EPA-HSRB-20-~~21~~2

Dr. Jennifer Orme-Zavaleta
EPA Science Advisor
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1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: January 30, 2020 EPA Human Studies Review Board Meeting Report

Dear Dr. Orme-Zavaleta,

The United States Environmental Protection Agency (EPA) requested that the Human Studies Review Board (HSRB) provide scientific and ethics review of a completed studies involving human participants. The Board considered a scenario monograph report and completed study report that summarize the Agricultural Handler Exposure Task Force, LLC (AHETF)-sponsored research to monitor the potential dermal and inhalation exposure for workers who transfer liquid pesticides from returnable or non-returnable containers using closed systems as documented within the AHETF Study Report & Monograph (AHE500 and AHE1022).

The HSRB's responses to the charge questions presented at the meeting on January 30, 2020 along with detailed rationale and recommendations for their conclusions are provided in the enclosed final meeting report.

Signed,

Jennifer Cavallari, ScD, CIH
Chair, EPA Human Studies Review Board

INTRODUCTION

On January 30, 2020, The United States Environmental Protection Agency (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to a completed scenario monograph report and completed study report (AHE500 and AHE1022) which summarized Agricultural Handler Exposure Task Force, LLC (AHETF)-sponsored research – Determination of Dermal and Inhalation Exposure to Workers during Closed System Loading of Liquids in Returnable and Non-Returnable Containers/Mechanical Transfer of Liquids. In accordance with 40 CFR 26.1601, EPA sought HSRB review of these completed studies.

REVIEW PROCESS

The Board conducted a public meeting on January 30, 2020. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL-10001-03-ORD). This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale and consensus in response to the charge questions on ethical and scientific aspects of the completed research.

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For each agenda item, the Agency staff presented their review of scientific and ethical aspects of the research, with each presentation followed by clarifying questions from the Board. The HSRB solicited public comments and next proceeded to address the charge questions under consideration. The Board discussed the science and ethics charge questions and developed a consensus response to each question in turn. For each of the charge questions, the Chair called for the Board to vote to confirm concurrence on a summary statement reflecting the Board's response.

For their evaluation and discussion, the Board considered materials presented at the meeting, study reports, related materials and documents provided by the study sponsors, the Agency's science and ethics reviews of the study, as well as oral comments from Agency staff and the investigators during the HSRB meeting discussions. A comprehensive list of background documents is available at https://www.epa.gov/osa/january-30-2020-meeting-human-studies-review-board.

AHETF Study Report & 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.

Charge to the Board- Science:

Is the research presented in AHE500 and the associated documents scientifically sound, providing reliable data useful for assessing the exposure of those who perform mechanical transfer of liquid pesticides using closed systems?

Response to the charge question:

The research presented in AHE500 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.

The HSRB also has specific comments, recommendations and additional minor points which are described in the discussion below.

HSRB detailed response and rationale:

The HSRB has reviewed and supports EPA's science review of AHE500. AHE500 details the justification, methods, results, and conclusions of a study aimed to provide measurements for a typical professional occupational handler's daily exposure to various pesticide products whose use and application requires the pouring of a liquid product (e.g., an antimicrobial concentrate that may be measured and diluted with water prior to use). The purpose of the study was to monitor the potential dermal and inhalation exposure for 36 workers while mechanically transferring liquid pesticides into application equipment or pre-mix tanks without having to pour from pesticide containers. Workers transferred liquids from returnable or non-returnable containers (e.g., disposed of or recycled) using closed systems. The protocol for this study was reviewed by the HSRB in 2011 (report provided in 2012). AHE1022 is a study scenario monograph which combines some of the data in AHE500 (N = 22) with some of the similarly collected data from two previous studies:

- AHE13: “Determination of Dermal and Inhalation Exposure to Workers During Closed-System Loading and ULV Application of a Liquid Pesticide Product to Cotton”; N = 9
- AH501: “Evaluation of Worker Exposures to Tribufos During Aerial and Ground Applications of DEF 6 to Cotton”; N = 7

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The scenario monograph is intended to provide a generic exposure scenario for the mechanical transfer of liquids. The scenario excludes workers who remove the suction probe prior to rinsing (which was demonstrated to have the potential to increase dermal exposures).

Subjects wore long-sleeved shirts or coveralls, long pants, shoes/socks. Chemical-resistant gloves and eyewear were required when the system used was under pressure. Participants wore an internal dosimeter under their own clothing (with the exception of 2 subjects who arrived wearing short-sleeved shirts and were given long-sleeved) and an OSHA Versatile Sampler (OVS). Face/neck were wiped and hands were washed to collect residue. Workers used 4 of 14 potential surrogate chemicals (i.e., chlorothalonil, 2,4-D, glyphosate, and imazapyr).

Previous HSRB comments and outcomes were discussed in the EPA AHE1022 and appear to have been satisfactorily addressed. The sampling procedures were conducted as described in the protocol. Protocol amendments and deviations were noted. The protocol was amended 3 times and 6 protocol deviations were noted. These were determined not to have adversely affected study results. There were 3 amendments and 6 deviations detailed in the study AHE500 report and the EPA review.

There was a good diverse set of conditions such as time (25 years), geographic areas/U.S. states (13 states), types of mechanical transfer systems, container size, transfer set-up and different workers/employers. The data from this study is acceptable and appropriate for use in assessing exposure and risk for workers using closed systems to mechanically transfer liquid pesticides.

Recommendations

The HSRB suggests the following changes and clarifications to the study report and/or EPA review document:

- In the EPA review, head patches are noted in Section 3.3. According to study protocol, no head patches were used. Please edit information to be consistent with the current study.
- AHE500 Study Report should include a Conclusion/Results Section that incorporates the comparison between the returnable or non-returnable container scenarios.
- Develop a plan for using the data from the scenarios when workers remove the suction probe prior to rinsing. These data represented a large proportion of the study population and may represent a common work practice. If in fact removing the suction probe prior to rinsing is a common work practice, excluding the data from the scenario would underestimate exposure and risk.
- If EPA continues to exclude workers who remove the suction probe prior to rinsing, EPA may consider developing guidance for proper suction probe use either through risk assessment- or training-based approaches, as EPA determines.

Statistical review

The data collected within AHE500 are to be combined with comparable data from previous studies, AHE13 and AH501-M-1. Once the set of MUs were selected, analyses were carried out to relate AaiH to inhalation exposure and dermal exposure.

The data collected using the current rules (in particular AHE500) provides superior data than was collected before. Instrumentation and technique improvements led the way, which helped improve data as well as the determination of LOQs and LODs.

Recommendations

The HSRB suggests the following clarifications:

- The Board recommends clarifying how randomization was or was not used. The protocol has a discussion of using randomization, but there is no mention as to how randomization was used to carry out the study.

- The Board recommends providing statistical evidence to show the Closed System Loading of Liquids in Returnable and Non-Returnable containers (CSLL-R and CSLL-NR) data sets are combinable. While, the analyses showed that the overall means were similar between CSLL-R and CSLL-NR, but there were no comparisons between the slopes when AaiH was used as a predictor. For example, the slopes and intercepts for the relationship between inhalation exposure and AaiH can be compared by carrying out a formal test of equality of slopes and (if the slopes are equal) a formal test of equality of intercepts. These tests can be accomplished within the mixed regression model that has be utilized for other aspects of the analyses, which are well supported.

- The sub-clusters from AH501-M-1 and AHE13 as shown in Figure 3 show the dermal data are more closely related with much less variation than the clusters from AHE501. Likewise, the inhalation data from AH501-M-1 and AHE13 have higher medians and possibly less variation than the clusters from AHE500. The graphical information in Figure 3 adds doubt that the data from AHE500 are similar to the data from AH501-M-1 and AHE13. These anomalies could be caused by the facts that the data from AH501-M-1 were collected in 1999, the data for AHE13 were collected in 2004 and the data from AHE500 were collected 2012 – 2016. More effort needs to be put into justifying the combining of the three data sets, and not just through the comparisons of means. If justification is not carried out then just use the data from AHE500 for the database.

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- The effect of environmental conditions such as temperature, humidity and wind speed may have an effect on the dermal and inhalation exposures and should be explored. The pesticides are likely to be more volatile in higher temperature and/or humidity and wind direction and speed may contribute to dermal deposition or inhalation. More discussion needs to be provided on this issue. The use of Box Plots with geometric means and medians provide useful representations of influence of environmental conditions on the data.

- The HSRB recommends additional information about the intra subclass correlation from AHE500 be provided. The investigation of the intra class correlation is useful and necessary to determine if a particular variance component is appropriate. The intra sub

class correlation is dominated by data from studies AHE13 and AH501-M-1 as there was only one subclass with two observations for AHE500.

- Given the sophistication of the SAS code, a read me file (See: Documenting Electronic Data Files and Statistical Analysis Programs Guidance for Industry CVM GFI #197, U.S. Department of Health and Human Services Food and Drug Administration Center for Veterinary Medicine May 2018) would facilitate the duplication of the analyses.

CHARGE TO THE BOARD - ETHICS

Does the available information support a determination that the study was conducted in substantial compliance with the applicable requirements of 40 CFR part 26?

Response to the charge question:

Based on the available information, the research performed and reported in AHETF Study Report & Monograph (AHE500 and AHE1022) supports a determination that the study was conducted in substantial compliance with the applicable requirements of 40 CFR part 26.

HSRB detailed response and rationale:

In its conduct, study AHE500 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied.

- The relevant sections of 40 CFR 26 Subpart Q are: 26.1703: Except as provided in 26.1706, EPA shall not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child. All AHE500 study participants were 18 years old or older. Screening and pregnancy testing was done on the day of monitoring and no subjects were pregnant or lactating. The research satisfies this requirement and so its results, ceteris paribus, may be used.
- 26.1705: Except as provided in 26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in

substantial compliance with all applicable provisions of subparts A through L of this part. Only subparts K and L are applicable to this research. Subpart K addresses “Basic Ethical Requirements for Third-Party Human Research for Pesticides Involving Intentional Exposure of Non-Pregnant, Non-Nursing Adults” and was satisfied. Subpart L is the detailed “Prohibition of Third-Party Research involving Intentional Exposure to a Pesticide of Human Subjects who are Children or Pregnant or Nursing Women” and was satisfied as no children, pregnant or nursing women were enrolled in the study.