August 22nd, 2016

EPA-HSRB-

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Subject: July 12-13, 2016 EPA Human Studies Review Board Meeting Report

Dear Dr. Burke,

The United States Environmental Protection Agency (EPA) requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of two completed studies from the Agricultural Handler Exposure Task Force (AHETF). These two studies were reviewed at a meeting of the Board on July 12-13, 2016:

- **The Completed Study and Monograph Report for Agricultural Handler Exposure for Wettable Powders**

- **The Completed Study and Monograph Report for Agricultural Handler Exposure during Mixing/Loading of Pesticide Products in Water Soluble Packets**

The Board's responses to the charge questions are detailed in the enclosed final report of the meeting.

Signed,

Liza Dawson, PhD
Chair
EPA Human Studies Review Board

INTRODUCTION

On July 12-13, 2016, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to two studies conducted by the Agricultural Handlers Exposure Task Force (AHETF):

- **The Completed Study and Monograph Report for Agricultural Handler Exposure for Wettable Powders (AHE80)**
- **The Completed Study and Monograph Report for Agricultural Handler Exposure during Mixing/Loading of Pesticide Products in Water Soluble Packets (AHE 120)**

REVIEW PROCESS

The Board conducted a public meeting on July 13-14, 2016. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA-HQ_____).

This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale and consensus in response to each charge question for each of these items.

For each agenda item, Agency staff first presented their review of the science and the Board asked the Agency presenters clarifying questions. The staff then described their review of the ethical aspects and the Board asked clarifying questions with regard to the ethical review. The HSRB solicited public comments and next proceeded to address the charge questions, first discussing scientific review and then ethical review, for each study. The Chair called for a vote to confirm concurrence on a summary statement in response to each charge question.

For their evaluation and discussion, the Board considered study reports, related materials and documents such as standard operating procedures provided by the AHETF, the Agency's science and ethics reviews of the studies, as well as oral responses from the AHETF and from EPA staff

at the meeting. A comprehensive list of background documents is available online at http://www.epa.gov/hsrb/.

The HSRB review of the two AHETF studies is presented below. This report presents the board's finding for each study in the order in which the studies were reviewed at the meeting. Because some of the same scientific concerns were raised for the two studies, the report makes note of the common issues raised but does not duplicate the discussion of issues when identical concerns were raised in the two reviews.

HSRB review of the Completed Study and Monograph Report for Agricultural Handler Exposure for Wettable Powders (AHE80 and AHE1015)

Science Review

Charge to the Board

1. Was the research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph report and associated field study report for AHE80 faithful to the design and objectives of the protocol?
2. Did the research generate scientifically reliable data, useful for assessing the exposure of individuals who mix and load conventional pesticides formulated as wettable powders?

Board Response

1. The research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph report (AHE1015) and associated field study report (AHE80) were faithful to the design and objectives of the protocol.

2. The research generated scientifically reliable data, useful for assessing exposures related to conventional pesticides formulated as wettable powders, subject to recognition of some limitations in the data, as described below.

HSRB Detailed Recommendations and Rationale

The Board commented that the study was well conducted and adherent to the protocol and research plan. However, given recruitment challenges and limited diversity of scenarios available for inclusion in the study, there are some limitations in the data that affect the conclusions that can be drawn from this study. In spite of consistent effort on the part of the study team to collect sufficient data to address study goals, there were three areas in which the study results were less than optimal: a) limited diversity in scenarios; b) failure to confirm proportionality of exposure with AaiH and c) uncertainty in estimates of inhalation exposures due to high variability. Each of these will be discussed in more detail below.

Given the limited use of wettable powder in current agricultural practice, in addition to ongoing challenges of locating enough companies interested in participating, there were challenges in recruiting sufficient numbers of monitoring units (MUs) for the study. In addition, the lowest AaiH stratum was not populated and therefore the range of AaiH was not as broad as desired to achieve better statistical power. The EPA scientific review acknowledged these limitations[1] but accepted them as unavoidable given current practices in the field and difficulties in recruiting. The HSRB agreed with this assessment.

Sufficient diversity was not achieved with regard to the type of mixing tank used.[2] This reflects the original concern from the HSRB review[3] about breadth and representativeness of scenarios but again, EPA reviewers provided a rationale for accepting this deficiency, given that the wettable powders are not commonly used, so it is difficult to recruit sufficient diversity in equipment. The HSRB also agreed with this conclusion.

Furthermore, the data collected are neither fully observational nor random (representative) but EPA recognizes and accepts this limitation and maintains that the new data is clearly an improvement over the earlier (PHED) data.[4] Limitations of existing database and need for new

[1] EPA Scientific review, page 9.
[2] Reference AHE report
[3] Reference previous HSRB review of protocol
[4] EPA – Page 19, paragraph 1

data are explained and need for new data clearly justified in the AHE1015 report,[5] and the HSRB concurs.

A key assumption for the validity of the study is that the exposure measurements are independent of the type of active ingredient handled—and that therefore results from this study should be suitable for extrapolation to other active ingredients used in the field. The AHE report states "Exposure is not determined by the properties of the active ingredient in a product but rather by physical factors …."[6] This may not be true in all cases, although in the case of the wettable powder mixing/loading scenario as tested in AEH80 and AEH39 the statement is likely true, but this should not be generalized to all exposure scenarios. A second critical assumption is proportionality of exposure to AaiH. The latter assumption of proportionality was not demonstrated in the study, but in part this may be due to the limited AaiH and small number of MUs.

Two observations may also be helpful for understanding the data: 1) most of the workers wash gloves with water then remove gloves between loadings and 2) some of the subjects actually got wet during the loading (likely to impact dissolution and transfer of S through outer clothes).

In terms of statistical soundness, the study met the primary criterion of estimating exposure to within three fold accuracy for dermal exposure. For dermal exposure, it was notable that Subject M13 is a potential outlier because of unusually small exposure value. The data from M13 was included in the analysis. For geometric and arithmetic means and 95th upper confidence limit, all estimates were within three-fold accuracy.

In contrast, inhalation exposure was not a priority for the three-fold accuracy requirement as part of the study, based on EPA's statement of objectives.[7] Subject M13's inhalation exposure value was within the range of the data from the remaining subjects and hence, not a potential outlier. Most of the exposure statistics estimates were not within three fold accuracy.

[5] AHE1015 page 25
[6] AEH1015 Page 26
[7] Memorandum on EPA's monograph review, page 14

The secondary statistical objective was to test for a proportional relationship between exposure and amount of active ingredient handled versus independence (no linear relationship) with at least 80% power. Assuming a straight line model for exposure as a function of amount of active ingredient handled (with or without accounting for the correlation structure generated by the design), testing the hypotheses

H_0: slope = 1 (proportionality)

H_1: slope = 0 (independence)

is equivalent to checking for one or zero in the 95% confidence interval for the slope.

For dermal exposure, when subject M13 was included, the confidence interval for the slope contained both 1 and 0 indicating that both proportionality and independence are feasible. Hence, the results should be considered as inconclusive. When subject M13 was not included, the confidence interval for the slope contained 1 but did not contain 0 indicating consistency with a proportionality assumption. However, based on the confidence interval width, the 80% power requirement was not met.

For inhalation exposure, when subject M13 was included, the confidence interval for the slope contained 1 but did not contain 0, indicating consistency with a proportionality assumption. However, based on the confidence interval width, the 80% power requirement was not met.

In conclusion, the principal criterion of three-fold accuracy was met for dermal exposure in the study; the other statistical criteria (three fold accuracy for inhalation and 80% power to determine proportionality for either dermal or inhalation) were not met. Given the limited diversity and small sample size, these results are not surprising.

Ethics Review

Charge to the Board: Does the available information support a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR Part 26?

Board Response to the Charge: The Board concurred with the EPA assessment that available information supports a determination that the studies were conducted in substantial compliance with 40 CFR 26 subparts K and L.

HSRB Detailed Recommendations and Rationale

The protocol was reviewed and approved by an independent human subject review committee, Independent Institutional Review Board, Inc. (IIRB, Inc.) of Plantation, FL (initial submission 9/30/10) and Schulman Associates IRB, Inc. (SAIRB) of Cincinnati, OH/Ft. Lauderdale, FL prior to submission and as the study progressed [note: during the conduct of this study, IIRB was acquired by Schulman Associates IRB on 10/24/12](AHE80 - IRB Correspondence Report 3-23-16). Both IRBs are fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Minutes of IRB meetings and copies of all correspondence were provided to the Agency. These documents indicate that the IRBs reviewed this protocol, amendments and reports in accord with the standards of the Common Rule (40 CFR Part 26, Subpart A).

The informed consent materials (AHE80 - IRB Correspondence Report 3-23-16, pp. 44-58; 143-154; 225-234; 248-259; 297-318; 338-350; and 351-364[Spanish]) contained adequate information for the subjects (n=21) about the risks, discomforts and benefits of participation, and of their right to withdraw (n=2). The risk-benefit ratio was determined to be acceptable and risks were minimized appropriately and were justified by the potential societal benefits associated with gathering data to determine the potential exposure for workers who mix and load wettable powder formulations using open pouring techniques. The selection of study participants (English or Spanish speaking) appeared to be equitable and no children or pregnant women were enrolled.

The submitted documents (AHE80 - Field Study Report Final 01-27-16, Heat Index from Field Notebooks for AHE80, and AHE1015 Monograph for Wettable Powder Mixer Loader – Final 4-7-16 [especially section 4.0]) indicate that the study was conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements of the US EPA Good Laboratory Practice (GLP) Standards described at 40 CFR 160. For the research conducted in California ("Area 84" of study AHE80), the requirements of the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (Ref 2010) applied. Requirements of FIFRA §12(a)(2)(P) also applied. Researchers who participated in the study and interacted with study participants were required to complete ethics training.

HSRB review of the Completed Study and Monograph Report for Agricultural Handler Exposure during Mixing/Loading of Pesticide Products in Water Soluble Packets (AHE 120 and AHE 1014)

Science Review

Charge to the Board

- Was the research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph reports and associated field study report for AHE120 faithful to the design and objectives of the protocol?

- Did the research generate scientifically reliable data, useful for assessing the exposure of individuals who mix and load conventional pesticides formulated in water soluble packets?

Board Response

- The research reported in the AHETF completed monograph reports and the associated field study report for AHE120 was faithful to the design and objectives of the protocol.
- The research did generate scientifically reliable data, useful for assessing the exposure of individuals who mix and load conventional pesticides formulated in water soluble packets, subject to some limitations in the data, as discussed below.

HSRB Detailed Recommendations and Rationale

Much of the discussion of the AHE 120 study was similar to that for the previous study of wettable powders. There was a small number of MUs and limited diversity in the sample, again due to recruitment difficulties. Barring unresolved concerns raised in the previous review regarding conflicts between the non-random, purposive study design and conventional statistical methodology, the study generated scientifically reliable data that may be useful for assessing

exposure of individuals who mix and load conventional pesticides formulated in water-soluble packets.

In a previous review the HSRB had commented that time on task might be an appropriate measure to help capture variability in exposures for a given AaiH. It does not appear that the ratio of time on task to the total monitored time was calculated. Regarding study design it should be noted that only 16 of the 25 sets of monitoring unit samples were used in the analysis given that nine MUs were invalidated due to equipment use or practices that were deemed inappropriate for the scenario; therefore the final sample size was smaller than planned. A total of 15 Amendments with no protocol deviations were reported and the amendments were considered to be scientifically appropriate. Of minor concern is the lack of an executive summary to capture the salient findings of the study.

Regarding the statistical aspects of the study, the primary benchmark objective is for select statistics (the geometric mean (GM), the arithmetic mean (AM), and the 95th percentile (P95)) to be accurate within 3- fold with 95% confidence. The primary benchmark of 3-fold accuracy for select statistics was met for both dermal but not for inhalation exposure data. The AHETF demonstrated both dermal and inhalation unit exposures were shown to fit lognormal distributions reasonably well.

The secondary objective of the study design is to be able to distinguish complete proportionality from complete independence between dermal exposure and amount of active ingredient handled with an 80% statistical power. The AHETF performed regression analysis of ln(exposure) and ln(AaiH) to determine if the slope is 1 (which provides support for a proportional relationship) or 0 (which provides support for an independent relationship). Simple linear regression and mixed-effects regression (that accounts for within-cluster correlation) were performed to evaluate the relationship between exposure and AaiH. A confidence interval of 1.4 (or less) indicates at least 80% statistical power. Based on the AHETF analysis, this benchmark was met and analyses for both dermal and inhalation exposure had 80% power to detect proportionality or independence. The 95% confidence interval slope of the mixed-effects regression suggested a proportional relationship is more plausible than an independent one based on data.

Ethics review

Charge to the Board:

Does the available information support a determination that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L?

Board Response:

The available information supports a determination that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L.

HSRB Detailed Recommendations and Rationale:

This protocol (AHE 120) was reviewed by the HSRB at its October 2010 meeting[8] and subsequently reviewed and approved by the Independent Institutional Review Board (IIRB), Inc. of Plantation, Florida in December 2010. According to the HSRB's December 13, 2010 Final Report, IIRB was fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) and listed as an active IRB by the Office for Human Research Protections (OHRP) at the time of IRB review. IIRB was later purchased by Schulman Associates IRB (SAIRB), though that transaction had no adverse impact on the IRB review process for this protocol. SAIRB is also fully accredited by AAHRPP and listed as an active IRB by OHRP. The July 31, 2015 IRB Correspondence Report for Study AHE120 indicate that the IRB of oversight reviewed the protocol and its 15 subsequent amendments in accordance with their responsibilities under subpart K. Amendments were not implemented until after receiving IRB approval.

The greatest risk to participants in this study was the potential for heat-related illness because they were required to wear two layers of clothing. However, the study protocol contained

[8] Philpott, S. October 27-28, 2010 EPA Human Studies Review Board Final Report, EPA-HSRB-10-02, (December 13, 2010).

oversight by an on-site medical professional and appropriate stopping measures (including cessation of monitoring activities when the ambient heat index exceeded 105°F). There were no heat-related adverse events reported in the AHE 120 Study Report of IRB Correspondence Report.

Risks were further minimized by enrolling only participants who were experienced in the mixing and loading by open pouring and by requiring training in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS) or be exempt from such training.

The study followed an appropriate IRB-approved consent process. The informed consent document was translated into Spanish and the consent process for four participants was led by a bilingual researcher. Spanish language materials were IRB approved.

Recruitment procedures for this study followed AHETF Standard Operating Procedures (SOPs) for recruitment. An HSRB ethicist reviewer expressed concern about the lack of women enrolled in the study, but information provided in the EPA ethics review during the HSRB meeting indicated that past experience strongly suggests that the general working population who engages in mixing and loading activities is overwhelmingly male, hence the all-male study population. This additional information assuaged the concerns of the HSRB ethicist reviewer.

AHETF SOPs, the AHE 120 protocol, and the AHE 120 informed consent document indicated that personal exposure results would be provided to participants upon request. At the July 13, 2016 meeting, AHETF representatives confirmed that those personal results had been given to all participants whose data were analyzed. For those two individuals who requested personal results but for whom none were available, they were informed of the lack of personal results.

Concerning subpart L considerations, the AHE 120 protocol specifically excluded pregnant or lactating women and minors from study participation. There was a pregnancy screening process approved by the IRB and deemed acceptable by HSRB in its December 2010 Final Report. However, no females enrolled in the study.

For these reasons, the HSRB concludes that the available information supports a determination that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L.