EPA-HSRB-19-2

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

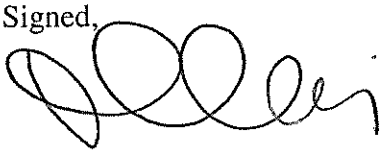
Subject: April 24th, 2019 EPA Human Studies Review Board Meeting Report

Dear Dr. Orme-Zavaleta,

The United States Environmental Protection Agency requested that the Human Studies Review Board provide scientific and ethics review of a completed human study sponsored by the Agricultural Handler Exposure Task Forces, LLC (AHETF). The AHETF Study Report and Monograph (AHE600 and AHE1023) summarize completed research that has monitored the potential dermal and inhalation exposure for workers who perform open pour mixing, loading and application activities, and where appropriate associated equipment clean-up activities, using powered handgun equipment to make foliar applications in managed horticultural facilities (nurseries and greenhouses).

The Board's responses to the charge questions presented at the April 24, 2019 meeting along with detailed rationale and recommendations for their conclusions on this study are provided in the enclosed final meeting report.

Signed,



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

INTRODUCTION

On April 24th, 2019, 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 study involving human participants measuring dermal and inhalation exposure for workers who perform open pour mixing, loading and application activities, and, where appropriate, associated equipment clean-up activities such as using powered handgun equipment to make foliar applications in managed horticultural facilities (nurseries and greenhouses). In accordance with 40 CFR 26.1601, EPA sought HSRB review of this completed study. The study is discussed more fully below.

REVIEW PROCESS

The Board conducted a public meeting via virtual meeting on April 24th, 2019. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL-9991-24-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 Agricultural Handler Exposure Task Forces, LLC (AHETF) completed research, *Dermal and Inhalation Exposure to Workers during Mixing, Loading and Application of Pesticides in Managed Horticultural Facilities using Powered Handgun Equipment as presented in the study report (AHE600) and monograph (AHE1023).*

Agency staff presented their review of scientific and ethical aspects of the study, with each presentation followed by clarifying questions from the Board. The HSRB solicited public comments and then took up 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 presentations given by EPA staff at the meeting, oral comments from Agency staff and the investigators during the meeting discussions, as well as the information contained within the following documents: AHETF AHE600 Study

Report, AHETF AHE600 IRB Correspondence Report, AHETF AHE1023 Monograph; EPA's science and ethics review memos, and AHE600 monograph data tables; the January 26, 2012 Board Meeting report all of which were provided to the Board prior to the meeting. .

Charge to the Board- Science:

Is the research presented in AHE600 and the associated documents scientifically sound, providing reliable data useful for assessing the exposure of those who manually open, pour and mix pesticide products in spray solution tanks and apply the solutions using powered handgun equipment in managed horticultural facilities such as greenhouse and nurseries?

Response to the charge question:

The HSRB concluded that the research presented in AHE600 and the associated documents are scientifically sound, and provide reliable data useful for assessing the exposure of those who manually open, pour and mix pesticide products in spray solution tanks and apply the solutions using powered handgun equipment in managed horticultural facilities such as greenhouse and nurseries.

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

HSRB Detailed Review and Recommendations:

HSRB reviewed information provided in advance of the meeting, as well as the EPA scientific and ethics presentations provided at the meeting. The Board noted and agreed with the EPA's assessment including: the study followed the protocol with amendments and deviations appropriately documented, and the analytical field and laboratory recovery results were acceptable. Furthermore, the Board agreed with EPA's assessment that the study is acceptable and appropriate for use in assessing exposure and risk for workers applying pesticides with handgun equipment in facilities such as greenhouses and nurseries. The workers' activities consisted of opening liquid or dry flowable pesticide products, manually mixing and/or loading the product into a spray solution tank, then spraying the solution on ornamental potted/hanging/bench plants or vegetables using gas-, electric-, or battery-powered handheld

spray guns or wands. Dermal exposures were measured using hand washes, face/neck wipes, and whole-body dosimeters. Dermal exposures were extrapolated to areas covered by eye protection and or respirators. Patches on top and beneath head chemical resistant hats were used to represent exposure without head protection. In effect, exposure monitoring aims to represent a worker wearing long-sleeved shirts, pants, shoes/socks and chemical resistant gloves.

Inhalation exposure was determined using personal air monitors air sampling pumps and OSHA Versatile samples (OVS) mounted on the shirt collar. An inhalation rate of 16.7 L/min was assumed for light activity. Environmental conditions of temperature, humidity, wind speed and direction and rainfall were recorded. Small holes (3) in worker clothing were repaired prior to the study monitoring. Researchers verified that clothing worn by subjects was clean.

The AHE600 protocol included specific restrictions (called similarity restrictions (SR)) to build variability into the study. Within one study location, all three MEs must have different degrees of openness or enclosure (SR 4) and each pair of MEs must have a difference in one of a number of characteristics such as container size, formulation or hose attachment (SR 6). SR4 was not met (protocol deviation made this allowed change), while SR 6 was met.

Although 30 monitoring events (MEs) were planned, 3 MEs were excluded due to deviations, providing a final count of 27 MEs. A "10 x 3" configuration was planned to meet study objectives (i.e., 3 subjects in each of 10 location). However, recruiting difficulties caused a deviation from the original "10 x 3" configuration resulting in 17 monitoring locations with 1 to 4 subjects per location. Analytical field and laboratory recovery results mostly averaged between 70 and 120% recovery, with coefficients of variation less than 25% again for the majority of results.

Within the final dataset including 27 unique workers, subjects ranged in age from 22 years to 60 years. There were 6 females and 21 males. Years of experience ranged from 1 year to 42. The total product loaded over the ME varied from 0.152 oz. to 6 lbs. Exposure times ranged from 0.6 to 8.5 hours and the amount of active ingredient handled ranged from 0.0023 to 5.85 lbs. Observation on subject activities/behaviors were recorded to potentially account for unusual deviations in measurements.

There were 9 protocol amendments and 3 protocol deviations. Protocol amendments occurred to account for additional surrogate active ingredients and allow for varied recruitment strategies. Protocol deviations resulted in the exclusion of 3 ME's (their data was invalidated).

The primary objective was not met. Estimates of arithmetic mean and the 95th percentile dermal exposure were not within 3-fold accuracy with 95% confidence. EPA plans to incorporate a multiplier to incorporate additional uncertainty beyond the 3-fold target level, which the Board supports. Although in the data that there is a relationship (positive upward trend) evident between pounds active ingredient and dermal/inhalation exposure, proportionality may be weak.

HRSB and EPA in 2012 made a number of comments based on the review of the protocols in 2012. Most comments referred to human subject clarification on risks and additional notes to the consent form, and were revised accordingly.

Recommendations

The Board recommends that EPA consider the following when using the data.

Accounting for hat residues: The chemical resistant hat was not analyzed. Ideally the residues from the hat would be combined with the inner and outer patches. Since residues were found on the inner patch, consider adding a safety factor on total head exposure to account for what is lost on the hat.

Activity level for inhalation calculations: If subjects are lifting/pulling anything during the application period, a moderate activity level can be assumed. EPA can consider using higher inhalation rate in calculating inhalation exposures based on a moderate activity level.

Extrapolating hand exposures with respect to glove use: If some pesticide application labels do not require the use of chemical-resistant gloves, dermal exposure estimates may be higher than anticipated. EPA should consider extrapolating exposure to the hand when no glove is used.

Hand wand versus hand gun: For dermal exposures, there was a non-linear relationship between amount of AaiH and log of total dermal exposure. The Board recommends analyzing the

relationships between dermal exposure and AaiH separately for workers who used the hand wand versus the hand gun during application. The application method (hand wand versus hand gun) may be a large source of variability and modeling them separately may better elucidate the relationship between dermal exposure and AaiH.

Exposure time and amount of solution sprayed: Due to the high variability in both amount of solution sprayed and exposure time, the Board recommends evaluating the relationship between exposure time and amount of solution sprayed or exposure time and the dermal or inhalation measurements.

Statistical review. In general, the proposed statistical design and analysis of the protocol are appropriate for EPA's intended use of the data. A detailed review follows.

Appropriate standard curves met AHETF accuracy requirements. Quality control samples were successfully analyzed at routine intervals with each batch of field study samples. Standard curves based on a set of standard concentrations versus the corresponding peak area responses were utilized in order to determine concentrations of the analyte found during sample analysis from the calculated regression line. Analytical data for the study samples were calculated and acquired using automated software applications based on the appropriate regression equation for each analytical set of samples.

For seven surrogates (i.e., acephate, azoxystrobin, chlorothalonil, fosetyl-aluminum, imidacloprid, mefenoxam, thiophanate-methyl), the response of the detectors used in the analyses was linear over the range of residues in the samples. For seven surrogates (i.e., acephate, azoxystrobin, chlorothalonil, fosetyl-aluminum, imidacloprid, mefenoxam, thiophanate-methyl), concurrent recoveries were measured with each set of samples to verify method performance. For acephate, fosetyl-aluminum, mefenoxam, and thiophanate-methyl, interferences for concurrent laboratory controls were less than the LOD for all the samples evaluated for each matrix.

For acephate, the correlation coefficients (r) were >= 0.993. For azoxystrobin, the correlation coefficients (r) were >= 0.994. For chlorothalonil, the correlation coefficients (r) were >= 0.985. For fosetyl-aluminum, the correlation coefficients (r) were >= 0.990. For imidacloprid, the

correlation coefficients (r) were >= 0.984. For mefenoxam, the correlation coefficients (r) were >= 0.998. For thiophanate-methyl, the correlation coefficients (r) were >= 0.996.

For azoxystrobin, interferences for concurrent laboratory controls were less than the LOD for all the samples evaluated for each matrix, except for 2 samples: 1 of 11 face/neck wipe controls and 1 of 11 OVS tube controls. The residues found were slightly higher than the LOD except for one of the hand wash controls that contained about 10-times the LOD. For chlorothalonil, interferences for concurrent laboratory controls were less than the LOD for all the samples evaluated for each matrix, except for: 3 of 6 inner dosimeter controls and 4 of 6 OVS tube controls. For imidacloprid, interferences for concurrent laboratory controls were less than the LOD for all the samples evaluated for each matrix except for 7 samples: 2 of 12 inner dosimeter controls, 1 of 10 head patch controls, 3 of 12 sock controls, and 1 of 12 OVS tube controls. The residues found were slightly higher than the LOD except for the OVS tube control that contained about 10-times the LOD.

For almost all of the surrogates and matrices, LODs were successfully determined using a one-tailed t-statistic on a minimum of seven fortification sample recoveries at the LOQ from the method validation trial using a procedure recommended by EPA (EPA, 2000). However, a theoretical LOD was calculated as a percentage of the LOQ for these surrogate/matrix combinations. Several sample results were below the LOQ and/or LOD. The following chromatography and detection methods used were used:

- Acephate: GC coupled with flame photometric detection operating in the phosphorus specific mode (GC-FPD).
- Azoxystrobin, imidacloprid, mefenoxam, and thiophanate-methyl: HPLC coupled with positive-ion electrospray tandem mass spectrometric detection (LC/MS/MS).
- Chlorothalonil: gas chromatography coupled with electron capture detection (GCECD).
- Fosetyl-aluminum: HPLC coupled with negative-ion electrospray tandem mass spectrometric detection (LC/MS/MS).

The amount of active ingredient in the test substances handled by subjects was successfully determined based on a sample of each lot of test substance. The results of these analyses were

used to determine the actual amount of active ingredient handled (AaiH) by each study participant. Each of the 27 valid MUs in this scenario handled a single lot of test substance, so a total of 27 different lots were analyzed. All 27 lots assayed within ±3% of the nominal concentration shown on the product label, except for the test substance sample for MU 01 which was 13% above the nominal concentration.

Secondary benchmark was successfully met. Analysis shows results are consistent with study design of at least 80% power. These statistical procedures were deemed appropriate. The research presented in AHE600 and the associated documents is scientifically sound, providing reliable data useful for assessing the exposure of those who manually open, pour and mix pesticide products in spray solution tanks and apply the solutions using powered handgun equipment in managed horticultural facilities such as greenhouses and nurseries.

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:

The Board believes that this study was conducted in substantial compliance with the applicable requirements of 40 CFR part 26.

HSRB detailed recommendations and rationale:

The Agency's rules at 40 CFR part 26 subpart Q that are applicable to this review include the following: §26.1703: Except as provided in §26.1706, EPA must 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. And §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.

The Final Report and supporting materials submitted by AEATF II for EPA review indicate that all planned recruitment procedures were followed in the conduct of the study. Thirty-four potential participants signed an informed consent document and 30 subjects were monitored.

For the 6 female subjects who completed study assessments, pregnancy testing was performed on the day of the monitoring procedures to ensure that pregnant women were not included in the study. Nursing women were excluded by the eligibility criteria.

The informed consent process was performed in an appropriate way, with privacy provided for the consent discussion with potential participants. A Spanish translation of the consent document was provided and a Spanish-speaking research team member was present for both the consent discussion and the research procedures day, for participants who asked to communicate in Spanish. Modifications to the consent process including reading the consent document out loud were in place for potential participants who were not literate.

Compensation for study participation included $20 for the consent discussion, and $80 for participation in the study monitoring. Payment was provided in cash at the end of each activity. The amount of compensation is reasonable and unlikely to cause undue influence on the decision to participate in the study.

Risks of the study participation were minimized by compliance with the protocol. Risks that were considered were related to surrogate chemical exposure and surfactants in the skin wipes used. The researchers incorporated all comments from the EPA HSRB in the initial protocol review, to reduce study risks. Subjects were also monitored for heat-induced illness during the monitoring period of the study, with a plan for action and care of heat illness should this be necessary. No adverse events were reported in the clinical study report.

Privacy of participants was respected by providing a private location for them to change clothing on the monitoring days, and if assistance was needed to change into the garments for the study, a same-gender researcher was available to assist. Confidentiality of pregnancy testing results was identified as a potential risk, and appropriate measures were taken to ensure that testing was conducted and the results communicated in a confidential manner.

The initial protocol, nine protocol amendments, annual continuing reports, and all ancillary materials including recruitment materials were reviewed and approved by an AAHRPP-accredited independent institutional review board (IRB). The IRB performing the initial approval was Independent Institutional Review Board, which was acquired by Schulman Associates Institutional Review Board, which then became Advarra Institutional Review Board. The events of protocol non-compliance were reported to the IRB, none were considered serious or continuing. Two protocol deviations were reported to the IRB. None of the reported events had any impact on the safety, welfare or rights of study participants.