EPA-HSRB-20-1

Dr. Jennifer Orme-Zavaleta
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1200 Pennsylvania Avenue, NW
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Subject: October 23rd and 24th, 2019 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 two completed studies involving human participants. The study report titled "Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida" summarized completed research sponsored by LivFul, Inc and conducted by the University of Florida Repellent Testing Lab to determine the efficacy of skin-applied repellents against mosquitoes in a field setting. The study report by the Antimicrobial Exposure Assessment Task Force II titled "A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer" (AEA10) summarized completed research to evaluate the potential dermal and inhalation exposures of workers using airless paint sprayer equipment to apply paints containing antimicrobial pesticides.

The HSRB's responses to the charge questions presented at the meetings on October 23rd and 24th, 2019 meetings along with detailed rationale and recommendations for their conclusions on these studies are provided in the enclosed final meeting report.

Signed,

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

INTRODUCTION

On October 23-24, 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 titled "Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida" and a completed study titled "A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer" (AEA10). In accordance with 40 CFR 26.1601, EPA sought HSRB review of these completed studies. Each study is discussed more fully below.

REVIEW PROCESS

The Board conducted a public meeting on October 23-24, 2019. 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.

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/october-23-24-2019-meeting-human-studies-review-board.

The HSRB review of each of the reported studies is presented below, in the order in which the studies were reviewed at the meeting.

Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida

Charge to the Board- Science:

Did the study "Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida" generate data that are scientifically reliable and useful for estimating the amount of time each of the products tested repels mosquitoes?

Response to the charge question:

The HSRB concluded that the research presented in the final report "Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida" generated data that are scientifically reliable and useful for estimating the amount of time each of the products tested repels mosquitoes where the Complete Protection Time (CPT) for both products can be established at 3 hours.

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

HSRB detailed response and rationale:

The IR3535 study is a field evaluation of two topically applied insect repellent products (i.e., wipe and a lotion) containing IR3535 in order to estimate the amount of time each of the products tested repels mosquitoes. Therefore, the study's aim is to determine the median Complete Protection Time (mCPT). The active ingredient in the product is 20% w/w of the active product ethyl butyl acetyl aminopropionate (IR3535).

On July 26th, 2017, the HSRB met to review the proposed study and EPA and the HRSB proposed a number of changes to the protocol and therefore study design. The proposed changes fell into five categories: 1) provision of more background information in the protocol document; 2) clarifications regarding the study design; 3) clarification of planned statistical methods; 4)

provision of further detail about study procedures; and 5) correction of minor discrepancies in the protocol document.

Through review of the amended study protocol (2018 version), the study sponsor's report and EPA science and ethical review, it appears that the study sponsor did an adequate job of responding to requested changes suggested by HRSB and EPA before the start of the study in summer of 2018. Some of the specific changes included: better description of demographic characteristics of the population within the recruitment area, description of pre-test aspiration and training requirements, provision of soap and how the test skin area will be cleaned, guidance for subjects between testing to prevent contamination of test area, separation of inclusion and exclusion criteria, testing for other vector-borne pathogens, provisions for health requirements of subjects, and other minor consent document changes.

Performance of Study

Researchers appeared to have followed all protocol stipulations in conducting the study in terms of pre-testing for attractiveness, capturing and testing mosquitoes for diseases (i.e., viral pathogen testing and pre testing of species distribution), use of aspirator training, selection of subjects and randomization into groups, product application and testing activities throughout test days. There are a number of aspects important to achieve during the study and those include: 1) adequate landing pressure on controls and 2) sufficient number of subjects achieving failure during the testing period, defined as of least 7 subjects failing (achieving confirmed landing) before the 16 hour post application period, where the product is applied 2 hours prior to any exposure to mosquitoes.

Test days (or Trials) 2 and 3 were excluded from the calculations due to low mosquito landing pressure. Test day 4 was excluded from calculations of mCPT as only 6 subjects experienced failure, which is below the requirement of at least 7 subjects failing; however, the data from this test day was used to estimate the CPT and considered by EPA. The mCPT was calculated using data from Test days 1 and 6 for the lotion application, and Test day 5 for the wipe.

Study Deviations and Protocol Amendments

Assessment of deviations and protocol amendments made during the study are important to consider and review as they may impact the scientific reliability of study results. It should be

noted that some of the items noted below were deviations, but later became protocol amendments.

1) Researchers implemented a key protocol change following test day 1 and test day 2: To reduce the testing requirement from landing pressure of 5 mosquito landings in 5 minutes or less on two control subjects to 5 mosquitoes landing within 5 minutes or less on one control subject.
    a. This amendment was submitted for the purposes of continuing the study, rather than for the calculation of mCPT.
2) Not all landing mosquitoes could be collected via aspirator on test days 1, 2 and 3. A protocol amendment was approved before test day 4, indicating that it was more important to avoid bites to subjects than to capture all mosquitoes.
    a. The HSRB agrees with the EPA and sponsor assessments that this did not have a significant impact on the scientific reliability of the study.
3) Some intervals were longer than the 30 minutes between exposure periods, due to logistical reasons.
    a. The HSRB agrees with the EPA and sponsor assessments that this did not have a significant impact on the scientific reliability of the study.
4) A protocol amendment was approved to clarify the language for skipping exposure periods due to low mosquito landing pressure. Some exposure periods were skipped on trial day 1.
    a. The HRSB agrees that with EPA that exposure periods should not be skipped for low landing pressure, and only for weather conditions. As clarified by EPA, only if a number of exposure periods have low landing pressure for all controls, the study should be stopped (i.e., for this study that should be 5 consecutive exposure periods). However, it is notable that at least two periods with insufficient landing pressure did achieve CPT (Test day 5). It is unclear as to whether activities before this change affected the outcome of the study.
5) A protocol amendment was approved to replace a spatula with a beaker for weighing of lotion applied, given fluidity and volume needs for the lotion.
    a. The HSRB agrees with the EPA and sponsor assessments that this did not have a significant impact on the scientific reliability of the study.

Determining a reliable and accurate mCPT for the two product applications (i.e., wipe and lotion).

The lotion and wipe products will be marketed and must perform according to labelling under low- or high-pressure biting conditions. Therefore, the product must be tested under adequate landing pressure as determined by the minimum requirement for 5 mosquitoes landing within 5 minutes or less on untreated controls. The study sponsor attests that the data support a CPT of 14 hours for both product formulations while EPA disagrees based on inadequate landing pressure on test days 5 and 6 and supports a CPT of 3 hours. The factors related to the difference in CPT are associated with both landing pressure as well as attractiveness of the controls. EPA identified inadequate landing pressure on test day 5 and test day 6 during the middle of the test period (between dawn and dusk) with inconsistency across subjects, which EPA interpreted was due to low activity, and not just to mosquitoes' preference for either subject. The HSRB agrees with this assessment. All subjects were tested for attractiveness and their suitability for the study was confirmed. It is the HSRB's assessment that lack of attractiveness for a control is then inappropriate to claim in the progression of the study. Low landing pressure can be due to a number of other undetermined factors.

Given the current data, specifically the failure to achieve agreed-on landing pressure, the HRSB agrees with EPA that the data do not support a CPT of 14 hours and a reasonable interpretation of 3 hours CPT is suitable and protective of public health at this time.

Recommendations

The HSRB suggests the following changes and clarifications to study protocols:

1) For field evaluation of insect repellents, test sites should be screened for a diversity of mosquitoes across time and adequate landing pressure prior to study initiation.
2) We urge better communication between the EPA and the Sponsor. In particular, EPA should provide adequate guidance on the adaptation of the landing pressure rule in OCSPP 810.3700 to longer exposure times (i.e., repellents expected to be effective for longer durations, and which therefore require longer testing periods during efficacy

trials), and when a study should be stopped (either for weather or the number of low landing pressure consecutive exposure periods).

3) Since the median complete protection time (mCPT) is the time when 50% of the treated people will remain protected from landings – this also means that 50% of the treated people will not be protected. The mCPT may not be sufficiently -protective of public health for CPT calculations and EPA should explore more conservative protection factors (e.g., the 10^{th} percentile).
4) In future studies, EPA should be concerned and work with study investigators when a number of deviations and amendments are requested as the study is being conducted. Neglecting to do this may lead to issues of result interpretation.
5) For both the wipe and the lotion applications, it is unclear how dose is translated to a usable metric for the public, particularly given how the wipe dose in the study was applied in a different manner than would be applied by the public. The wipe was squeezed to release the product. This product amount was then weighed and applied to the skin for this study. EPA or sponsor needs to clarify whether the public is likely to get a similar product dose by using the wipe directly to the skin.

Statistical review

The statistical design and analysis of the protocol are appropriate for EPA's intended use of the data. Kaplan Meier survival analysis is appropriate for calculating mCPT for test day 1, 5, and 6. Test day 4 has more than 50% of data censored so the Kaplan-Meier analysis should not be used for computing mCPT for Day 4. The treatment of censored observations is also appropriate.

CHARGE TO THE BOARD - ETHICS

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

Response to the charge question:

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

HSRB detailed response and rationale:

This study was conducted to determine the complete protection time/efficacy of repellents applied to the skin that contained 20% IR3535 (ethyl butyl acetyl aminopropionate). A lotion and a wipe formulation were tested. Testing was conducted at the University of Florida Repellent Testing Lab.

Independent ethics review:

The draft protocol was approved by the University of Florida Institutional Review Board (IRB) #1 which is registered with the Office of Human Research Protections (OHRP) and accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). The draft protocol was reviewed by the EPA, and by the HSRB at the 26 July 2017 public meeting. Changes to the protocol were proposed by both EPA and the HSRB. The researchers revised the protocol to address the EPA and HSRB requested changes. The IRB approved the protocol, consents and other study materials on 21 March 2017 and the study was closed on 20 December 2018.

Selection of subjects

Recruitment was conducted in the Gainesville, FL area using IRB-approved materials and was in substantial compliance with the protocol. A total of 70 persons were recruited for the study, 68 completed the consent process and 38 subjects (20 males, 18 females) participated in at least one test day.

Potential participants who responded to advertisements were contacted by phone using a script and, if interested, were invited to a meeting with the study team to learn more and to consent to participate. Study subjects were screened via questionnaire and required to be between 18 and 55 years old. Other inclusion/exclusion criteria were as defined in the protocol. Subjects were required to speak and understand English. Pregnant and nursing women were excluded, as well as employees of the University of Florida, the study sponsor, and their spouses.

Next, subjects had a training visit. One deviation occurred during a training visit when a female subject participated in the mosquito attractiveness test before completing the screening questionnaire and pregnancy testing protocol. The subject subsequently completed the pregnancy

test and was not pregnant. This deviation was reported to the IRB but it was determined that it was not serious and not continuing, so no action was needed. However, the study director subsequently created an additional checklist to prevent this from occurring again.

All subjects were at least 18 years of age. Pregnancy testing of female subjects was conducted on each day of testing and no pregnant or lactating women were enrolled in the study.

Informed consent

At the on-site recruitment meeting, the study was outlined and the group was allowed to ask questions. It was emphasized that participation was completely voluntary. Subjects were allowed to ask further questions in a private meeting and given the option to take the consent documents home to review or to sign at the meeting. All participants signed consent documents at the initial private meeting. Randomization and testing were performed satisfactorily as outlined in the protocol, study report and EPA ethics review memo.

Minimization of risks

Safety precautions included limiting the amount and region of skin (lower legs) exposed to mosquitoes during testing, use of protective gear (head nets and clothing) to cover areas not involved in testing, use of lab-raised mosquitoes that had never received a blood meal during mosquito attractiveness and aspirator training, testing in areas identified as not having mosquito-borne pathogens, and coordination with local health departments and mosquito control districts. A shaded, screened in area with chairs, snacks, water, and other drinks was provided to subjects between testing episodes.

There was one adverse event (AE) when a subject reported a skin rash that appeared to be poison ivy and that the subject believed was contracted during participation in the study. This AE was reported to the IRB which recommended revising the consent form to note poison ivy was a risk due to the wooded location of testing sites, but this was not done as the study was already fully enrolled.

Confidentiality was maintained throughout the study. Subjects, including alternates, were compensated per the protocol. The amount of compensation for each subject was consistent with the time spent on the various study-related activities and was not excessive.

There were 8 protocol amendments and these were addressed consistently with IRB and protocol procedures. One amendment noted that epi-pens would not be available during testing and included a change in the screening questionnaire to exclude subjects who did not know how they reacted to mosquito bites to minimize the chances of enrolling a subject with an unknown, severe allergy to mosquito bites.

One deviation involving a subject participating in the mosquito attractiveness test prior to completing the pregnancy test has already been discussed.

Another deviation involved the study team being unable to contact one subject despite multiple attempts until 73 hours after a test day to inquire about adverse events. The allowed time was 72 hours, but the subject had been out-of-town with a dead phone battery. The subject reported no adverse events.

Another deviation involved difficulty capturing "all" mosquitoes landing on test and control subjects during the test day. This resulted in a protocol amendment stating that "attempts will be made to capture all" mosquitoes. More emphasis was also placed on not allowing mosquitoes to bite test and control subjects. This deviation and subsequent amendment appropriately prioritized the subject's safety and welfare.

Several protocol deviations were reported to the IRB related to implementation of the testing and did not impact subject health or welfare.

EPA has noted that the effective dates of some amendments predate the dates of the IRB's approval of the amendments. The HSRB agrees with the EPA that amendments are not effective until they have been reviewed and approved by an IRB. The HSRB agrees with the EPA's recommendation for future studies.

A deviation related to mosquito landing pressure on untreated controls and stopping rules was reported and resulted in an amendment to the protocol to clarify the stopping rules.

A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer (AEA10)

Charge to the Board- Science:

Did the research in study AEA10 generate scientifically reliable data, useful for assessing the exposure of individuals who apply paint containing antimicrobial pesticides using airless sprayers?

Response to the charge question:

The HSRB concluded that the research presented in study AEA10 are scientifically reliable data, useful for assessing the exposure of individuals who apply paint containing antimicrobial pesticides using an airless sprayer.

HSRB detailed response and rationale:

HSRB reviewed information provided in advance of the meeting, as well as the EPA scientific and ethics presentations provided at the meeting. The HSRB was in agreement with the assessment of the results as presented in the EPA scientific report and the superiority of the AEATF II airless sprayer data and associated unit exposures to the existing airless sprayer data set derived from PHED data.

Working with EPA, AEATF II adequately addressed each of the concerns raised by EPA and HSRB within the study protocol and related documents including, but not limited to, randomization of ME assignments, adequate range of variation and acknowledgement of limitations, respirator use, justification of 30 gallons of paint maximum, and adequate drying time for dosimeters.

The sampling procedures were performed as outlined in the protocol. Protocol and SOP deviations were noted, appropriately handled and did not adversely affect the outcomes of the study.

The study achieved a sample size of 18 MEs performed under 2 AaiH concentrations (1,200 or 12,000 PPM) and 3 paint volumes (10, 15, or 30 gallons). A variety of room configurations were

used (2 home and 1 office simulations) with a range of surface areas (1,040 ft^2 to 13,673 ft^2) over 58 to 192 minutes.

The QA/QC procedures were adequately performed and accounted for in the final results.

Unit exposure results were calculated for dermal and inhalation exposure routes (Table 1, EPA report). Test subjects wore both inner and outer whole-body dosimeters that were later sectioned and analyzed by body part to allow for the estimation of unit exposures under various clothing conditions including long/short pants and/or long/short sleeves.

With regard to data generalizations and limitations, the HSRB is in agreement with the EPA that:

1) the choice of one study location by AEATF II was reasonable;
2) the data are acceptable to use as a surrogate when assessing other chemicals with low volatility;
3) the extrapolation of unit exposures to larger volumes of paint is possible up to 100 gallons of paint according to EPA's analysis;
4) the potential exposures appear to be acceptable based on the Margins of Exposure (MOE) calculations provided;
5) the limitations of the data include:
    a. the data are not derived from a fully stratified random sample of ME;
    b. there is a potential underestimation of the face/neck wipe samples; and
    c. care must be taken to extrapolate exposure/risk to consumers, whose behaviors may be less understood.

The HSRB had no additional recommendations beyond those already presented by EPA and summarized above.

Statistical review

The results of the lognormal simple random sampling model are most appropriate for presenting the statistics for the unit exposures. The calculations utilizing substitution of half the LOD for non-detected values below the LOD, or of the average of the LOD and LOQ for non-detected

values between the LOD and the LOQ are most appropriate. These methodologies and results were deemed appropriate.

CHARGE TO THE BOARD - ETHICS

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

Response to the charge question:

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

HSRB detailed response and rationale: Independent ethics review

The protocol was conditionally approved by Schulman IRB in August 2017 and discussed with the EPA HSRB on 25 October 2017. Schulman IRB and the HSRB made a number of recommendations that were appropriately addressed by AEATF II, the sponsor, prior to final approval of the protocol and consent (English version) by Schulman IRB in February 2018. Schulman provided a certified Spanish translation of the consent and all relevant documents. Oversite of the study was transferred from Schulman to Advarra in late July 2018. Both IRBs hold Federal Wide Assurances from OHRP and are registered with OHRP, and both are accredited by AAHRPP.

Selection of subjects

Recruitment was accomplished via English and Spanish advertising via newspapers, radio, printed flyers, and (following an amendment due to low enrollment) Craigslist. Both English and Spanish speaking individuals responded and were initially screened by phone and, if they met the inclusion criteria, were invited to consent meetings. Four potential candidates requested Spanish communications and materials, 24 requested English communications and materials. A bilingual researcher participated in all sessions with the individuals who requested Spanish communications and materials.

Potential subjects were asked to complete an online, English-only health questionnaire as part of the medical evaluation for the respirators. For the four Spanish speaking subjects, the bilingual researcher was present and available to translate as needed as these subjects completed this form.

35 respondents were successfully screened, 28 participated in a consent meeting and were consented to enroll in the study. Three individuals did not pass a medical screen and one did not pass the respirator fit test. Two subjects withdrew from the study prior to being monitored, one due to a family emergency and one due to scheduling difficulties. In the end, 24 subjects were enrolled in the study and 18 subjects were monitored. Five were female and 13 were male, 1 preferred Spanish and the rest preferred English. The 6 subjects who were not monitored were alternates.

All subjects were at least 18 years old, and no pregnant or lactating women were involved in the study.

Informed consent

Potential candidates read the informed consents, had the consents reviewed with them by the researcher conducting the meeting, and had their questions answered. Potential candidates were informed that they were free to withdraw from the study at any time. Potential candidates were also informed of the need to wear a properly fitted respirator during the study and the medical evaluation and fit testing processes were explained. Researchers asked a standard set of questions to ensure comprehension of the consent materials.

Minimization of risks

During the study, subjects were monitored for safety purposes as outlined in the protocol, study report and EPA ethics review memo. There was one deviation regarding handwashing that occurred across all MEs and involved the amount of wash fluid (rather than using a pre-measured amount for the first rinse and the remaining wash fluid for the second rinse, the same total volume was used as described in the protocol but the first rinse did not use a pre-determined amount) and having subjects, rather than the researchers, use the gauze provided to wipe dried paint from the subjects' hands. This is a minor deviation that did not affect study integrity and was more efficient and effective.

The respirator fit test was conducted as outlined in the protocol, study report and EPA ethics review memo. There was one minor deviation when a subject went through the fit test before receiving approved medical recommendations. All elements of the medical clearance and fit test were completed before the subject's monitoring event. This deviation did not affect the subject's welfare or safety and was appropriately considered minor.

One deviation occurred when a subject removed her safety glasses when pouring paint and had paint splashed in her eye. She was treated per protocol, recovered, and subsequently was allowed to complete her monitoring event. EPA recommended to AEATF to consider revising the pre-monitoring discussion to note where and when safety equipment must be worn, and the HSRB agrees with that recommendation.

Subjects were monitored for heat stress, informed of signs of heat stress and told to inform study staff if they experienced signs or symptoms of heat stress, reminded to take breaks as needed, and provided with cold water and sports drinks while in the study. Hearing protection was offered, but none of the subjects opted to use hearing protection.

One subject was found to have dermal irritation on the forearms at the post-monitoring skin check. This was attributed by the subject to sweat and they were not concerned. The area was washed, and the irritation was gone later the same day.

Confidentiality was maintained throughout the study. Subjects, including alternates, were compensated per the protocol. The amount of compensation for each subject was consistent with the time spend on the various study-related activities and was not excessive.

There were 5 protocol amendments which were handled consistent with the IRB practices and the protocol. There were 7 reported protocol deviations, 3 of which have been previously described. 4 other deviations were reported, none of which affected the study's scientific integrity or placed the subjects at risk.