March 12h, 2018

EPA-HSRB-18-2

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

Subject: January 23-24, 2018 EPA Human Studies Review Board Meeting Report

Dear Dr. Orme-Zavaleta,

The United States Environmental Protection Agency requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of two studies. One study was a protocol titled, "Laboratory Evaluation of Bite Protection from Repellent-Impregnated Fabrics." The second item reviewed was a completed study, the Agricultural Handler Exposure Task Force (AHETF) Study Report AHE170: "Determination of Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules." The Board's responses to the charge questions and detailed rationale and recommendations for each of these studies are provided in the enclosed final meeting report.

Signed,

Liza Dawson, PhD
Chair
EPA Human Studies Review Board

INTRODUCTION

On January 23-24, 2018, 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 the following two studies: a protocol titled "Laboratory Evaluation of Bite Protection from Repellent-Impregnated Fabrics;" and the Agricultural Handler Exposure Task Force (AHETF) Study Report AHE170: "Determination of Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules."

REVIEW PROCESS

The Board conducted a public meeting on January 23rd and 24th, 2018. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL-9972-41-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 two studies.

On January 23rd, following welcoming remarks from Agency officials, the Board began its review of the protocol "Laboratory Evaluation of Bite Protection from Repellent-Impregnated Fabrics." On January 24th, the Board reviewed the AHETF study report, "Determination of Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules." For each of the studies, Agency staff presented their review of scientific and ethical aspects of the completed 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 the materials submitted to EPA and provided to the Board, presentations given by EPA staff at the meeting, oral comments from Agency staff and from the investigators during the meeting discussions, and the Agency's written reviews, which were provided to the Board prior to the meeting.

Laboratory Evaluation of Bite Protection from Repellent-Impregnated Fabrics

SCIENTIFIC REVIEW: CHARGE TO THE BOARD AND BOARD RESPONSE

Charge to the Board:

Is the protocol, "Laboratory Evaluation of Bite Protection from Repellent-Impregnated Fabrics" likely to generate scientifically reliable data, useful for estimating the level of mosquito bite protection provided by fabrics treated with permethrin or etofenprox?

Board Response:

After addressing revisions recommended by EPA and HSRB, the protocol "Laboratory Evaluation of Bite Protection from Repellent-Impregnated Fabrics" is likely to generate scientifically reliable data, useful for estimating the level of mosquito bite protection provided by fabrics treated with permethrin or etofenprox.

HSRB Detailed Recommendations and Rationale:

HSRB reviewed information provided in advance of the meeting, as well as the EPA scientific and ethics presentations provided at the meeting.

Documents Reviewed or used as Reference

a) EPA Science and Ethics Review of Landis Pinebelt Protocol, dated 12/29/17
b) Pinebelt Protocol Lab Evaluation of Bite Protection of Treated Fabrics, dated 8/9/17
c) IRB Correspondence Report – Pinebelt Bite Protection Protocol, dated 11/7/17

Study Summary:

The protocol under review is similar to a previously approved protocol (HSRB, April 2014) and subsequent approved study (HSRB, October 2015). The study is testing commercially available fabrics treated with 0.52% permethrin or 0.9% etofenprox, and tests repellency of the fabric after 0, 20, 50, and 75 washes. The testing is an arm-in-cage design in which human subjects wear treated and untreated fabric sleeves over an exposed forearm that is inserted into a cage.

Laboratory reared, disease-free mosquitoes are released into the cage for a 15-minute period and allowed to land and bite. The subjects' hands are covered with gloves such that only the sleeve is accessible to mosquitoes for blood feeding. After the test period, the mosquitoes are captured and crushed to determine blood feeding and percentage protection is calculated.

The study tests two mosquito species: *Aedes aegypti* and *Anopheles albimanus*. The study will enroll 10 subjects, and each human subject serves as their own control by testing the untreated fabrics as well as the range of treated and washed fabric sleeves.

EPA Scientific Review:

EPA's scientific review of the protocol identified the main differences between this protocol and the previously HSRB-approved protocol and completed study. The following differences were noted: number of study subjects increased from 8 to 10 (based on EPA's statistical analysis to support another arm-in-cage protocol reviewed by the HSRB in October 2016); another active ingredient was added for testing (0.52% w/w permethrin, in addition to the 0.9% w/w etofenprox under the April 2014 protocol); and a second fabric type, a knit fabric that is representative of consumer products, was added to the testing, in addition to the U.S. Military Fire Resistant Army Combat Uniforms (FRACU).

The previous HSRB review of the completed study (October 2015) recommended including specific criteria for adequate biting pressure for a specific assay such that any judgment about inadequate biting pressure is made on objective pre-specified criteria. This has been addressed in the current protocol stopping rules, which specify to stop the assays on a given day if biting pressure drops below 50%. In addition, for the previous study, the HSRB recommended that specific conditions under which subjects may be replaced should be included, to avoid subjective decisions or the possible introduction of bias into study procedures and data collection. This recommendation was accepted, and data from subjects that withdraw will not be used.

HSRB Scientific Review:

The HSRB review of the earlier protocol (April 2014) had several recommendations all of which were addressed in the completed study and/or the current protocol except one. The Board had recommended randomizing treatment order to provide a more representative control. The Board

discussed whether having 100 bites on a section of the arm will attract/detract from bites in subsequent exposures. The Board is aware of the concern about carry over from the unwashed treated fabric (0x washes), and that systematically assigning the order of fabrics, starting with the controls and 75x fabric, will likely get less active ingredient on the arm to minimize risks of carryover. However, washing of the forearm between treatments is included in the study procedures, and this might alleviate carryover problems. A better measure of uncertainty in measurement could be achieved by randomizing the treatment order. Given the systematic order of testing from least concentrated to most concentrated pesticide, subjects' arms will more likely be bitten in early rounds and then exposed again in subsequent rounds with fabric that presumably has higher concentration pesticide (fewer washes). HSRB discussed the concern that mosquitoes might be deterred from biting when the subject who has already been bitten in previous rounds. In discussion, the study investigator, Dr. Ulrich Bernier, indicated that this phenomenon has not been observed in previous studies and there is no source in the literature describing this kind of effect on mosquito biting behavior. The HSRB recommended describing this background information in the protocol—that there is no evidence of effect of previous bites on subsequent mosquito biting behavior - as part of the rationale for the study design using systematic assignment of sleeves.

The previous study initially planned to test a maximum of 50 washes, but investigators found that the etofenprox-treated fabric was still performing well after the 50 washes and modified the protocol to add a 75-wash treatment. The HSRB discussed the question of whether 75 washes would be sufficient to see loss of performance for the treated fabric or not. If 75 washes retrained good repellency activity, it would make sense to increase the number of washes, (i.e., drop the 20X wash group and add a 100X wash group). In discussion with the investigators and EPA staff, HSRB decided that due to uncertainty about whether the 75-wash fabric would retain activity, it was better to leave the study design as currently configured.

The earlier, similar, repellency study and the protocol under review at the January 2018 meeting were both designed around the assumption that washing is the primary aging mechanism for treated fabric. The Board recognizes that it is important to have a consistent measure of performance and the washing protocol is expected to provide this consistency. However, there may be other loss mechanisms for the active ingredients on/in the fabric. For example, with

normal use in the field, the treated fabric will be exposed to some amount of sunlight and sweat and abrasion during the time between typical washings. These processes can result in loss of active ingredient. EPA may want to consider how much time these fabrics will spend in the sun and/or wetted by sweat for an equivalent 75 wash lifetime and estimate possible photolytic degradation/hydrolysis during that same period to get a rough approximation of the loss of active ingredient by chemical transformation.

With regard to dermal exposure to pesticides in the treated fabrics, the HSRB has no concerns with the proposed work from a toxicological standpoint. Both test ingredients, permethrin and etofenprox, have approved uses in the U.S and in the E.U. There is ample body of research supporting their relative safety at typical exposure levels. Margins of Exposure (MOEs) for this study are at a level that do not raise concerns. However, the Board did note that MOE calculations in the protocol differed from those presented by EPA staff in their written review and in the HSRB meeting on January 23rd. Specifically, the dermal absorption factors used in the calculations were different from both permethrin and etofenprox, and the level of concern for etofenprox cited in the protocol also differed from the value cited by EPA. In discussion with Agency staff, the Board learned that EPA used more recent data, on dermal absorption and level of concerns, compared to data used in the protocol. Board members commented that the protocol should be harmonized to EPA calculations using more recent data.

Statistical Review:

In the past several years, EPA has considered two types of situations related to disease transmission from mosquitos, leading to both field and laboratory studies. The field studies have mosquito-landing rates as their endpoint while the laboratory studies address bite protection rates. The differences between field based and laboratory-based studies create some differences in the statistical analyses.

With regard to this study, the systematic assignment of the number of washing cycles to the subjects within each day is adequately justified, as previously mentioned, due to the concerns about the potential for carryover from higher concentrations of treated fabric to lower concentrations.

The use of the SAS procedure GLIMMIX is appropriate for binomial data. However, the default link for GLIMMIX is the logit function, not the natural logarithm as stated in the Statistical Design section 6. In addition, the natural logarithm is not one of several potential alternative link functions. The logit link naturally addresses odds ratios which are reasonable for landing rates (as in previous studies measuring landing rate in field studies) but not for ratios of treatment to control bite through rates which is what is measured in the present study. The advantage of the natural logarithm link is that it allows for estimation of the bite through ratios in a straightforward manner; therefore, the natural log is appropriate in this study.

If the natural logarithm link is to be used for a model in which species as well as number of washing cycles are factors, additional information on the analysis of such data should be included. In particular, the protocol, as well as the SAS code in Appendix K, do not offer any specifics on the following: 1) which repeated measures covariance structures will be considered, 2) how they will be evaluated to make a final choice, 3) whether or not the choices will be affected by the mosquito species, 4) the number of washing cycles, and/or 5) the subject demographic factors such as gender. These computational issues can become a challenge for model selection and parameter estimation.

The HSRB recommends that the investigators explore the correlation structure of the repeated measures in the study. Further, if the investigators have access to data from previous similar studies, they could explore correlation structure using existing data, which would help inform analysis plans for the present study.

ETHICS REVIEW: CHARGE TO THE BOARD AND BOARD RESPONSE

Charge to the Board:

Is the research described in "Laboratory Evaluation of Bite Protection from Repellent-Impregnated Fabrics" likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response:

When changes suggested by EPA and HSRB are incorporated, the proposed research will likely meet the applicable requirements of subparts K and L of 40 CFR Part 26.

HSRB Detailed Recommendations and Rationale:

40 CFR subpart K outlines ethical requirements for third party research for pesticides involving intentional exposure of non-pregnant non-nursing adults. Specifically, the subpart requires that IRBs approve research before it is initiated, that risks to subjects are minimized, risks to subjects are reasonable in relation to anticipated benefits, selection of subjects is equitable, informed consent will be sought and documented, subjects with be compensated for their participation, data monitoring will be conducted as appropriate, and privacy and confidentiality are protected.

40 CFR subpart L prohibits third-party research for pesticides involving intentional exposure of human subjects who are children or pregnant or nursing women.

The Board agrees with all the requested changes from the EPA ethics review. The Board has the following comments related to satisfying the subpart L criteria.

Minimize Risk:

Risks are appropriately minimized by subject selection, i.e., excluding individuals with sensitivity or anxiety about mosquito bites or skin conditions that could be exacerbated by wearing treated fabric or receiving mosquito bites, and by using laboratory reared mosquitos, which are free of pathogens for the bite protection assays. Pregnant women and children are excluded.

However, there is no screening question for nursing women and this should be added to the screening question list ("subject self-certification questionnaire") and to the exclusion criteria. The exclusion criteria currently state that lactating women are excluded (page 18) but the correct

exclusion is nursing or breastfeeding women. Also, for clarity, it would be best to separate exclusion and inclusion criteria into two separate lists. "People with latex sensitivity will be offered nitrile gloves" is not an exclusion criterion so this should be described in the prose section regarding subject selection.

The self-screening also includes the questions, "are you in poor health" and "are you in poor physical condition?" These questions are so general that it may be difficult to answer meaningfully. The protocol should be revised to ask more specifically about conditions that may impact study participation.

The screening by telephone is described but the protocol does not describe what the in-person screening step consists of. The screening questions asked by phone should be repeated in person. Government issued ID should be checked to verify age, given the requirement of subpart L that no one under the age of 18 should be enrolled.

In two places in the protocol the topic of care for research-related injuries is mentioned (Section 10, Risks to subjects). The protocol should be clarified to explain who would determine that an injury is research-related and what the procedure would entail.

Equitable Selection:

Selection of subjects does not target vulnerable populations or unfairly exclude members of specific groups. Participants must speak, read and write English, which is a reasonable requirement given that they must be able to understand study directions for the bite protection tests and must be able to read the informed consent document.

The exclusion criteria lists "relationship to study director to sponsor" as an exclusion criterion—this needs to be defined. What kind of relationship? If the sponsor is Pine Belt Processing, Inc, then this should be specified in this section of the protocol and in the consent form.

The recruitment flyer states that "volunteers are sought for participation in a study of treated fabric…." This should specifically state "insecticide-treated fabric." Also, it should be clarified that the total time commitment (2.17 hours) occurs over two separate days, since the two different mosquito species are not tested on the same day. It might be best to provide an approximate estimate of time rather than a precise number. The flyer should also note that government issued ID is required to verify age.

Informed Consent:

The informed consent document appropriately provides information about risks of the study, risk mitigation procedures, opportunity to withdraw, and compensation.

However, some corrections are needed. In the "Summary" section, the bullets state that "scientists have been working on a new pesticide to go on fabrics." In fact, the pesticides used for this test are not new and this should be described. More information should be provided about the two products being tested, their safety in use for bite protection, and the estimates of dermal absorption when used in treated fabrics.

The section on "risks of exposure to disease" states "in the unlikely event that they are found to carry disease, you will be notified immediately and will receive appropriate treatment at the hospital." This is inconsistent with statements in the protocol that there is virtually no risk of disease in the laboratory reared mosquitos.

The section on "compensation for injury" should distinguish between compensation for injury versus care and treatment for injury, which are two different things. The study offers care and treatment for injury but not compensation. This should be clarified.

Privacy and Confidentiality:

Confidentiality is appropriately protected.

In summary, the HSRB expressed no major ethical concerns about the study and recommended only minor changes to the protocol and study procedures.

Determination of Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules (AHE170)

SCIENTIFIC REVIEW: CHARGE TO THE BOARD AND BOARD RESPONSE

Charge to the Board:

Is the research presented in AHE170 and the associated documents scientifically sound, providing reliable data useful for assessing the exposure of those who perform open pour loading of granular pesticide products?

Board Response:

The HSRB has concluded that the protocol "Determination of Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules" is likely to generate scientifically reliable data, useful for assessing the exposure of those who perform open pour loading of granular pesticide products, provided the changes requested by EPA and the changes requested by the HSRB below are taken into account and implemented.

HSRB Detailed Recommendations and Rationale:

The HSRB Board reviewed a scenario monograph report and a completed study report that summarize the Agricultural Handler Exposure Task Force, LLC (AHETF)-sponsored research to monitor dermal and inhalation exposure during open pour loading of granular pesticide products. Previously, the HSRB reviewed the protocol and related materials on November 5, 2014. This review covers the results of research based on implementation of that study protocol. A number of documents were reviewed by the HSRB in order to respond to the charge.

Documents Reviewed or used as Reference

a) EPA DRAFT Review of "Determination of Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules" (AHE170)
b) EPA Field Analytical Review of Data from Agricultural Handler Exposure Task Force (AHETF) Monograph: "Open Pour Loading of Granules" (AHE1017) – Excel spreadsheet

c) EPA Ethics Review of Completed AHETF Study AHE170 on Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules
d) EPA Summary of files associated with AHE170
e) AHETF AHE170 Study Report: Determination of Dermal and Inhalation Exposure to Workers During Open Pour Loading of Granules, dated October 3, 2017
f) AHETF IRB Correspondence Report for Study AHE170, Dated September 25, 2017
g) AHETF Agricultural Handler Exposure Scenario Monograph: Open Pour Loading of Granules (Report No. AHE1017), dated October 25, 2017
h) AHETF Standard Operating Procedures, dated January 12, 2015
i) AHETF Governing Document, dated August 12, 2010.
j) HSRB November 5, 2014 EPA Human Studies Review Board Meeting Report, dated January 20, 2015 (https://www.epa.gov/sites/production/files/2015-01/documents/hsrb-5nov-2014-final-report.pdf)

Study Summary:

Twenty-one subjects were monitored on actual days of work and loaded between 50 and 2,720 pounds of product over 3 to 6 separate loading events in 2 to 8 hours. These 21 subjects were loading pesticide granules into various application types (row planter and spreaders) and from various heights (e.g., abdomen, waist). Subjects' ages varied in age from 20 to 78, and workers had from less than 1 to 50 years of experience. Bags were opened using hands or knives. The study only addresses "opening granule pesticide product bags/packages, typically by hand or using a knife, and manually pouring of contents into application equipment such as tractor planters or spreaders." Other methods of pouring or application of the granule pesticides are not represented. Formulation type (i.e., granule), and application and packaging is expected to influence the exposure to a greater extent than the pesticide active ingredient. If the data are rich enough, there are opportunities to look at exposure not only based on amount of ingredient handled, but based on time of handling, by age and experience of worker, and level of loading. Similarly, if the data are rich enough, the influence of environmental conditions, wind speed in particular, can also be addressed.

EPA Scientific Review:

EPA's review determined that the study meets EPA standards for occupational pesticide exposure monitoring and is considered acceptable and appropriate for use in occupational exposure/risk assessments of workers performing open pour loading tasks with granule pesticide products. In addition, the primary quantitative objective for dermal exposure was to report the normalized dermal exposure results within 3-fold of the geometric mean, arithmetic mean and 95th percentile. The second objective was to evaluate whether there was 80% statistical power to detect independence versus proportionality between dermal exposure and the amount of active ingredient. Both objectives as evaluated by EPA were met.

HSRB Scientific Review:

HSRB's review identified two main areas of importance: (1) AHETF's response to the HRSB 2014 review of the protocol; and (2) deviations from the original approved protocol and study design. The Board developed recommendations for clarifications in the meeting report as well as additional issues to consider regarding future data analysis and uses of the data.

The Board reviewed how the AHETF addressed HSRB comments from the 2014 review.[1] As noted in EPA's scientific review [2], the Board made comments in the 2014 review concerning lack of intra-person variability; potential for loss of product to volatilization; loss of the ingredient through absorption throughout the day; possible safety concerns related to that absorption; documentation of recruitment mechanisms; and the possibility of underestimation of exposure due to clean gloves.

EPA's scientific review documented responses or accounted for those comments and concerns by explaining the greater importance of inter-person variability; use of field fortification results to look at volatilization; accounting for absorption into skin through modeling; looking at the safety of these pesticides; documentation of recruitment mechanisms; and recognition of

[1] (https://www.epa.gov/osa/hsrb-november-5-2014-meeting-final-report)
[2] https://www.epa.gov/sites/production/files/2018-01/documents/a._epa_review_ahe170_opg_field-analytical_review.pdf; https://www.epa.gov/sites/production/files/2018-01/documents/b._epa_review_ahe1017_opg_monograph_review.pdf

underestimation in using clean gloves in the exposure and dose estimates. For some of these issues, further clarification is needed, as addressed below.

Clarifications requested by the HSRB:

1) Please add in the report that study objectives (3-fold accuracy and statistical power to detect proportionality) applied only to dermal exposure, and not to inhalation exposure, as dermal exposure was the likely route of importance. However, please clarify whether, after analyzing the data, these objectives were also met for inhalation exposure.
2) The HSRB agrees with the statements made regarding recovery and fortification: "Analytical field and laboratory recovery results were acceptable, generally averaging between 70 and 120% recovery, with coefficients of variation largely less than 25%." However, further explanation is needed for this statement: "Hand wash fortification samples were also broken/compromised for those corresponding to M1 and M2 (monitoring date 3/21/15). However, the fortification level corresponding to the field samples still had useful/reliable results." In discussion with EPA staff, HSRB learned that only one of three fortification levels were compromised and an extrapolation or an average was used for the missing value. The HSRB requests that this be documented more clearly on page 14 or 20 of AHE170 study report.
3) The report describes an incident in which a subject handled pesticide-treated seeds during one of the monitoring events. Although no additional exposure may occur from seeds, since the surrogate active ingredient being monitored was not in the seeds, the handling of the seeds might lower exposure due to transfer to seeds. The Board requests that the report acknowledge this possibility on page 18 of document.
4) The Board agrees with the imputation method used by EPA to address the missing dermal hand wash samples for workers M1 and M2. Since the average AaiH- normalized hand exposure of 1.44 µg/lb ai was calculated by taking the average of all hand wash samples across all workers, the Board suggests language be added to further clarify this. For example, the average AaiH- normalized hand exposure across all samples (or all worker samples) versus across all workers.

Deviations or changes from original protocol and design plan:

1) Notably, two workers had incomplete dermal exposure monitoring as some of their hand exposure samples were broken and lost following collection. EPA made suggestions for imputation (i.e., replacement of values) of the lost samples to make use of complete dermal exposure results. These suggestions were reported in documents. Statistical comparisons were made for imputation versus leaving out these missing values.
2) Due to recruitment issues in some regions (rainfall in northwest region), monitoring was conducted across 9 U.S states over 15 months. This altered the cluster design. The original cluster design was 3 workers in 7 regions/monitoring area/clusters to satisfy benchmark data analysis objectives. Instead there were 8 clusters (7 distinct geographical locations), with 4 workers (instead of 3) monitored in each of 2 monitoring areas.
3) An additional surrogate active ingredient was added (i.e., 2,4-D). Monitored workers used 5 of 11 surrogate active ingredients. This is acceptable and does not adversely affect the soundness of the study, given that the formulation was the most important characteristic of the surrogates.
4) Use of valid analytical methods not specified in the protocol. Methods were added for 2,4-D and clarified for chlorpyrifos and tefluthrin. HSRB found these acceptable.

In sum, the HSRB did not view these changes and deviations as having negative impact on the scientific soundness of the study overall.

Statistical Review:

The primary benchmark objective for AHETF scenarios 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. (1) The structure of the final dataset (8 clusters 1-4 workers per cluster) was evaluated in comparison to the intended study design (7 clusters 3 workers per cluster). (2) Both dermal and inhalation unit exposures were shown to fit the lognormal distribution reasonably well. (3) The statistical analysis results in the AHETF submission based on the final datasets and the SAS code were confirmed. (4) The primary benchmark of 3-fold accuracy for select statistics was met for both the AHETF and the EPA-revised datasets.

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. (1) Regression analysis of ln(exposure) and ln(AaiH) was performed to determine if the slope is 1 (which provides support for a proportional relationship) or 0 (which provides support for an independent relationship). (2) There was no substantive difference between the AHETF submission and the EPA-revised dataset and for both, the confidence interval for dermal exposure was less than 1.4 with at least 80% statistical power and the relationship was proportional with 95% confidence. (3) The dermal exposure data based on both the AHETF submission and the EPA revision indicated a level of precision consistent with the benchmark.

The statistical analysis appears to be adequate with both the primary objective and the secondary objective met. The randomization process for data collection is appropriate and the imputation methods for dealing with missing data and limits of detection, although simple, are sensible. A more comprehensive simulation study to evaluate these simple methods may be worthwhile in a future project.

In summary, a proportional relationship between dermal/inhalation exposure and the amount of active ingredient is more evident than an independent one. The AHETF data developed are reliable for assessing exposure during open loading of granule pesticide products.

HSRB recommendations for issues to consider in the use of or further analysis of data:

1) The Board recommends considering if there a way to account for the underestimation of clean gloves in the model estimates of dermal exposure when applying the data to longer-term exposures. This was a previous concern of HSRB and it is not clear if this was addressed or how it will be addressed in the model or use of the model.
2) EPA may consider how accounting for dermal absorption through the day will be addressed in accounting for all the dermal exposure that occurs during the day.
3) EPA could consider whether the dermal and inhalation exposures could be measured be in light of time of application in addition to amount of active ingredients handled. For example, persons handling the larger amount of active ingredients could also have handled these products over the longer time period (e.g., 1000 pound handled over 7 hours). This time element will eventually affect time on skin for dermal uptake. The

Board recommends considering how will this be handled in the exposure/dose modeling. The report mentioned accounting for dermal uptake throughout the day in the exposure measurement, and this time accounting does play role in dermal absorption.

4) EPA might consider looking at ways to categorize the field observations into low, medium, or high opportunities to influence loadings (i.e., a summary of influence), as well as considering how these categories would influence labelling.

Summary: The HSRB agrees with EPA's assessment that the AHETF followed the protocol as best as possible under the circumstances. Sample design and data analysis plan with some minor adjustments were also followed as planned. Quality assurance and quality control methods and procedures are expressed for field and measurement methods. The Board therefore agrees with EPA that these results can be used in the routine regulatory assessment of human exposure and risk as part of the federal pesticide registration process. The Board further agrees that the deviations and changes will not impact the science value of this study.

ETHICS REVIEW: CHARGE TO THE BOARD AND BOARD RESPONSE

Charge to the Board:

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

Board Response:

The HSRB concludes that the available information supports a determination that the study detailed in the AHETF170 Study Report and it supporting materials was conducted in substantial compliance with the applicable requirements of 40 CFR part 26.

HSRB Detailed Recommendations and Rationale:

As noted elsewhere, the AHETF170 protocol and supporting materials were reviewed by the HSRB at its November 5, 2014 meeting. No ethical deficiencies were noted at that time. The

Board determined that the proposed study was likely to satisfy applicable regulatory requirements and that no revisions were needed to address any ethics-related issues. Based on our review of the materials presented by AHETF for this meeting, the HSRB agrees with the Agency's ethics assessment (December 29, 2017) in its determination that this study was conducted in substantial compliance with applicable requirements of 40 CFR part 26.

1. Independent Ethics Review

Schulman Associated Institutional Review Board (SAIRB) provided independent ethics oversight for this study and AHETF has provided an extensive trove of correspondence between the research team and SAIRB. SAIRB has been fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) since June 2008 and is a registered IRB with both the U.S. Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA). SAIRB approved the study's protocol, consent materials, study brochure, and letter to qualified employers on June 30, 2014. SAIRB provided continuing review oversight until the study's closeout on September 8, 2017. During this time, SAIRB reviewed four amendments to study materials prior to their implementation. One of these amendments, the addition of 2-4,D as a potential surrogate substance, required additional consent discussions with one subject on the day of his participation since 2-4,D was not originally identified as a potential surrogate substance on the IRB-approved consent form. Researchers reviewed the product's labeling with this subject in order to minimize additional risk to this subject as a result of his handling of that surrogate substance. As detailed in section 2 below, the researchers submitted four protocol deviations to SAIRB for their review.

2. Assessment of risks and benefits

As outlined in section 2.3 of the study's 2014 protocol, risks to participants included: a) risk of heat-related illness, b) risk associated with scripting of field activities; c) psychological risks; d) risk of exposure to surfactants, and e) risk of exposures to surrogate chemicals.

AHETF follows specific SOPs that adequately address many of those risks. Researchers were trained to identify symptoms of heat-related illness and a medical professional was on site during each monitoring event in case of such illness. There were no reported incidents of subjects experiencing such illness. Risks associated with the scripted activities is also minimal, as they involved reducing material load sizes to achieve three cycles per monitoring unit. Further, all subjects enrolled in the study were experienced in performing the types of activities observed in this study. Psychological risks were also minimal, given that that AHETF SOPs specify privacy measures to be in place when subjects are robing and disrobing for study participation. The surfactant used in this study was used in a very dilute solution and there were no adverse events reported associated with its use. Subjects wore appropriate personal protective equipment (PPE), such as proper gloves as recommended by product labels. Subjects using chlorpyrifos-containing products used employer-provided dust/mist filtering respirators (Report, p. 57).

Protocol deviations were submitted to SAIRB on four different occasions, but none of the deviations represented a serious risk to the subjects. Of note: 1. One subject wore the wrong protective gloves (based on the label of the product he handled), but there were no adverse effects observed for that subject. 2. One subject loaded treated corn seed into a seed hopper one time without gloves, but did not experience any adverse effects. 3. That same subject lit and smoked part of a cigarette during his monitoring period before washing his hands, but this subject did not experience any adverse effects.

There were no direct benefits to subjects for study participation, but the study may benefit society by providing new data about dermal and inhalation exposure of workers who perform open pour loading of granular pesticides. The risks to which subjects were exposed are reasonable in relation to this potential benefit.

3. Equitable selection of study participants

Study recruitment followed procedures outlined in the AHE170 Study Report (pp. 23-53) and in accordance with established AHETF standard operating procedures that were previously

reviewed by the HSRB. Twenty-one subjects enrolled in the study, all of whom were males at least 18 years of age. The Agency's Ethics Review refers to an email exchange between AHETF and EPA in which AHETF states that they did not implement any measures to intentionally avoid selecting female subjects, but rather the scenarios used in this study are "male-dominated" activities. One potential participant who expressed interest was female, but she did not enroll in the study because the monitoring units in her area were completed before her farm was ready to be planted. Recruitment and consent materials were available in both English and Spanish. No potential subjects expressed a desire or need to communicate in Spanish, so all enrolled subjects spoke English. While subject selection may not appear balanced with regard to gender or language, there are no data or information to suggest that this was intentional on the part of the researchers.

4. Voluntary and informed consent of all participants

AHETF followed their standard SOPs (specifically SOP AHETF 11.I.3) for obtaining and documenting the voluntary and informed consent of all participants. As noted above, consent materials were available in both Spanish and English, but only English speaking subjects were enrolled in the study. Consent materials, including the informed consent document itself, were reviewed and approved by SAIRB.

5. Intentional exposure of children or pregnant or nursing women

As noted above, all subjects who participated in this study were male and at least 18 years of age. As a result, the completed study did not involve intentional exposure of children or pregnant or nursing women to any substance. As a result, the completed study satisfies requirements at 40 CFR part 26.1703.