EPA Human Studies Review Board (HSRB)

October 23 and 24, 2019 Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A)

Date and Time: Wednesday, October 23, 2019, and Thursday, October 24, 2019, both 1:00 to 5:30 pm EST.

Locations: Via teleconference and webinar

Purpose: The HSRB provides advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research.

October 23 meeting:

Meeting was called to order at 1:00 p.m. by Tom O'Farrell, designated federal official (DFO) for the HSRB. Roll was taken and the following members and observers were present:

HSRB members	EPA staff members
Jennifer Cavallari, Sc.D., (Chair) Alesia Ferguson, Ph.D. , (Vice-Chair) Mark Aulisio, Ph.D. Janice Britt, Ph.D. AJ Allen, Ph.D., M.D. Ann Um, Ed.D. Lisa Corey, Ph.D. George Milliken, Ph.D. Beth Roxland Julia Sharp, Ph.D. Kendra Lawrence, Ph.D. (consultant)	Michelle Arling (EPA, OPP) Clara Fuentes (EPA, OPP) Eric Bohnenblust (EPA, OPP) Linda Hollis (EPA, OPP) Mary Rust (EPA, OPP) Shannon Borges (EPA, OPP) James Nguyen (EPA, OPP) David Miller (EPA, OPP) Menyon Adams (EPA, OPP) Jeff Dawson (EPA, OPP) Tom O'Farrell (OSAPE)
Members of the public, representatives of research sponsor and research team Hogan Bassey (LivFul, Inc.) Emma Weeks (University of Florida) John Manwell (LivFul, Inc.) Sarah Dewhirst (ARCTEC) Robert Jones (ARTEC)	

Tom O'Farrell provided an introduction to the meeting and outlined the Federal Advisory Committee Act (FACA) procedures and took role of the meeting participants. Tom O'Farrell introduced new Board members: Mark Aulisio, Janice Britt, Julia Sharp, Beth Roxland, and George Milliken.

Ms. Michelle Arling announced that there are no research updates from the last HSRB meeting and one study is expected at the January 2020 HSRB meeting.

The Board reviewed one study during the session on October 23, 2019, "Field Evaluation of Two Topically Applied Insect Products Containing IR3535 Against Mosquitoes in Florida".

The Agency's scientific review of this study was presented by Dr. Clara Fuentes of EPA OPP. The study was submitted for registration of two skin-applied mosquito repellents, one a lotion, and the other a wipe, both containing the active ingredient IR3535 at a concentration of 20%. Each product was tested at two distinct sample sites with 13 test subjects and two untreated control subjects who were monitored for mosquito landing pressure during the test days. The test subjects were treated with the repellent on one of their lower legs, transported to the field testing location, and then treated skin was exposed to mosquitoes for 5 minute intervals every 30 minutes for up to 14 hours or until the repellent failed. EPA presented the protocol for this study and its review to the HSRB in July 2017. The protocol was revised based on recommendations from both the EPA and the Board (www.epa.gov/osa/july-26-2017-meeting-human-studies-review-board). One recommendation was to expand the sample size to 13 subjects to achieve a more statistically-supported design. Another recommendation was for the study director to capture and test mosquitoes at each test site for all mosquito-borne pathogens that could be present rather than only those specified in the protocol, and coordination between the study director and the Florida Department of Health to receive updates of pathogens detected around the study test sites. The HSRB also recommended training subjects for proficiency in collecting mosquitoes. To ensure randomization of the treatment leg, the HSRB recommended that the Study Director clarify the description of procedures for assigning the leg on which each subject would receive the test substance. Finally, the HSRB recommended that the protocol reference dosimetry studies supporting the use of the standard dose rather than conducting a dosimetry testing phase to establish the dose for the efficacy test. All these recommendations and others were incorporated in the revised protocol. The revised protocol was approved by the overseeing institutional review board (IRB) in March 2018, and testing was conducted from August 15 to September 16, 2018. During the study, there were four deviations from the protocol that were related to how the study was conducted. These deviations included the length of time between exposure periods that were longer than 30 minutes (but less than an hour); the procedure for weighing dose of lotion applied to the test subjects for testing efficacy in the field; the failure to capture all mosquitoes that landed on test and control subjects; and skipping three exposure periods during test day one due to low mosquito pressure. These deviations did not compromise the integrity of the study. The median complete protection time (mCPT) for each product and site was calculated using Kaplan-Meier Survival Analysis. Difficulties encountered during the study included low mosquito landing pressures on control subjects (i.e., fewer than 5 landings in a 5 minute period), insufficient confirmed mosquito landings on treated subjects, and difficulty of subjects capturing all of the mosquitoes that landed on their skin. After full consideration of data from multiple test days, the EPA set the CPT for the lotion and wipe at three hours.

The Board asked questions about the science presentation. Dr. Lisa Corey asked why some of the data on days five and six were excluded. Dr. Fuentes said that it was due to low mosquito landing pressure on the untreated controls after the third exposure period on those dates. Dr. Alesia Ferguson suggested that the report reflect that there were several dominant mosquito species at site #2, not just one.

Ms. Arling of EPA OPP reviewed the ethical aspects of the study protocol. Recruitment for the study was conducted in the Gainesville area using social media, newspapers, websites, and traditional billboard advertising. Potential subjects who qualified based on initial criteria met the study team to learn more about the study and go through the consent process if they chose to. Potential subjects then met with a member of the research team individually in a private location and asked if they had any questions. Those willing to participate signed the consent form. Subjects then completed a health screening questionnaire. A total of 38 subjects participated in a least one test day; 20 were male and 18 were female. Subjects received $20 each for the consent meeting and the attractiveness test/aspirator use training day, as well as $10 per hour for the first 8 hours of each study day and $15 per hour for any additional hours. One adverse event occurred during the study - a subject was exposed to poison ivy. The Study Director reported the incident to the IRB who recommended revising consent forms to prevent future occurrences. The protocol was amended 8 times, including clarifying language for GLP compliance, testing two products rather than three as originally identified, generally clarifying the original protocol, adding a recruitment method, clarifying application techniques, and noting that an EpiPen would not be available during testing. The HSRB in 2017 concluded that the research would likely meet the ethics requirements if all recommendations by the EPA and HSRB were addressed before it was finalized. The research team revised the protocol to address the recommendations. The IRB approved the final protocol on March 21, 2018 and approved the study close out on December 20, 2018. No pregnant or lactating women were enrolled in the study and all subjects were at least 18 years old. EPA concluded that the study was conducted in substantial compliance with EPA's Human Studies Rule.

The Board then asked questions regarding ethics review of the study. Dr. George Milliken asked about the demographics of the study, specifically whether all subjects were students as the research was conducted at the University of Florida. Ms. Arling responded that there was a range of participants beyond students. A study team member also said that there was a broad range of participants. AJ Allen noted that the consent was only in English.

A public comment was given by Hogan Bassey of LivFul, Inc.

The HSRB's scientific review was presented by Board members Drs. Ferguson, Corey, and consultant Kendra Lawrence. Dr. Ferguson stated that the study sponsor did an adequate job in responding to the recommendations by EPA and the HSRB for the study. They appeared to follow the stipulations in terms of testing for attractiveness, capturing and testing mosquitoes for diseases, aspirator training, infectious subjects, randomization, product application and testing in the course of a day. Dr. Ferguson noted that not all landed mosquitoes could be collected on test days 1, 2, and 3, and there was a protocol amendment to say it was more important to avoid the bites than to capture all the mosquitoes. Dr. Ferguson questioned how the mosquitoes were counted if they were not all collected. Dr. Ferguson also stated that the conditions for stopping a test based on low landing pressure should be clarified. Dr. Ferguson agreed with EPA on the current data that a CPT for 3 hours is reasonable based on the presented data. The product may be able to perform for a longer period of time but more testing is needed. Dr. Ferguson said that the median CPT presented on the label may not be the most protective approach. Dr. Ferguson

suggested better defined study sites regarding the abundance of different mosquito species present, the use of a more protective CPT (as opposed to median CPT), and a better way (as opposed to weighing the wipes) to determine how much of the repellent consumers are exposed to. Dr. Corey agreed with these suggestions. Dr. Lawrence agreed with the CPT being set at 3 hours. Dr. Lawrence did not agree with the sponsor's assertion that a 14 hour CPT for *Aedes* can be extended to all mosquito species and that the EPA should have guidelines regarding protecting for different species. Dr. Lawrence was also concerned about amendments to the protocol being made during the course of the field testing because of deviations.

The Board's statistical review was given by Drs. Julia Sharp and Ann Um. Dr. Um stated that the randomization for the study was good, Kaplan-Meier survival analysis is the most appropriate for calculating CPT and the statistical procedures were good. Dr. Sharp said Kaplan-Meier analysis is appropriate for measuring CPT. Dr. Milliken asked about requiring a more protective CPT. Ms. Arling responded that EPA guidelines finalized in 2010 suggest using median CPT and she is not sure of the reason for deciding on that number. Dr. Ferguson recommended that these protocols in the future should be clear on when to skip exposure periods and when to stop the test day based on control landing pressures. Dr. Eric Bohnenblust of EPA OPP said that the reason the wipes are squeezed out to measure the amount of repellent applied is to make sure the dosing is consistent. The Board voted unanimously yes on the response to the charge question, with the response "Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida" generated data that are scientifically reliable and useful for estimating the amount of time each of the products tested repels mosquitoes where CPT for both products can be established at three hours."

Dr. AJ Allen presented the HSRB's ethics review of the study. Dr. Allen said the recruitment was conducted in the Gainsville FL area and within substantial compliance with the protocol. There was one adverse event regarding a subject contracting a skin rash, which was reported to the IRB. Dr. Allen stated that there were several deviations in the study that did not affect the subjects' safety and welfare. Dr. Allen stated that it was his opinion that the study was conducted with substantial compliance with 40 CFR 26 Subparts K, L, and Q. The HSRB had no questions on the Boards Ethics Review. The Board voted unanimously in favor of the response to the charge question "After review, based on review of the available data, the HSRB concludes that the research was conducted with substantial compliance with the applicable requirements of 40 CFR 26 Subpart Q."

This concluded the Board's session for October 23, 2019 and the meeting was adjourned.

October 24th meeting:

Meeting was called to order at 1:00 p.m.by Tom O'Farrell, designated federal official (DFO) for the HSRB. Roll was taken and the following members and observers were present:

HSRB members	EPA staff members
Jennifer Cavallari, Sc.D., (Chair) Alesia Ferguson, Ph.D. , (Vice-Chair) Mark Aulisio, Ph.D. Janice Britt, Ph.D. AJ Allen, Ph.D., M.D. Ann Um, Ph.D. Lisa Corey, Ph.D. George Milliken, Ph.D.	Michelle Arling (EPA, OPP) Timothy Leighton (EPA, OPP) Tim Dole (EPA, OPP) Melissa Panger (EPA, OPP) Tom O'Farrell (OSA)
Members of the public, representatives of research sponsor and research team Jonathan Cohen (ICF, EPA contractor) Has Shah (ACC) Leah Rosenheck (LR Risk Consulting) Michael Bartels (AEATF II) Brian Lange (Lange Research and Consulting) Cameron Lange (Lange Research and Consulting)	

Tom O'Farrell provided an introduction to the meeting and outlined the Federal Advisory Committee Act (FACA) procedures and took role of the meeting participants.

The Board reviewed one study during the session on October 24, 2019, "Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial Using an Airless Sprayer", sponsored by the Antimicrobial Exposure Assessment Task Force II.

The Agency's scientific review of the protocol was presented by Tim Leighton of EPA OPP. The study assessed dermal and inhalation exposure monitoring for painting indoors with an airless sprayer using a surrogate antimicrobial compound. The study was specifically designed for commercial applicators and was conducted in a warehouse in Orlando Florida. Three modules were built in the warehouse and subjects painted approximately 20 rooms within each module. Eighteen subjects participated in the study. Subjects were evenly split into groups using 10, 15, or 30 gallons of paint with either 1,200 or 12,000 ppm of antimicrobial in the paint. Subjects wore inner and outer dosimeters, and were medically cleared and fit-tested to use respirators in response to earlier HSRB suggestions. The study report included several amendments and deviations. Deviation 4 changed the hand-wash procedure from having the researchers wash the paint off the subjects' hands to the subjects doing the washing. This increased the efficiency of washing the paint off the hands. The QA/QC data for the study were very good. The results showed that dermal exposure increased as the total amount of active ingredient increased. It was determined that 80% statistical power for the study was achieved. The results can be generalized to other low volatility chemicals based on the QA/QC results.

EPA determined that the study results were scientifically sound enough to support estimates of dermal and inhalation unit exposures found in the study.

The Board asked questions about the science presentation. Dr. Jennifer Cavallari noted that the subjects finished the painting quickly and asked if there was a concern about whether the highest exposures were being accurately captured. Tim Leighton of OPP responded that he believed the highest exposure levels were being accurately measured. Dr. Milliken asked whether the use of fans had an effect on the exposure. Tim Leighton indicated that it would be difficult to assess given other confounding factors. Dr. Milliken also asked if the painters could choose the clothes they wore and Tim Leighton responded that clean clothes were provided by the researchers.

Michelle Arling of EPA OPP reviewed the ethical aspects of the study. Newspaper recruitment advertisements ran in English and Spanish language periodicals and flyers were posted in local paint stores. Advertisements were also placed in Craigslist as approved by IRB amendment. Study staff interviewed interested callers in their preferred language to determine if they met the inclusion criteria, and to provide an overview of the study to the potential subject. Respondents who were both eligible for the study and interested in learning more were invited to attend a consent meeting. The researcher who conducted the consent meeting provided information about the study that covered the content of the consent form, and then asked a standard set of questions to ensure the subject's comprehension of the consent materials based on an AEATF SOP. The candidate was asked to sign the consent form if they were willing to participate. Consented subjects then completed an on-line health questionnaire to determine whether they were medically cleared to wear a respirator. Subjects enrolled in the study were fit tested for their respirators prior to the monitoring day. Ultimately 24 subjects were enrolled in the study, five female and thirteen male. On the day of monitoring, females were required to take a pregnancy test. Subjects were compensated in accordance with the protocol. In conclusion, the information indicates that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

There were no questions about the ethics review from the HSRB.

Tom O'Farrell announced there were no comments from the public.

The HSRB's scientific review was presented by Board members Drs. Cavallari and Janice Britt. Dr. Cavallari thought that the sponsors adequately addressed EPA and HSRB concerns with the protocol including randomizations on ME assignments, adequate range of variation of potential exposures, as well as acknowledging the limitations of the study. Some of the limitations include underestimate of head and neck samples, limitations of extrapolating risk to non-professional painters, and the data not being derived from a fully stratified random sample of ME.

The Board's statistical review was given by Drs. Ann Um and George Milliken. Dr. Milliken noted that the study was well executed and could have been improved by controlling for some of the external issues like the effect of using a fan on exposure. Dr. Milliken also asked

whether the exposure levels in this study would be harmful to painters. Tim Leighton explained that toxicology studies are performed to ensure no harm is done to users of the chemical. Dr. Um noted that the study had greater than 80% statistical power and the sample size and recoveries were good.

The Board voted unanimously that the research in this study by the AEATF is useful for assessing the exposure of individuals who apply paint containing antimicrobial pesticides using and airless sprayer.

Dr. AJ Allen presented the HSRB's ethics review of the study. Dr. Allen stated that subjects were monitored for safety purposes as outlined in the EPA ethics review memo. One deviation in the study related to hand washing procedures but did not affect the study integrity. Another deviation related to a subject being fit tested before receiving medical clearance to wear a respirator but this did not affect the subject's welfare. Another subject splashed paint in their eyes but the subject was treated according to protocol and allowed to continue participation. Dr. Allen noted that there were five protocol amendments and none of those involved a substantial impact on subject safety. The Board voted unanimously that the study was conducted in substantial compliance with the applicable requirements of 40 CFR, part 26, Subpart Q.

This concluded the Board's session for October 24, 2019 and the meeting was adjourned.

Respectfully submitted:

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

Certified to be true by:

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

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Board members during the course of deliberations within the meeting. Such ideas, suggestions and deliberations do not necessarily reflect definitive consensus advice

from the Board members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final report prepared and transmitted to the EPA Science Advisor following the public meeting.

Attachment A
EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Jennifer Cavallari, Sc.D., CIH
Associate Professor
Department of Public Health Science
University of Connecticut School of Medicine
Farmington, CT

Vice Chair

Alesia Ferguson, Ph.D.
Associate Professor
Department of Built Environment
North Carolina A&T University
Greensboro, NC

Members

Janice Britt, Ph.D.
Managing Scientist
ToxStrategies, Inc.
Tallahassee, FL

Lisa Corey, Ph.D.
Toxicologist
Intertox, Inc.
Seattle, WA

George Milliken, Ph.D.
Consultant
Milliken Consultants
Manhatten, KS

Beth Roxland
Senior Consultant
Roxland Consultants
New York, NY

Mark Aulisio, Ph.D.
Professor
Case Western Reserve University
Cleveland, OH

Albert J. Allen, M.D., Ph.D.
Senior Medical Fellow
Eli Lilly
Indianapolis, IN

Eun Um, Ed.D.,
President and CEO
AMSTAT Consulting
Bethesda, MD

Julia Sharp, Ph.D.
Associate Professor
Colorado State University
Fort Collins, CO

Lindsay McNair, M.D., Ph.D.
Chief Medical Officer
WIRB-Copernicus
Princeton, NJ

Consultants to the Board

Kendra L. Lawrence, Ph.D., BCE, PMP
Health Sciences Product Manager
U.S. Army Medical Materiel Development Activity
Fort Detrick, MD

Attachment B
Federal Registers Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10001-03--ORD]

Human Studies Review Board; Notification of Public Meetings

AGENCY: Environmental Protection Agency.

ACTION: Notice.

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

DATES: A virtual public meeting will be held on Wednesday, October 23, 2019 and Thursday, October 24, 2019 from 1:00 pm to approximately 5:30 pm Eastern Time on both dates. A separate, subsequent teleconference meeting is planned for Tuesday, December 10th, 2019, from 2:00 pm to approximately 3:30 pm Eastern Time for the HSRB to finalize its Report of the October 23 and 24, 2019 meeting and review other possible topics.

ADDRESSES: All of these meetings will be conducted entirely by telephone and on the Internet using Adobe Connect. For detailed access information visit the HSRB Website: http://www2.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), Thomas O'Farrell on telephone number (202) 564-8451; fax number: (202) 564-2070; email address: ofarrell.thomas@epa.gov; or mailing address: Environmental Protection Agency, Office

of the Science Advisor, Mail code 8105R, 1200 Pennsylvania Avenue NW, Washington, DC 20460.

SUPPLEMENTARY INFORMATION:

Meeting access: These meetings will be open to the public. The full Agenda and meeting materials will be available at the HSRB Website: http://www2.epa.gov/osa/human-studies-review-board . For questions on document availability, or if you do not have access to the Internet, consult with the DFO, Thomas O'Farrell, listed under FOR FURTHER INFORMATION, CONTACT.

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

How May I Participate in this Meeting?

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

1. Oral comments. To pre-register to make oral comments, please contact the DFO, Thomas O'Farrell, listed under FOR FURTHER INFORMATION, CONTACT. Requests to present oral comments during the meeting will be accepted up to Noon Eastern Time on Tuesday, October 15, 2019, for the October 23 and 24, 2019 meeting and up to Noon Eastern Time on Tuesday, December 3, 2019 for the December 10, 2019 meeting. 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 either meeting 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. Submit your written comments prior to the meetings. For the Board to have the best opportunity to review and consider your comments as it deliberates, you should submit your comments via email or Fax by Noon Eastern Time on Tuesday, October 15, 2019, for the October 23 and 24, 2019 meeting and by Noon Eastern Time on Tuesday, December 3, 2019 for the December 10, 2019 meeting. If you submit comments after these dates, those comments will be provided to the HSRB members, but you should recognize that the HSRB members may not have adequate time to consider your comments prior to their discussion. You should submit your comments to the DFO, Thomas O'Farrell listed under FOR FURTHER INFORMATION, CONTACT. There is no limit on the length of written comments for consideration by the HSRB.

Background

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act 5 U.S.C. App.2 § 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.

Topic for discussion. On October 23, 2019, the Human Studies Review Board will consider a study report submitted by LivFul, Inc. titled "Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida". On October 24, 2019, the Human Studies Review Board will consider a study submitted by the Antimicrobial Exposure Assessment Task Force (AEATF II) titled "A Study for Measurement of Potential Dermal and

Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer" (AEA10).

The Agenda and meeting materials for this topic will be available in advance of the meeting at http://www2.epa.gov/osa/human-studies-review-board.

On December 10, 2019, the HSRB will review and finalize their draft Final Report from the October 23 and 24, 2019 meeting, in addition to other topics that may come before the Board. The HSRB may also discuss planning for future HSRB meetings. The agenda and the draft report will be available prior to the meeting at http://www2.epa.gov/osa/human-studies-review-board.

Meeting minutes and final reports. Minutes of these meetings, summarizing the matters discussed and recommendations made by the HSRB, will be released within 90 calendar days of the meeting. These minutes will be available at http://www2.epa.gov/osa/human-studies-review-board. In addition, information regarding the HSRB's Final Report, will be found at http://www2.epa.gov/osa/human-studies-review-board or from Thomas O'Farrell listed under FOR FURTHER INFORMATION, CONTACT.

Date: _____

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Jennifer Orme-Zavaleta, Ph.D.
EPA Science Advisor