**EPA Human Studies Review Board (HSRB)**

**January 23-24, 2018 Meeting Minutes**

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

**Date and Time: Tuesday, Jan. 23, 2018 and Wednesday, Jan. 24, 2018, 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.**

**January 23rd 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 |
|---|---|
| Liza Dawson, Ph.D. (HSRB Chair)<br>Edward Gbur, Jr., Ph.D. (HSRB Vice-Chair)<br>Jennifer Cavallari, Sc.D., CIH<br>Alesia Ferguson, Ph.D.<br>Kyle L. Galbraith, Ph.D.<br>Walter T. Klimecki, D.V.M., Ph.D.<br>Randy Maddalena, Ph.D.<br>Jun Zhu, Ph.D. | Michelle Arling (EPA)<br>Timothy Dole (EPA)<br>Timothy Leighton (EPA)<br>Tim Ciarlo (EPA, OPP)<br>Tom Sinks (EPA, OSA)<br>Eric Bohnenblust (EPA, OPP) |
| Members of the public, representatives of research sponsor and research team<br>Ulrich Bernier (USDA)<br>Lisa Setliff (Landis International)<br>Dan Hollas (S.C. Johnson & Son)<br>Kevin Sweeney (Landis International)<br>Dave Barnekow (AHETF, Dow AgroSciences)<br>AJ Allen (Eli Lilly)<br>Richard Collier (Landis International)<br>Tiffany Stecker (Bloomberg)<br>Ron Lack (public)<br>Kevin Dunn (Endyna, meeting support contractor) | |

Tom O'Farrell provided an introduction to the meeting and outlined the Federal Advisory Committee Act (FACA) procedures. Dr. Tom Sinks of the EPA Office of the Science Advisor welcomed the Board. Ms. Michelle Arling provided updates regarding respirator use in a study previously reviewed by the HSRB.

The Board reviewed one protocol during the session on January 23rd, "Laboratory Evaluation of Bite Protection from Repellent-Impregnated Fabrics." The Agency's scientific review of this protocol was

presented by Mr. Tim Ciarlo of the EPA Office of Pesticide Programs (OPP). Mr. Ciarlo highlighted key features of the study, which is similar to studies of repellent-treated fabric that the HSRB has previously reviewed. The study is testing commercially available fabrics treated with 0.52% permethrin or 0.9% etofenprox and tests repellency of the fabric after 0, 20, 50, and 75 washes. The testing is an arm-in-cage design in which human subjects wear treated and untreated fabric sleeves over an exposed forearm that is inserted into a cage. Laboratory reared, disease-free mosquitoes are released into the cage for a 15-minute period and allowed to land and bite. The subjects' hands are covered with gloves such that only the sleeve is accessible to mosquitoes for blood feeding. After the test period the mosquitoes are captured and crushed to determine blood feeding and percentage protection is calculated.

The study tests two mosquito species: *Aedes aegypti* and *Anopheles albimanus*. The study will enroll 10 subjects, and each human subject serves as their own control by testing the untreated fabrics as well as the range of treated and washed fabric sleeves. Mr. Ciarlo described power calculations showing adequate statistical power for the study using the 10 subjects with repeated measures testing the 5 sets of sleeves (control untreated sleeves and four different washing conditions). He also described dermal toxicity calculations demonstrating that the concentrations of permethrin and etofenprox lead to Margins of Exposure (MOEs) which are well above the agency's level of concern for these two products; hence there is no concern about dermal exposure in this study.

Ms. Arling of EPA OPP reviewed ethical aspects of the study protocol. Risks to subjects are appropriately minimized by using disease-free mosquitoes, excluding individuals with skin conditions, reactivity to pesticide-treated fabrics, or severe reactivity to mosquito bites; and providing a confidential mechanism for conducting pregnancy testing for female potential participants. Plans for recruitment and informed consent were deemed to be appropriate and the study was reviewed by an accredited IRB, the Western Institutional Review Board (WIRB). EPA staff recommended minor changes to the protocol related to timing of procedures and additions to the consent form. The study sponsor and research team agreed to the requested changes from EPA.

The Scientific review was presented by HSRB board members Randy Maddalena and Walt Klimecki, and statistical review by board member Ed Gbur. Dr. Klimecki remarked that MOE calculations for permethrin and etofenprox needed to be harmonized, as the calculations in the protocol did not match the calculations presented by EPA staff in their review. Dr. Maddalena commented that it was unclear whether there were issues related to repeated measurements of repellency on a single subject, since there was no information provided about whether mosquitoes might be more or less attracted to a subject with previous bites, compared to a subject without bites. Dr. Gbur addressed the statistical analysis, also commenting on repeated measures and recommending that some analysis of correlation structure of the repeated measures be undertaken.

There was discussion of these issues by the full board. The Board agreed that the protocol was scientifically sound and responded affirmatively to the science charge questions. The Board also recommended some clarifications and corrections in the protocol to address comments by Drs. Klimecki and Gbur.

HSRB board chair Liza Dawson presented the ethics review of the study. Dr. Dawson stated that there were no major ethical concerns with the study, but recommended some minor changes for clarity, addressing inclusion/exclusion criteria, compensation for injury, care and treatment for injury,

recruitment materials, and informed consent. The Board discussed these changes and responded affirmatively to the charge question, stating the protocol would be likely to meet the requirements of 40 CFR 26 Subparts K and L if minor changes were made. This concluded the Board's session for January 23rd and the meeting was adjourned.

**January 24th meeting**

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

| HSRB members | EPA staff members |
|---|---|
| Liza Dawson, Ph.D. (HSRB Chair)<br>Edward Gbur, Jr., Ph.D. (HSRB Vice-Chair)<br>Jennifer Cavallari, Sc.D., CIH<br>Alesia Ferguson, Ph.D.<br>Kyle L. Galbraith, Ph.D.<br>Walter T. Klimecki, D.V.M., Ph.D.<br>Randy Maddalena, Ph.D.<br>Jun Zhu, Ph.D. | Michelle Arling (EPA)<br>Timothy Dole (EPA)<br>Timothy Leighton (EPA)<br>Matt Crowley (EPA, OPP)<br>Jeff Dawson (EPA, OPP)<br>David Miller (EPA, OPP)<br>Dave Jones (EPA, OPP)<br>Maria Spassova (EPA, NCEA)<br>Christine Cai (EPA, NCEA) |
| Members of the public, representatives of the Agricultural Handlers Exposure Task Force (AHETF) and research team<br><br>Dave Barnekow (AHETF, Dow AgroSciences)<br>Kevin Dunn (Endyna, meeting support contractor)<br>Eric Bruce (AHETF)<br>Dave Johnson (Johnson Management & Consulting)<br>Jeff Holmsen (BASF Corp.)<br>Leah Rosenheck (LR Risk Consulting, Inc.)<br>Larry Holden (AHETF, Sielken & Associates Consulting, Inc.)<br>Steve McEuen (public)<br>William Jordan (independent consultant) | |

The HSRB reviewed the Agricultural Handler Exposure Task Force, LLC (AHETF) Study Report AHE170: "Determination of Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules." Mr. Matt Crowley provided EPA's scientific assessment of the study. The study assessed dermal and inhalation exposure of workers pouring five different granular pesticides products: 2,4-D, chlorpyrifos, permethrin, pendimethalin and tefluthrin. The monitoring methods were similar to other scenarios used in previous AHETF studies. Hand exposures were assessed with a handwash method, using multiple samples taken throughout the day and analyzed separately. Head exposure was assessed with wipes, which were combined and analyzed as one sample. Other dermal exposure was monitored using a whole-body dosimeter worn under the clothes and which was analyzed in two separate sections. Inhalation exposure was assessed using an OSHA versatile sampler worn by the worker, which includes a small motorized pump for air flow to assess inhalation exposure of each individual worker.

The study design consisted of seven sites monitoring three workers per site. Several amendments were made to the protocol during the study, mostly with the aim of increasing recruitment and finishing the study on schedule. None of the amendments were deemed to adversely affect the scientific integrity of the study. There were also some protocol deviations, most of which related to missing samples. Again, the deviations were not considered by EPA to affect the soundness of the study or the ability to draw

conclusions from the results. The study had a good geographic range and distribution of different products and a wide range of amount of product handled. Positive and negative controls were appropriate.

With regard to missing hand wash samples, EPA assessed different methods of imputing missing data. The final method chosen was to simply impute the missing values based on the average across all hand wash samples. Other methods of imputation did not significantly affect the conclusions of the study.

EPA reviewed the study's ability to meet the two main benchmarks, namely 3-fold accuracy in the dermal exposure measurements, and statistical power to assess proportionality between exposure and amount of active ingredient handled (AaiH). Three-fold accuracy, also called a K-factor, refers to the 95% confidence interval around the mean exposure falling within a factor of three relative to the mean. In this case the three-fold accuracy benchmark was met. With regard to the proportionality question, the study had greater than 80% power to detect proportionality.

EPA staff described proposed uses of the data as part of risk assessments for worker exposure to new pesticide products in the agricultural sector, or for re-registration of currently approved products. In sum, EPA concluded the study was scientifically sound and provided reliable data for decision-making.

Ms. Michelle Arling provided the EPA ethics review of the study. The study was reviewed and approved by the Schulman IRB, an accredited independent IRB. Ms. Arling described recruitment for the study, which involved several steps: constructing a list of growers using granular pesticide products; contacting these employers and inviting them to participate; then visiting the participating growers and meeting with them to describe the study. Potentially eligible employees were recruited and informed consent discussions were held. Inclusion criteria specified that workers must be experienced handling granular pesticides, be non-pregnant adults, and be over the age of 18. Consent materials were prepared in both English and Spanish; however, none of the participants requested Spanish language consent discussions or materials. During the study, all workers wore personal protective equipment (PPE) specified by the product label of the products they were loading. Heat stress was monitored throughout the study. A nurse was available in case of any medical issues during the conduct of the study, but no medical issues requiring nurse assistance were identified. There were several amendments to the protocol, all of which were reviewed and approved by the IRB prior to implementation. In short, there were no ethical concerns with the study conduct or ethical review procedures. EPA concluded that the study satisfied the criteria of 40 CFR 26 parts K and L.

The HSRB presented their scientific and statistical review of the study. Dr. Alesia Ferguson raised a question about missing samples and asked for clarifications about how the data were handled from missing samples. Dr. Cavallari also requested clarification on the method of data imputation for missing samples. Both Dr. Cavallari and Dr. Ferguson commented that the study was sound and well conducted and that they had no major concerns. Dr. Jun Zhu reviewed the statistical aspects of the study and commented that the mixed effects model used for statistical analysis was appropriate. The HSRB concluded that the study raised no major scientific concerns and responded affirmatively to the charge question that the study was scientifically sound, producing reliable results.

The HSRB ethics review was presented by Dr. Kyle Galbraith. Dr. Galbraith commented that the IRB review of the initial protocol and amendments was handled appropriately, that inclusion and exclusion criteria were reasonable. Recruitment and informed consent were done appropriately and risks to subjects were minimized. Dr. Galbraith noted that one issue with the study was the fact that only men

were enrolled, but because the agricultural workers are overwhelmingly male, it would not have been feasible or realistic to expect female participants. Dr. Galbraith stated that there was no criticism of the study about the lack of enrollment of female subjects. In short, the study met the criteria of 40 CFR 26 parts K and L. The HSRB agreed with this assessment and responded affirmatively to the charge question. This concluded the review of the study, and the meeting was adjourned.

Respectfully submitted:

Thomas J. O'Farrell, 9/23/18

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

Certified to be true by:

Liza Dawson, Ph.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

Liza Dawson, Ph.D.
Research Ethics Team Leader
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

## Vice Chair

Edward Gbur, Jr., Ph.D.
Professor of Statistics
Director, Agricultural Statistics Laboratory
University of Arkansas
Fayetteville, AR

## Members

Jennifer Cavallari, Sc.D., CIH
Assistant Professor
Division of Occupational and Environmental Medicine
University of Connecticut
Storrs, CT

Alesia Ferguson, Ph.D.
Associate Professor
Department of Environmental and Occupational Health
University of Arkansas
Little Rock, AR

Kyle L. Galbraith, Ph.D.
Human Subjects Protection
Carle Foundation Hospital
Urbana, IL

Walter T. Klimecki, D.V.M., Ph.D.
Associate Professor
Departments of Pharmacology and Toxicology
The University of Arizona Health Sciences
Tucson, AZ

Randy Maddalena, Ph.D.
Physical Research Scientist
Indoor Environment Group
Lawrence Berkeley National Laboratory
Berkeley, CA

Jun Zhu, Ph.D.
Professor of Statistics and of Entomology
Department of Statistics
University of Wisconsin–Madison
Madison, WI

**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 REGISTER* NOTICE ANNOUNCING MEETING**

**ENVIRONMENTAL PROTECTION AGENCY**

[FRL-9972-41-ORD]

**Human Studies Review Board; Notification of Public Meetings**

**AGENCY:** Environmental Protection Agency.

**ACTION:** Notice.

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**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 Tuesday, January 23, 2018 and Wednesday, January 24, 2018, from 1:00 pm to approximately 5:30 pm Eastern Time on both dates. A separate, subsequent teleconference meeting is planned for Thursday, March 15, 2018, from 2:00 pm to approximately 3:30 pm Eastern Time for the HSRB to finalize its Final Report of the January 23 and 24, 2018 meeting and review other possible topics.

**ADDRESSES**: Both 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 either meeting will be accepted up to Noon Eastern Time on Tuesday, January 16, 2018, for the January 23 and 24, 2018 meeting and up to Noon Eastern Time on Tuesday, March 8, 2018 for the March 15, 2018 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 by Noon Eastern Time on Tuesday, January 16, 2018, for the January 23 and 24, 2018 meeting and up to Noon Eastern Time on Tuesday, March 8, 2018 for the March 15, 2018 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 January 23 and 24, 2018, EPA's Human Studies Review Board will consider two topics: 1) A completed study and monograph report titled "Agricultural Handler Exposure during Open Pour Loading of Granules" by the Agricultural Handlers Exposure Task Force, and 2) a study protocol titled "Laboratory Evaluation of Bite Protection From Repellent-Impregnated Fabrics" by Pinebelt Industries.

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 March 15, 2018, the HSRB will review and finalize their draft Final Report from the January 23 and 24, 2018 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