and stated the purpose of the meeting was to review and discuss "Laboratory efficacy test of an Oil of Lemon Eucalyptus (OLE)- and Picaridin-based skin-applied repellent spray against ticks (Ixodidae) using a human-subject test method" by Carroll-Loye Biological Research. He noted that the minutes of the meeting and a report will be prepared, certified, and posted on the website within 90 days of February 14, 2024.

D. Introduction of EPA Staff

Michelle Arling, J.D., OPP

Ms. Michelle Arling introduced the members from EPA OPP staff to the Board.

E. Opening Remarks and Meeting Process

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

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

F. Updates from EPA HSRB Review Official

Monique E. Tadeo, HSRB Review Official, PHERO

Ms. Monique Tadeo noted there were no updates to share with meeting participants.

G. Updates from OPP

Michelle Arling, J.D., OPP

Ms. Arling stated that EPA has settled on a topic for the April 12, 2024, meeting. It is a dermal exposure study of pesticide applicators in vineyards in France. The materials will be shared with the Board prior to the April meeting. Mr. Tracy indicated that the meeting would last one day.

H. Public Comment

Ms. Arling stated that there were no public comments for the present meeting.

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February 14, 2024 Meeting Minutes

I. Review and Finalize HSRB Report

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

Dr. Corey displayed the comments from the Board's report on "Efficacy Test of an Oil of Lemon Eucalyptus and Methyl Nonyl Ketone-Based Repellent Spray with Ticks Under Laboratory Conditions." Dr. Corey summarized EPA comments which concerned the dose difference between dermal application and spray application, the value of a positive control during testing, and needing additional information from EPA on the scientific methodologies. Dr. Corey welcomed the discussion. She clarified that any recommendations brought up by the Board could address both this current study proposal or be a broader recommendation for future direction, and minor edits regarding grammar and punction would be made later by Dr. Corey and Dr. Sharp. Dr. Corey turned the discussion over to Dr. David Williams for the first comment on the report.

- **David Williams:** The first comment was on the use of positive controls within the study. EPA recognizes that a positive control can be of value. However, in this case the use of positive controls would require more exposure, more volunteers, a longer study period, and more resources. The potential benefit may not outweigh the cost. The second comment was on the use of dermal application when the product will be used in the form of a spray. EPA says that use as a spray for dermal application is acceptable, however a spray makes it harder to determine the Complete Protection Time (CPT). A dermal application would be the maximum dose, and you would presume that a spray would be a fraction of that highest dose. It may be a high fraction, but it will still be a fraction. Because of this you end up with an overestimation of CPT. This could be a problem if the licensing of the product depends on the CPT number. This raises another issue of how the sprays are tested. It has been recommended that the spray is tested in a laboratory setting rather than a field setting, because of the issues associated with an open field test. However, the spray will be used in the field, not a laboratory, and this is something EPA may want to weigh in on how it is tested. These comments on dermal vs. spray testing and the use of positive controls are not a recommendation but more of a concern raised to the Board, and something we may have to think about again in the future when we review similar proposals.
    - **Lisa Corey:** One suggestion would be to request additional scientific support for some of the methods that are repeatedly in these studies.
    - **David Williams:** I agree. EPA might find it useful when addressing the issue of dermal versus spray CPT to complete a study where they compare the dermal dose from spraying, potentially under different conditions, to get an idea if this is even going to be an issue. If 90%-95% of the spray ends up being applied, then it may not be worth the hassle of trying to complete a spray study because it is trickier. But if that number is closer to 20% then the CPT number will be unrealistic for the use of the product being tested.

  - **Lisa Corey:** I agree. This will be a general recommendation but not specific to this study. i.e., needing additional scientific report on the methodologies that are used for these studies moving forward.
  - **Julia Sharp:** I agree with all that has been said. A general recommendation supporting the science would be helpful as we review these types of studies.
  - **Lisa Corey:** Does that work for everyone, to include this recommendation in studies moving forward?

The Board verbally agreed to include the recommendation.

- **George Milliken:** A lot of studies have a negative control to look at what is happening when subjects are unexposed. Usually, a positive control is used because it would be detrimental if we do not treat the subjects. In this case I am not sure if we need a positive control if we use the other arm of the subject as a negative control.
  - **Lisa Corey:** In this case, we are not recommending that they include both positive and negative controls. Instead, we are asking that EPA consider the use of positive controls and provide the Board with support for what their decision and methodology is.

Dr. Corey moved onto the next comment for the Board to discuss. The comment was about needing more information from EPA on the methodologies of the current study being reviewed.

- **Srikumaran Melethil:** Normally the control is the test without ingredients. In this instance we do not have any data on what happens to the CPT when there is nothing in the spray. This is how I would think of using a control in the experiment. The word control is not correct, because they are using the dominant arm to test the viability of the ingredients as repellents. In my opinion this is not a control, it would be more appropriate to call it just the other arm. If this is the gold standard in repellent testing, then someone who is new to this area like me would be able to check out the validity of the science being used.
  - **Lisa Corey:** I can see the conflict in calling it a control because a lot of us are used to a different definition of the word control.
- **Sinziana Seicean-Boose:** The control can be related to the scientific question. It is not clear whether one of these proposals suggests combining two active ingredients, that we already know are effective on their own, into a new product. In medical research, you must look for benefits when combining two products into a new one, for scientific and ethical reasons. Each active ingredient has benefits and they can interact, having additive or multiplicative effects. Combining products just because they work as individual components may not necessarily have added benefits. We should prove that combining these two products creates a new benefit before moving onto additional aims.
  - **Julia Sharp:** That recommendation can be found in the general recommendations of the report.
  - **Sinziana Seicean-Boose:** I wanted to reinforce that it is important that EPA pays

attention when a proposal like this comes up. The ingredients are combined because they are effective as individual products. Just because they are effective as individual products does not mean that there is any benefit in combining those active ingredients. You will not know if the new product is necessarily going to be more effective or worse without having a study done on them without ethical concerns.

  - **Michelle Arling:** I know a lot of you have experience in medical and clinical research, but this is slightly different than both clinical and medical research. The EPA does not dictate whether two ingredients should be combined or decide how the regulations work to register a product. The company is responsible for providing data that shows the product that is intended to be sold is effective and that it works. This requires testing on human subjects. EPA does not complete a different benefit analysis of the separate active ingredients and the merits of combining or not combining the ingredients. That is something done at the company level when they are determining if something will be marketable. The job of EPA is to look at the protocol and look at the data supporting the product will not harm subjects if used as intended. EPA also ensures that the research as designed is likely to generate results that EPA can consider in determining whether to grant a registration for a product. This is a slightly different paradigm of reviewing research.
  - **Sinziana Seicean-Boose:** It is more than a rational and scientific purpose. It is more about whether exposing human subjects with something is worth the ethical concerns. Can one of the ethical reviewers comment?

- **Phillip Day:** This is not clinical or medical research, so it does not fall within that analysis. Was this approved by an Internal Review Board (IRB)?
  - **Michelle Arling:** Yes.
  - **Phillip Day:** The approvals you are talking about have already occurred for this product. It has gone through an IRB and other reviews and approvals as if it were medical research. As far as the Board can tell the participants are consenting and volunteering for the study, so it does not require another ethical analysis.
  - **Albert J. Allen:** I completed the ethics review for this product, and it does follow all the required standards that EPA has to follow for this type of research.
- **Srikumaran Melethil:** What is efficacy when measuring CPTs? Is there a limit or a number we need for efficacy because of the inadequate number of controls in this study?
  - **Clara Fuentes:** The limit for efficacy is two hours of repellency. Below two hours is not effective for registration. It must be two hours or longer.
  - **Srikumaran Melethil:** That translates to CPTs of 120 minutes.
  - **Clara Fuentes:** Yes.

Dr. Corey stated that the Board is including a recommendation to EPA to provide additional scientific support for the methodology that has been completed. This will go in the section titled

"future directions" of the report. Dr. Corey opened the meeting up for voting by the Board, indicating approval of the Report except for small formatting changes. The Board approved unanimously.

J. Adjournment

Dr. Corey and Mr. Tracy thanked the HSRB, and the meeting concluded.

The meeting adjourned at 1:36 p.m. EDT.

Attachment A: HSRB Current Committee Membership

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

Attachment B: Federal Register Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10408-01-ORD]

Human Studies Review Board (HSRB) Meetings—2023

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of public meeting.

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

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

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

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

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

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

SUPPLEMENTARY INFORMATION:

Background

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

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

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

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

How May I Participate in this Meeting?

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

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

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

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

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

Dated:

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