EPA Human Studies Review Board (HSRB)

January 30, 2020 Meeting Minutes

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

Date and Time: Thursday, January 30, 2020, 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.

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 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. Julia Sharp, Ph.D. Lindsay McNair, M.D.	EPA staff members Michelle Arling (EPA, OPP) Matt Crowley (EPA, OPP) Jeff Dawson (EPA, OPP) Ed Messina (EPA, OPP) Tom O'Farrell (OSAPE)
Members of the public, representatives of research sponsor and research team Mike Krolski (AHETF) Steve McEuen (AHETF) Jeff Holmsen (AHETF) Eric Bruce (AHETF) Dave Barnekow (AHETF) Jonathan Cohen (ICF) David Johnson (Johnson Management & Consulting) Thomas Lewandowski (Gradient) Kevin Dunn Kurd Ali	

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.

Ms. Michelle Arling announced that the report from the October HSRB meeting was distributed to the study sponsors (LivFul, arctec, and the University of Florida). The research discussed included a field study for a skin-applied mosquito repellent with the active ingredient IR3535. The study sponsors indicated that they may want to conduct a similar study at a different site with more consistent mosquito landing pressure in order to support a claim for a longer complete protection time. If so, they will develop a new protocol based on EPA and HSRB's recommendations. A revised protocol may be reviewed by the HSRB in the future.

The Board reviewed the Agricultural Handler Exposure Task Force (AHETF) Study Report and Monograph (AHE500 and AHE1022): Determination of Dermal and Inhalation Exposure to Workers during Closed System Loading of Liquids in Returnable and Non-Returnable Containers/Mechanical Transfer of Liquids.

The Agency's scientific review of this study was presented by Mr. Matt Crowley of EPA OPP. The objective of the study was to capture the range of dermal and inhalation exposures for workers loading liquid pesticides using closed systems with returnable and non-returnable containers with various types of available systems. Standard methods for monitoring dermal and inhalation of pesticides were used. The protocol was approved in 2012. Most of the amendments to the protocol involved finding potential study participants, and one added a surrogate active ingredient chlorpyrifos. There were a few deviations to the protocol. A worker of a pesticide company participated in the study as a result of a merger, though employees of pesticide companies were to be excluded. One subject was not trained as a handler under the Worker Protection Standard (WPS), which occurred because neither the employer nor the subject thought the requirement applied to them. . Also, for a short time, one of the study workers did not wear chemical-resistant gloves as required in the protocol. A deviation that occurred many times during the study was failure to observe that the closed system was operating properly before monitoring occurred. EPA concluded that these deviations did not undermine or compromise the resulting exposure data.

The primary objective of the analytical benchmarks was not met for dermal exposure, normalized by the amount of active ingredient handled, estimates of key statistics (GM, AM, P95) to be accurate to within 3-fold (k-factor, or fold relative accuracy). A log-normal mixed model was used for statistical analysis. The accuracy benchmark being not met for dermal exposures was not surprising .because the pre-study design simulations assumed a lower variability than what was observed during the study based on then currently available information. The secondary objective of normalized exposure to the amount of active ingredient handled was met and the statistical analysis indicated that results of at least 80% power were achieved. The EPA will consider incorporating an adjustment/multiplier to exposure values because the study results showed less accuracy than that of the pre-study simulations and the 3-fold accuracy was not met. The Worker Protection Standard has exceptions for not using certain personal protective equipment while working with closed systems. However, since the exposure data from this study represent workers wearing gloves in closed systems and there appears to be significant dermal exposure, the AHETF recommended that gloves being worn is appropriate to

reflect the closed systems scenario. EPA accepts how the study was designed and the diversity of conditions.

The data showed that subjects who were handling unrinsed probes had significantly higher dermal exposures relative to other types of monitored systems. The study sponsor decided to separate out the data from monitoring units where unrinsed probes were used across all 3 data sets considered, and EPA agreed. EPA plans to consider the data from subjects using unrinsed probes separately. For example, a similar situation arose in a previous AHETF study that was reviewed by the HSRB in 2016. The study showed that some subjects were using water soluble packets in a manner that was not intended and that resulted in very high exposure. The high exposure data were segregated out from the exposure database and used by EPA to inform label and policy changes that provided clearer instructions on proper use. In this instance, EPA will consider the data from subjects using unrinsed probes, and develop options for mitigating the high exposure, for example through training and outreach and/or revisions to the product labels.

The Board asked questions about the science presentation. Dr. Lisa Corey asked if study AT-500 used head patches. Mr. Crowley responded that head patches were not used in AT-500. Dr. Janice Britt asked how the range of active ingredient and application rates were chosen. Mr. Crowley said the ranges were chosen by interviewing workers in the industry and chosen to cover a wide range of conditions. Dr. Jennifer Cavallari asked why the data from the procedures where the workers did not rinse the probe prior to removal will be excluded. Mr. Crowley responded that EPA will consider the data from subjects handling of unrinsed probes, and it may be used to support actions to mitigate exposure such as amending product labeling or developing training materials.

Ms. Arling of EPA OPP reviewed the ethical aspects of the study protocol. When the HSRB reviewed the protocol in 2011, it had a few recommendations regarding providing contact information for subjects to use in the event they had post-study symptoms or adverse effects, or question about the research, establishing criteria for deciding if a subject was too sick to make a decision about getting medical treatment, and providing exposure results to participants. All of the HSRB recommendations were addressed prior to finalizing the protocol. The IRB approved the final protocol on Feb. 22, 2012.

Subjects were recruited using several methods, including purchasing lists of growers, working with state regulatory agencies to obtain lists of commercial applicators, contacting local agricultural specialists, and obtaining data from the National Agricultural Aviation Association. Recruitment and informational materials provided were approved from the IRB. Informational and informed consent meetings for interested participants were conducted, and all information specified in the protocol and consent form was covered. Where necessary, all employers signed a non-coercion agreement before employees were recruited to participate. Consent meetings were held one-on-one in a private location. All subjects met the eligibility criteria, which included experience using closed systems within the last year and willingness to wear chemical-resistant gloves even if not specified in the protocol. Sometimes the complete consent form was not available until the day of monitoring, when the product to be used was identified, but all subjects

received a copy of the consent form and were instructed about the requirements for using the product safely as found on the label. The subjects were between 23 and 55 years old and there were 35 males and one female. No subjects withdrew from the study.

On the day of monitoring, the female subject took a pregnancy test prior to starting to ensure she was eligible to participate. After subjects were dressed in the dosimeters and outer clothing, they were reminded about label-based and general pesticide safety requirements, the product's directions for use, and that they were free to withdraw at any time. They were also reminded about the need for handwashes prior to eating, drinking, smoking, and using the bathroom. Subjects wore all personal protective equipment as specified in the product labeling and protocol. A medical professional was present for the duration of each monitoring event and monitored subjects for signs of illness and heat stress. Researchers monitored the heat index to ensure subjects' safety.

Two MEs were invalidated. One was invalidated because a portion of the inner dosimeter and the OVS sampler did not have a valid result. The second was invalidated because during the ME, a subject accidentally left valve open without jug on top to be rinsed and liquid was sprayed from the mix tank. The system had been plumbed to used diluted product, rather than clean water, to rinse the containers. The subject cleaned the spill in accordance with label requirements and did not experience any adverse effects. However, AHETF invalidated the results.

Subjects were compensated in accordance with protocol. Subjects were also offered the option to receive a summary of their personal monitoring results, including information about the subject's exposure relative to all monitored subjects, observed practices that resulted in higher exposure, and information on minimizing exposure. The protocol was amended three times. The first amendment added another method for monitoring the heat index during the study for subjects' safety. The second amendment added a surrogate ingredient, chlorpyrifos, that could be used during the study. The third amendment revised the protocol and consent form to specify that the subjects needed to be trained as a handler under the WPS or be exempt from the training requirement. It also updated the consent process and pre-monitoring discussion related to the labeling of the pesticide being used to note that the researcher would discuss with the subjects pertinent sections of the directions for use, and allowed the final three monitoring events to be collected in any of the monitoring areas. None of these amendments adversely affected subjects welfare or safety.

Ms. Arling noted that Mr. Crowley covered many of the deviations in his presentation. However, she drew attention to a deviation that occurred throughout the conduct of the study and was reported twice, in deviations 4 and 6. The protocol noted that: "Prior to use in the study, the closed system and mixing/loading procedures shall be evaluated and discussed by the Study Director or a designated researcher to ensure the system is operating properly and the anticipated procedures do not involve open-pouring. This examination will include ensuring no significant leaks; discussing how connections will be made between containers and closed systems and between systems and hoses or tanks; and ensuring the system meets one of the four system types discussed above." (AHE500 Study Report, pp. 474-5 of 1386) Deviations 4 and 6 note that this failure to conform to the protocol occurred because "it was often not possible to see the system

in operation, for example to verify there were no significant leaks." (AHE500 Study Report, p. 510 of 1386) The report notes that although pre-use inspections were not done in all instances, researchers made note of leaks in their observation reports from the MUs and asked subjects whether leaks could be fixed and to do so early in the course of the MU. Some leaks could not be stopped and were contained by placing a bucket or cloth under the leak. The report indicates that the impact of these deviations was minimal to moderate, and that there were no reported incidents of overexposure to the test substances or adverse effects reported by subjects. It was not immediately apparent that these systems were leading to increased exposure to the subjects, such that an MU or the entire study should be stopped. The data collected provide valuable real-world information about subjects' exposure, and appears to not have impacted subjects' safety or welfare. In the future, EPA recommends that when AHETF encounters a situation where they cannot follow the protocol, they consult with EPA before deviating from the protocol requirements for the duration of the study.

The requirement of the EPA Human Studies Rule for providing documentation of the ethical conduct of the study was satisfied. EPA concluded that the study was conducted in substantial compliance with the relevant subparts of EPA's Human Studies Rule.

The Board had no questions about the ethics portion of the study.

Public comments were called for, but none were given.

The HSRB's scientific review was presented by Board members Drs. Britt and Corey. Dr. Britt said that she agreed that the deviations and amendments did not affect the study. Dr. Britt stated that the data from the study and monograph were acceptable and appropriate and resulted from diverse conditions. Dr. Cavallari asked if EPA had made any labeling or other decisions based on the study results from the AHETF study involving water soluble packets. Mr. Jeff Dawson said that EPA may use it as a training mechanism for clarifying requirements in WPS and training materials and that it also may be included quantitively in the risk assessment process. This was another situation where a worker practice during the study resulted in high exposure. Dr. George Milliken commented that there could be information on the labeling but

The Board's statistical review was given by Dr. Milliken. Dr. Milliken had a concern that analyzing putative differences in exposure between returnable vs. non-returnable containers using unit exposure measurements and standard ANOVA techniques might produce different results than if it were to be analyzed using lbs. applied and (raw) exposure values (e.g., regression techniques). Dr. Milliken was also concerned that exposure might increase with temperature and/or other ambient conditions. Mr. Crowley said that it would be appropriate for the HSRB to recommend additional regression analyses to evaluate container type, but that, with respect to evaluation of ancillary factors like temperature, the protocol was not designed to take into consideration ambient and exposure conditions and that these are not meant to be considered individually. Dr. Milliken was also concerned that a someone was allowed to participate that had no training and had high exposures. The HSRB recommended handling his concern during the ethics review portion of the meeting. Dr. Cavallari summarized the recommendations by the Board which included additional data analysis for returnable vs. nonreturnable containers, gloves vs. no gloves, and to determine the temperature effect on exposure. The Board voted unanimously in the affirmative to the

charge question with the response of: "The research presented in AHE 500 and the associated documents are scientifically sound and provide reliable data, useful for assessing the exposure of those who perform mechanical transfer of liquid pesticides using closed systems."

Dr. Mark Aulisio presented the HSRB's ethics review of the study. Dr. Aulisio stated that the ethics review considered relevant current ethical standards and was careful, meticulous, and thorough and found that ethical concerns, and appropriate standards were satisfied. Participants were at least 18 years old and pregnancy screening was done on the day of monitoring. Dr. Aulisio asked if everyone in the study had to have training if they were working under the supervision of a certified applicator. Ms. Arling responded that the person who participated in the study did not raise any ethical concerns for EPA because he was working under the supervision of a certified applicator. Also, Ms. Arling noted that he had at least one year of experience working with closed systems because it was one of the eligibility criteria and his participation probably reflected his normal work activity and posed no additional risks to his safety or welfare. The Board voted unanimously in the affirmative to the charge question with the response of: "Based on the available information the research performed and reported in AHETF study report in monograph AHE 500 and AHE 1022 support the determination the study was conducted in substantial compliance with the applicable requirements of 40 CFR Part 26."

This concluded the Board's session for January 30, 2020 and the meeting was adjourned.

Respectfully submitted:

Thomas J. O'Farrell, 4/28/20

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 Register Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10004-35-ORD]

Human Studies Review Board; Notification of Public Meetings

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA), Office of the Science Advisor, Policy, and Engagement 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 Thursday, January 30, 2020 from 1:00 pm to approximately 5:30 pm Eastern Time. A separate, subsequent teleconference meeting is planned for Tuesday, March 17th, 2020, from 2:00 pm to approximately 3:30 pm Eastern Time for the HSRB to finalize its Report of the January 30, 2020 meeting and review other possible topics.

ADDRESSES: All of these meetings will be conducted entirely by telephone and on the Internet. 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 with access information 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 Thursday, January 23, 2020, for the January 30, 2020 meeting and up to Noon Eastern Time on Tuesday, March 10, 2020 for the March 17, 2020 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 Thursday, January 23, 2020, for the January 30, 2020 meeting and by Noon Eastern Time on Tuesday, March 10, 2020 for the March 17, 2020 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 30, 2020, the HSRB will consider a study titled "Determination of Dermal and Inhalation Exposure to Workers during Closed System Loading of Liquids in Returnable and Non-Returnable Containers" and a report titled "Agricultural Handler Scenario Monograph: Mechanical Transfer of Liquids", both submitted by the Agricultural Handlers Exposure Task Force.

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 17, 2020, the HSRB will review and finalize their draft Final Report from the January 30, 2020 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