EPA-HSRB-11-01

Paul Anastas, PhD
EPA Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: January 26, 2011 EPA Human Studies Review Board Meeting Report

Dear Dr. Anastas,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of one new protocol for a study involving intentional exposure of human subjects to pesticides: a proposed Agricultural Handler Exposure Task Force, LLC (AHETF) scenario measuring dermal and inhalation exposure of professional agricultural workers who perform open mixing and loading of pesticides formulated as wettable powders.

The Agency also requested that the HSRB review five completed, interrelated studies of dermal and inhalation exposure of professional agricultural handlers spraying pesticides with closed-cab airblast equipment, conducted by the AHETF. These studies (AHE55, AHE56, AHE57, AHE58 and AHE59) were conducted after publication of the EPA's final rule for protection of subjects in human research (40 CFR 26) on February 6, 2006 (71 Federal Register 24, 6137). The data from these studies were combined into a single scenario monograph (MRID 48314201). This dataset will be posted to the Agricultural Handlers Exposure Database (AHED®), and used generically to estimate daily dermal and inhalation exposures of workers who treat agricultural crops with conventional pesticides using closed-cab airblast equipment.

The enclosed report provides the Board's response to EPA charge questions presented at the January 26, 2011 meeting.

<u>Assessment of Proposed AHETF Research Study AHE80: Determination of Dermal and Inhalation Exposure to Workers During Mixing/Loading Wettable Powders in the United States</u>.

<u>Science</u>

The Board concluded that the proposed AHETF scenario and field study proposal AHE80, if revised as suggested and performed as described, is likely to generate scientifically reliable data, useful for assessing the exposure of handlers who perform open mixing and loading of pesticide end use products formulated as wettable powders.

Ethics

The Board concluded that the proposed AHETF scenario and field study proposal submitted for review, if revised as suggested and performed as described, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

Assessment of Completed AHETF Research Studies AHE55, AHE56, AHE57, AHE58 and AHE59: Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment (MRID 48280601, 48289602, 48303501, 48289604 and 48303502).

Science

The Board concluded that the research reported in the completed monograph, associated field study reports, and associated supplemental documents was conducted in a manner that was reasonably faithful to the design and objectives of the protocol and governing documents of the AHETF.

The Board also concluded that the Agency has not completely considered the limitations on these data that should be considered when using the data in estimating the dermal and inhalation exposure of those who apply conventional pesticides with closed-cab airblast equipment. Additional limitations and concerns have been identified by the Board, and the conclusion as to the generalizability of these data requires further consideration and analysis.

Ethics

The Board concluded that the study was conducted in substantial compliance with subparts K and L 40 CFR 26.

Sincerely,

Sean Philpott, PhD, MSBioethics
Chair
EPA Human Studies Review Board

NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use. You may obtain further information about the EPA Human Studies Review Board from its website at http://www.epa.gov/osa/hsrb. You may also contact the HSRB Designated Federal Officer, via e-mail at ord-osa-hsrb@epa.gov

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

US ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD

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* Not in attendance at January 26, 2011 Public Meeting

INTRODUCTION

On January 26, 2011, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning one new protocol for research involving human participants: one new study measuring levels of exposure received by agricultural handlers when mixing and loading pesticides formulated as wettable powders under various conditions. In accordance with 40 CFR 26.1601, EPA sought HSRB review of this proposed protocol. The protocol is discussed more fully below.

In addition, the Agency has data from five completed, interrelated studies measuring levels of dermal and inhalation exposure received by pesticide applicators spraying pesticides with closed-cab airblast equipment. The data from these studies were combined into a single scenario monograph (MRID 48314201). This dataset will be posted to the Agricultural Handlers Exposure Database (AHED®), and used generically to estimate daily dermal and inhalation exposures of workers who treat agricultural crops with conventional pesticides using closed-cab airblast equipment. In accordance with 40 CFR 26.1602, EPA sought HSRB review of these five completed studies. The completed studies are discussed more fully below.

REVIEW PROCESS

On January 26, 2011, the Board conducted a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the Federal Register as "Human Studies Review Board; Notice of Public Meeting" (76 Federal Register 8, 2107).

Following welcoming remarks from Agency officials, the Board heard presentations from EPA on the following topics: one new study measuring levels of exposure received by agricultural handlers when mixing and loading pesticides formulated as wettable powders under various conditions, and five completed studies measuring dermal and inhalation exposure received by pesticide applicators spraying pesticides with closed-cab airblast equipment.

The Board also asked clarifying questions of several study sponsors and/or research investigators, including:

Dr. Victor Cañez, Technical Chair, Agricultural Handler Exposure Task Force (AHETF)

Public oral comments were provided by:

Dr. Victor Cañez, Technical Chair, AHETF

One written public comment was submitted by Ms. Barbara Sachau of Florham Park, NJ (writing under the pseudonym Ms. Jean Public). That comment did not specifically address any of the completed studies or proposed protocols under review at the January 26, 2011 meeting.

For their deliberations, the Board considered the materials presented at the meeting, oral comments, and Agency background documents (e.g., published literature, sponsor and investigator research reports, study protocols, data evaluation records, and Agency science and ethics re-

views of proposed protocols and completed studies). A comprehensive list of background documents is available online at http://www.regulations.gov.

CHARGE TO THE BOARD AND BOARD RESPONSE

Assessment of Proposed AHETF Research Study AHE80: Determination of Dermal and Inhalation Exposure to Workers During Mixing/Loading Wettable Powders in the United States.

Overview of the Study

This proposal presents an agricultural handler exposure scenario involving pesticides formulated as wettable powders. The activities to be monitored in this scenario include a variety of mixing and loading activities, including pouring the wettable powder into a spray tank, preparing the pesticide in a separate holding tank and then transferring the formulated product into the pesticide application equipment, and mixing and transferring a concentrated slurry of the pesticide. The protocol calls for study participants to mix and load one of four surrogate pesticides: copper, DCPA (dacthal), sulfur or thiophanate-methyl. A total of 25 participants (described in the protocol as "Monitoring Units" [MUs]) will be observed for each scenario; five volunteers from each of five geographically distinct growing regions will be enrolled using a purposive sampling method (with some elements of random selection).

Dermal exposure will be measured by a whole body dosimeter worn beneath the subject's outer clothing. Hand wash and face/neck wipe samples will also be collected prior to, during, and after completion of pesticide loading and mixing procedures. Airborne concentrations of the surrogate will be monitored in the participant's breathing zone using an OSHA Versatile Sampler (OVS) tube sample collector connected to a personal sampling pump. Additional measures will also record environmental conditions at the time of monitoring, and observers will make field notes, photographs and videos of participant activity throughout the monitoring event.

The results of sample analysis under the backpack and handgun application scenario will be posted to the Agricultural Handlers Exposure Database (AHED®), where they will be available to the EPA and other regulatory agencies for statistical analysis. The proposed documentation will report a confidence-interval-based approach to determine the relative accuracy for the arithmetic mean and 95th percentile of unit exposures. The Agency proposes to use these data to estimate daily dermal and inhalation exposures of agricultural handlers who are mixing and loading pesticides formulated as wettable powders under a variety of scenarios.

Science

Charge to the Board

If the proposed AHETF scenario and field study proposal AHE80 is revised as suggested in the EPA's review and if the research is performed as described, is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who perform open mixing and loading of pesticide end use products formulated as wettable powders?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment that the proposed AHETF scenario and field study proposal AHE80, if revised as suggested in EPA's review (Evans et al. 2010) and performed as described, is likely to generate scientifically reliable data, useful for assessing the exposure of handlers who perform open mixing and loading of pesticide end use products formulated as wettable powders.

HSRB Detailed Recommendations and Rationale

The Board concluded that the research is likely to generate scientifically reliable data, useful for assessing the exposure of handlers who perform open mixing and loading of pesticide end use products formulated as wettable powders. However, two significant issues were raised: one concerning how the new MUs should be distributed among the proposed strata to achieve the second stated goal of the research, and the other questioning whether or not the primary objective is valid. Several other less pressing questions were raised concerning information that was not presented clearly within the protocol.

The first significant issue that was raised concerned how the new MUs should be distributed across the strata of amount of active ingredient handled (AaiH). On page 8 of 58 (and in essence again on page 14) in the Agency's Review, the Agency states its desire that "the AHETF must ensure that all strata be used in each of the four remaining clusters" (Evans et al. 2010, 8). That desire may or may not be a conflict with an extrapolation of a statement on page 27 and 33 of that same document which states a conclusion from the AHETF computer simulation runs that:

> [T]he primary benchmark will still be satisfied providing:
>
> - The total number of new MUs is at least 20; and
> - No new cluster has more than five MUs.
>
> This rule implies that if a new cluster has fewer than 5 MUs then more than 4 new clusters will be necessary (Evans et al. 2010, 27).

While this conclusion was based on the distribution of MUs among clusters, it may also apply to the distribution of MUs among strata. If the five MUs in each new cluster include all five of the strata, there will be four new MUs at each stratum. When these four MUs are added to the five MUs that were already completed within the middle stratum, the final distribution of MUs across the five strata will be: 4, 4, 9, 4, and 4. Such a distribution is not optimal to achieve the secondary objective of 80% power to test for proportionality between dermal exposure and AaiH. Power is increased when more observations are made at extreme values of AaiH, whereas the middle set of values will be over sampled here. The Board recommended using further simulations to explore the effect of the distribution of MUs among AaiH strata on the power associated with Objective 2, viz. the proposed distribution, making allocations so that the number of MUs is the same within all strata, or having an allocated distribution intermediate to these two extremes.

The second significant issue raised concerned the primary objective of the study. As stated in the AHETF submission (Collier 2010a, 23), the primary objective is to estimate the geometric mean, the arithmetic mean, and the 95th percentile of exposure within 3-fold. To be meaningful, however, the population for which these quantities are being estimated must be clearly defined. By design, five different regions involving different crops were chosen, and the mean exposure could change with region. Further, within a region, AaiH is purposively different for each monitoring unit. The mean exposure for each region-AaiH combination is likely to be different. Thus, it is unclear what the overall scenario means (e.g. the means of the 25 region-AaiH combinations) would be estimating. Because these measures depend heavily on the design, the primary objective as currently stated in the protocol may not be achievable and the limitations imposed by the study design should be considered carefully when using the data.

An additional concern raised by the Board is whether the last of four "restrictions" listed on page 9 of the Agency's assessment, to be employed when selecting MUs, is adequate to both include all three possible ways to mix and load wettable powders into the various spray tanks. This restriction states that:

> When mixing/loading procedures in a given area involve participants either pouring directly into the application tank, using pre-mix tanks (holding dilute sprays), or slurry tanks or buckets (holding concentrate sprays), then the MUs may not all be associated with the same equipment and procedure category (Evans et al. 2010, 9).

Although the Board agreed with the desire of the Agency as stated in the meeting that all three sub-scenarios should be included in each new cluster, such a statement was not found within either the proposal or the Agency's Review. The exact nature of the agreed upon restriction should be clarified.

A somewhat related suggestion was made (without a particular recommendation) that the proposal makes no attempt to assess the limited breadth of equipment and/or processes that will be assessed in the context of a possibly wider range used in the field. A particular challenge (and possible concern) is to ensure that the exposures that are assessed in a given study do not underestimate the exposures to those applicators who use equipment or processes that are specialized for or relegated to small loads or/and small acreages (some of these were discussed on page 30-31 of the Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held January, 2007 on the Review of Worker Exposure Assessment Methods [FIFRA Scientific Advisory Panel. 2007]; see also page 14 and 42-43 of the same Meeting Report). In this regard, it may not be sufficient in such a proposal (or future reports) to ask experts just "how the selected employers and equipment compare to the local population of similar employers" (i.e., are the equipment or/and processes typical?). They should also be asked about the extent to which the selection process excluded any specialized equipment or processes, e.g., those specialized for use in small loads. Such information could be used to inform the Agency of limitations to the end result.

A question was raised regarding the appropriateness of the proposed range of AaiH values, in particular the feasibility of achieving the upper two strata (viz., 183 to 603 and 604 to 2000 lb a.i. handled). This question was raised because the highest stratum proposed for the OPM/L scenario is up to 20 times larger than the range of AaiH studied in AHE80 study of

closed-cab airblast (CCAB) applications. However information pointed to on page 36-37 of 403 of the Wettable Powder Mixer/Loader Scenario Submission showed that it is feasible to apply up to 350 acres per day via aircraft (Collier 2010a, 36-7), and examples of product labels obtained later from the web show that wettable sulfur can be applied to grapes at rates of up to 20 lb/acre. Based on the label's maximum rate of application of sulfur on grapes (a pair of scenarios included within the proposal), then mixing/loading up to 7000 lb. in a day is feasible, well above the proposed upper limit.

Three points of clarification were raised concerning the proposal. First, the last sentence in the first paragraph of page 19 of 403 of the Wettable Powder Mixer/Loader Scenario Submission seems to indicate that a large overhead is better when it comes to cost (Collier 2010a, 19). A large overhead would not make the study less expensive, but more expensive, and thus less cost effective. For a given outcome the less expensive option is more cost effective, the more expensive one is less cost effective. The latter is the case with a high overhead. Second, if one examines the table on page 31 of 403 of the Wettable Powder Mixer/Loader Scenario Submission, the numbers for total a.i. usage are all in decreasing order until the items of strawberries and cherries (Collier 2010a, 31). This appears to be an error, but should be clarified. Finally, the first paragraph page 273 of 403 of the Wettable Powder Mixer/Loader Scenario Submission discusses "drugs and devices" (Collier 2010a, 273). However, there are no drugs or devices that are a part of this scenario. Perhaps this verbiage was copied from the referenced document that came from the Department of Health and Human Services and in all likelihood pertained to the FDA, and either "pesticides" or "chemicals" should be stated.

Ethics

Charge to the Board

If the proposed AHETF scenario and field study proposal AHE80 is revised as suggested in the EPA's review and if the research is performed as described, is the research likely to meet the applicable requirements of 40 CFR 26, subparts K and L?

Board Response to the Charge

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Parsons and Sherman 2011) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendation and Rationale

The submitted documents assert that the study will be 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's Good Laboratory Practice (GLP) Standards described at 40 CFR 160, and, for research conducted in California, the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (Ref 2010). Requirements of FIFRA §12(a)(2)(P) also apply. Researchers who participate in the study and interact with study participants will be required to undergo ethics training. The training will include the successful

completion of the course from the National Institutes of Health (Protecting Human Research Participants) and/or the Basic Collaborative IRB Training Initiative Course.

The protocol was reviewed and approved by an independent human subjects review committee, Independent Institutional Review Board, Inc. (IIRB, Inc.) of Plantation, FL prior to submission. IIRB, Inc. is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). IIRB, Inc. is also listed as an active Institutional Review Board (IRB) on the Office of Human Research Protection (OHRP) website (Reg. #IORG0002954). Minutes of IIRB, Inc. meetings and a copy of IIRB, Inc. policies and procedures were provided to the Agency (IIRB, Inc. 2010). These documents indicate that IIRB, Inc. reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

1. Except as noted below, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Parsons and Sherman 2011). The proposed study is likely to meet the applicable ethical requirements for research involving human subjects, in accordance with the following criteria:

    a. Acceptable risk-benefit ratio. The risks as noted in the study protocol are fourfold:

        1) *The risk of heat-related illness.* The study will likely involve an increased risk of heat-related illness due to study participation. All participants in the study will be wearing an extra layer of clothing that they would not normally wear when mixing and loading wettable powder formulations into a pre-mix or application tank and diluting it under such conditions. In addition, mixing/loading activities might occur indoors or outdoors and some locations and dates are likely to result in hot and/or humid conditions.

        2) The risk associated with scripting of field activities. In order to ensure all monitoring units (MUs) involve handling at least three loads, AHETF may ask some workers to use a smaller tank size than they would normally select or to dilute the product more than usual. This might lead to a slightly longer work period for those workers which may increase the risks of acute toxicity to the surrogate chemical and of heat-related illness.

        3) Exposure to surfactants. A very dilute surfactant solution (0.01% v/v Aerosol® OT in water) is used for face/neck wipes and hand washes for all MUs. This surfactant is in a very dilute solution and its use represents a very short exposure period, but the undiluted surfactant causes mild to moderate skin and eye irritation in animals.

        4) Psychological risks. Participating in AHETF exposure monitoring studies involves activities that are unusual and might cause subjects psychological distress. These include performing an over-the-counter pregnancy test prior to participation (females only) and allowing a researcher to assist with the removal of the whole body dosimeter. Participating in AHETF exposure monitoring studies involves activities that are unusual and might cause subjects psychological distress.

AHETF has proposed several procedures to minimize these risks:

1) Monitoring and stopping procedures will be instituted. The AHETF will monitor ambient conditions to determine the heat index near the mixing/loading station and base monitoring decisions on the current heat index. Exposure monitoring will be discontinued if the heat index cutoff of 105 degrees F (adjusted for direct sun, if applicable) is reached or exceeded. The Study Director or other researcher shall stop the monitoring and/or move the worker to a cooler environment until monitoring can be resumed. If necessary, some monitoring will take place at night or early in the morning to avoid excessively hot and humid conditions.

2) Clear inclusion/exclusion criteria have been established. Only experienced pesticide handlers who consider themselves in good health will be included in the study. Experience with the mixing/loading equipment to be used in the study and with the mixing/loading of wettable powder products will be required of all participants. Participants must also understand Spanish or English.

3) Workers will be reminded of safe chemical handling practices, and research staff will practice the face wipe and hand wash procedures with each participant before pesticide handling begins.

4) Appropriate medical management procedures are in place. Eye rinse stations will be on hand in case of an accidental exposure. Medical treatment facilities will be identified in case of an emergency. A medical professional will be on site to observe study participants and provide urgent care.

5) Minors and pregnant or lactating women are excluded from participation, with pregnancy status confirmed by over-the-counter pregnancy testing within 24 hours prior to study participation. All female volunteers will be notified that an additional pregnancy test may be required if there are any delays in the planned start of the study. Only non-pregnant volunteers will be allowed to participate.

6) Procedures have been instituted to decrease psychological risks. Pregnancy tests will be conducted in a private place and information regarding pregnancy tests will be kept confidential. Private dressing areas will be provided and researchers of the same gender will be available to assist study participants.

These risks are minimized appropriately and are 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 for workers in four regions of the United States.

b. Voluntary and informed consent of all participants.

1) There is the possibility that the participants in this study might represent particularly vulnerable populations, susceptible to coercion and undue influence. The study proto-

col, however, includes several mechanisms designed to minimize coercive recruitment and enrollment.

2) The informed consent materials, if changed as recommended by the HSRB below, will adequately inform the subjects of the risks, discomforts and benefits from participation, and of their right to withdraw.

3) Monetary compensation is not so high as to unduly influence participants.

c. Equitable selection of study participants.

1) AHETF will first determine a pool of growers and/or commercial pesticide application companies who are eligible to participate in this study. Agricultural workers who work for these eligible businesses will be recruited as study participants. Employers will be required to affirm in writing that they will not influence their employees' decisions about whether to participate in this study. AHETF has developed complete and appropriate inclusion/exclusion criteria.

2. The Board recommended that the study protocol be modified to address the concerns noted in the EPA's Ethics Review (Evans et al. 2010). In addition, the Board raised additional concerns:

a. The Board concurred with the Agency's recommendation (Evans et al. 2010, 5) that the protocol standard operating procedure (SOP) AHETF-11-B.5 should be revised to specify that potential study participants will be asked about what they normally wear when handling pesticides in a way that does not direct them to a particular answer or lead them to agree to wear less personal protective equipment (PPE) than they normally would out of a desire to participate in the research.

b. The Board concurred with the Agency's recommendation that the language in the consent form about refusing medical treatment should be revised. However, the Board did not concur with the suggested revisions. The Agency recommends that the language be revised to read as follows: "You may refuse medical treatment unless the medical professional decides you are too sick to make a rational decision about getting medical treatment." The Board recommended that the language be revised as follows: "You may refuse medical treatment unless the medical professional decides (based on established criteria) that you are too sick to make a decision about getting medical treatment." In addition, it recommended that in an appropriate SOP, the criteria for decision-making capacity are provided as guidance for medical professionals who perform this function in AHETF research. The criteria for decision-making capacity can be found in the clinical and clinical ethics literature (e.g., Appelbaum 2007) and generally include all the following: The patient a) can appreciate the situation and its consequences; b) can understand the relevant information; c) can reason about the treatment decision; and d) can communicate a choice.

c. The Board partly concurred with the Agency recommendation that the AHETF should revise its plan for providing exposure information to subjects to address subjects who might

not speak English and/or are illiterate, and also to incorporate any future guidance from the HSRB's working group on this issue. The Board concurred that the AHETF and the Agency need to develop procedures to protect the needs of study participants who do not speak English or who have low levels of literacy. However the Board recommended that these procedures need to be rooted in the vocabulary and best practices of appropriate fields such as cultural competence and literacy. For example, the term illiterate is no longer used by literacy experts. The Agency should consider seeking guidance on these issues from the report of the US Department of Health and Human Services, National Action Plan to Improve Health Literacy (2010) and reports from the Institute of Medicine, Health Literacy: A Prescription to End Confusion (2004); Toward Health Equity and Patient-Centeredness: Integrating Health Literacy, Disparities Reduction, and Quality Improvement, Workshop Summary (2009). The Board concurred that AHETF should incorporate any future guidance from the HSRB's work group on return of results to participants after it submits its reports.

d. The Board concurs with the Agency that AHETF should clarify the discrepancy about whether hand wash samples are to be collected prior to water breaks (Evans et al. 2010, 2).

e. The Board concurs with the Agency review that future AHETF protocols or SOPs should incorporate information about how subjects are presented with individual exposure information, including how this process will be handled for research participants who do not speak English or have low levels of literacy; and an explanation of the process that the AHETF follows to improve and verify the accuracy of the Spanish translations (Evans et al. 2010, 2). The Board recommends that these future protocols be grounded in best practices in literacy and cultural competence and that the Spanish translations be in the appropriate dialect of the research participants.

3. The Board added these additional recommendations:

a. The requirement for additional pregnancy tests should be clarified throughout the documents. The Agency review indicates without explanation that the consent form states that "more than 1 pregnancy test may be required" (Evans et al. 2010, 5). However, on page 268 of the protocol it states that female volunteers "will be notified that an additional pregnancy test may be required if there any delays in the planned start of the study" (Collier 2011, 268). This explanation for why additional pregnancy tests may be required should be made explicit in the informed consent document.

b. The Agency review states that the return of individual exposure results may benefit research subjects (Evans et al. 2010, 15). The Board recommended that this language be deleted until the Board Working Group finishes its report and the Board reviews it.

c. The Board recommended that AHETF clarify how witnesses will be selected for workers who self-identify as non-readers. According to the protocol they "may choose a witness, or a third-party witness will be identified by the Study Director or designee and provided to the worker during the private consent meeting" (Collier 2010a, 292). It needs to be clarified that these witnesses are not associated with the research project.

d. The Board recommended that the risk of surrogate chemicals be included as one of the risks associated with participation in this study and be listed in the consent forms and in the protocol. It appears that the Task Force understood a prior Board recommendation that the physical risks associated with agricultural work should not be listed in the protocol and informed consent document to mean that exposure to the surrogate pesticides should likewise not be listed. The AHETF's perspective on this issue is reflected on page 109 of the protocol:

> AHETF generally monitors exposure to professional workers that normally use one of the surrogate chemicals approved by AHETF. Therefore, AHETF does not consider the risk of toxicity from pesticide handling to be strictly due to study participation (Collier 2010a, 109).

Because the study involves scripted activities and may require use of a pesticide that workers would not have applied that day if not for the study, however, the Board concluded that exposure to the surrogate compound should be listed in the protocol and consent document. When exposure to surrogate pesticides is re-included as a risk of the study, several documents will need revisions, including SOP AHETF-11.J.2. with IC checklist; DSM Form 386; and the Governing Document.

The AHETF also contends that the short duration of the study (generally one day) limits the toxic risk of exposure to the surrogate chemicals to acute or short-term effects. These effects are currently not listed in the consent forms or in the protocol, but the protocol states that the acute toxic effects from each surrogate product handled in this study will be discussed with the study participant before their participation begins (Collier 2010a, 109, 111). The Board concluded, however, that the discussion of these effects is conspicuously absent from the consent form and recommended that they either be listed explicitly or, at a minimum, that the consent document be revised to include a statement like:

> The label for the [surrogate compound] will be reviewed with you before you take part in the study. This review will include how much of that product you might handle during the study, *the symptoms and short-term health effects of accidental exposure to the product,* what clothing and personal protective equipment you must wear, the importance of washing your hands before eating, and other safety precautions that should be followed" (c.f. Collier 2010a, 146-7).

e. The Board recommended that the discussion of "greater than minimal risk" in the protocol be clarified. On page 44, the EPA review states:

> In this study risks to subjects are classified as 'greater than minimal', primarily since agricultural work is considered a high risk occupation where the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life (Evans et al. 2010, 44).

However, on page 106, the AHETF protocol states,

> In this study, risks to subjects are classified as "greater than minimal", since the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation (Collier 2010a, 106).

It is not clear whether "greater than minimal risk" refers to agricultural work or the risk of heat-related illness associated with participation in the study or to both.

Assessment of Completed AHETF Research Studies AHE55, AHE56, AHE57, AHE58 and AHE59: Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment.

Overview of the Study

Five separate field studies were conducted, each monitoring dermal and inhalation exposure of workers to commercially available pesticides while spraying tree or trellis crops in five different U.S. states where closed-cab airblast equipment is commonly used in production agriculture. A total of 24 professional agricultural handlers were monitored as they applied pesticides using closed-cab airblast equipment: five adult men applying pesticides to citrus trees in Florida (AHE55), five adult men applying pesticides to pecan trees in Georgia (AHE56), four adult men and one adult woman applying pesticides to cherry trees in Michigan (AHE 57), five adult men applying pesticides to grape vines in California (AHE58), and four adult men applying pesticides to apple trees in Washington state (AHE59). The scenario design, protocols for the five studies, SOPs and governing documents were reviewed favorably by the HSRB at its June 24-25, 2008 meeting (EPA HSRB 2008).

Monitored on actual days of work, study participants handled from 7 to 90 lbs of active ingredient (carbaryl, malathion, or chlorothalonil), spraying 4 to 30 acres in 2 to 9 hours. Dermal exposure was measured using hand washes, face/neck wipes, and whole body dosimeters (100% cotton union suits) for the remainder of the body (torso, arms, and legs). Inhalation exposure was measured using personal air sampling pumps and OVS mounted on the shirt collar. Results represent dermal exposure while wearing a long-sleeved shirt, pants, shoes/socks and chemical-resistant gloves, and inhalation exposure without respiratory protection.

The Agency proposes to use data from these five studies, posted to AHED®, to estimate generically daily dermal and inhalation exposures of workers who treat agricultural crops with conventional pesticides using closed-cab airblast equipment.

Science

Charge(s) to the Board

1) Was the research reported in the AHETF completed monograph report and associated field study reports faithful to the design and objectives of the protocol, SOPs and governing documents?

2) Has the Agency adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply conventional pesticides with closed-cab airblast equipment?

Board Response to the Charge(s)

HSRB Recommendation

The Board concurred in part with the Agency's assessment (Crowley 2011; Crowley and Sarkar 2011). The research reported in the completed monograph, associated field study reports, and associated supplemental documents (Bruce 2010a, 2010b, 2010c, 2010d; Klonne and Holden 2010; Smith 2010a, 2010b, 2010c, 2010d, 2010e, 2010f) was conducted in a manner that was reasonably faithful, to the extent possible under field conditions, to the design and objectives of the protocol and governing documents of the AHETF.

The Board also concluded that the Agency has not completely considered the limitations on these data that should be considered before using the data to estimate the dermal and inhalation exposure of those who apply conventional pesticides with closed-cab airblast equipment. Additional limitations and concerns have been identified by the Board, and conclusions as to the generalizability of these data require further consideration and analysis.

HSRB Detailed Recommendations and Rationale

While any field study of the nature of these AHETF studies have unanticipated deviations from the protocol and SOPs, this completed study was reasonably faithful to the design and objectives of the protocol, SOPs and governing documents. Many of the reported protocol deviations were minor, but some were not. However, it was unclear the effect these deviations would have, if any, on the results; the effect of these deviations of the data has not yet been determined.

With some exceptions, the quality assurance results appeared to be good. In terms of measured values below the limit of detection (LOD) or the limit of quantitation (LOQ) -- 7/48 inner dosimeters, 21/24 total head exposures, 4/36 hand wash samples, most OVS inhalation tube back samples -- the use of ½ LOD in such cases to extrapolate face/neck wipe exposure measurements to un-wiped portions of the face and head may have significantly affected the reported analyses and results.

It also is unclear whether temperature, humidity, wind speed, foliage density and/or the type of equipment used had any effects on exposure and whether or not these variables should be included in further exposure modeling. Additional questions raised by the Board included: 1)

wondering what was so different about the California grape study (AHE58; Bruce 2010a, 2011b) that the actual AaiH exceeded the upper limit in three of the five strata; and 2) questioning why the whole body dosimeter field fortification samples in the California grape study also exceeded the appropriate range at times.

Despite these concerns and questions, the Board concluded that the data obtained from these completed studies are likely to be reasonably accurate from the standpoint of the collection and handling of samples, and from chemical analysis. The data collected may not accurately account for all of the potential sources of exposure to pesticides by agricultural workers using closed-cab airblast pesticide application equipment. However, although the Board raised concerns regarding the utility of these data for predicting proportionality in a closed-cab airblast scenario, this concern does not invalidate the scientific validity of the actual data.

In its Scientific Review of the AHETF Closed Cab Airblast Monograph (Klonne and Holden 2010), the Agency stated that, "the secondary objective to evaluate proportionality between dermal and inhalation exposure and the amount of active ingredient handled with 80% statistical power – a key assumption in the use of exposure data as 'unit exposures' – was not met" (Crowley and Sarkar 2011, 2) such that the null hypothesis was not rejected. The Board agrees with this conclusion; the fact that the 95% confidence interval includes one does not mean that the assumption of proportionality is correct.

The EPA Scientific Review of the AHETF Closed Cab Airblast Monograph further states that, "additional analyses point to incidental exposure sources such as contacts with exterior surfaces having a more substantial impact on exposure" (Crowley and Sarkar 2011, 2). This is not unreasonable, specifically for dermal exposure. The fact that the reported data do not seem to reflect the proportionality of exposure to AaiH suggests that the engineering controls used here (i.e., a closed-cab air-conditioned vehicle) are likely to be effective in preventing exposure of the agricultural handler to the bulk of the pesticide being applied. The data also indicate that the study did not record or report all the activities or sources of "incidental exposures" (as defined in the AHETF Monograph) to pesticide, such as contaminations occurring outside the cab, in a manner that yielded good correlations with measured exposures that would have been helpful in interpreting these exposure data. The prominence of incidental exposure in this scenario may not have been anticipated in advance of the study. As the surrogates selected are pesticides that are appropriate and registered for the crops of the scenarios, they would be expected to be used in the field on some occasions. Finally, the reported results also suggest that the number of MUs may be too small to assess the proportionality of exposure to AaiH.

Given these issues, the Board raised concerns that the assumption of proportionality could not be demonstrated for dermal exposure without accurately measuring and factoring in incidental exposures and then recalculating the regression. Inhalation exposure estimates would be much less affected by such incidental exposures. The Board concluded that the assumption of proportionality is not correct for such exposures as confirmed in Table 1 of the EPA Review (Crowley and Sarkar 2011, 2).

The range of dermal and inhalation exposures was very great and, as predicted, skewed toward larger exposures even after normalizing the data. This range makes statistical estimation

of exposure difficult, and the Board recommended that a different type of probability density function should be used in statistical analyses.

The Board also raised concern that the method efficiency adjusted (MEA) correction factor used in estimating dermal exposures was not as accurate as it should be. This suggests that additional lab work is required to develop more accurate ways of obtaining exposure estimates for the various dermal exposures. The secondary analyses performed utilizing observations on clothing and on number of times exiting and entering the cab were very illuminating, indicating a different type of statistical regression model might be used if either field measurements or lab data could be combined. (It is questionable, however, given the limited number of observations whether sensitivity analyses could or should be performed.) Even considering alternative uses of these existing data, additional exposure 'models' should be investigated before final conclusions are made as to the use of the results in AHED®. The Agency should be careful, however, not to make any inferences from discoveries that the closed cab airblast scenario was not designed to address; they should not conclude, for example, that incidental exposures are the primary source of dermal exposure to pesticides as these five studies were not designed to measure the contribution of these sources of contamination to overall handler exposure estimates.

Finally, the Board agrees with the Agency's conclusion in its Scientific Review of the AHETF Closed Cab Airblast Studies that, given that some field control samples for the air samplers were found to have detectable residues, this finding "may impact field fortification recovery estimates, which in turn could alter actual field sample measurements" (Crowley 2011, 6). It was assumed by AHETF that, as the amounts of such residues in the field control samples were small, they could be ignored. Adjusting the data to account for the presence of detectable residues in the field control samples would have been more appropriate.

Ethics

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

HSRB Recommendation

The Board concurred with the Agency's assessment (Sherman 2011) that the study was conducted in substantial compliance with subparts K and L 40 CFR 26.

HSRB Detailed Recommendation and Rationale

The documents provided include reports of each of five field studies conducted on behalf of the Agricultural Handler Exposure Task Force (AHETF) (Bruce 2010a, 2010b, 2010c, 2010d; Klonne and Holden, 2010; Smith 2010a, 2010b, 2010c, 2010d, 2010e, 2010f). The five protocols were each reviewed and approved by an independent human subjects review committee, IIRB, Inc. of Plantation, FL prior to submission. Minutes of IIRB, Inc. meetings and a copy of IIRB,

Inc. policies and procedures were provided. This IRB is fully accredited by AAHRPP and listed by OHRP, as described above in the Board's review of proposed AHETF research study AHE80: Determination of Dermal and Inhalation Exposure to Workers During Mixing/Loading Wettable Powders in the United States.

1. The Board concurred with the conclusions and factual observations relating to the study, as detailed in the EPA's Ethics Review (Sherman 2011) and summarized briefly below.

    a. *Prior HSRB and Agency Review.* Because each of these five studies was initiated after 7 April 2006, prior submission of the protocol and supporting materials to EPA was required by 40 CFR §26.1125. The requirements of 40 CFR §26.1125 for prior submission of the protocol to EPA and of §26.1601 for HSRB review of the protocol were satisfied. The scenario design and study were approved by IIRB, Inc. in March 2008 (for protocols AHE55 and AHE56) and in August 2008 (for protocols AHE57, AHE58, and AHE 59). The HSRB discussed protocols AHE55 and AHE56 at its June 2008 meeting, and AHE57, AHE58, and AHE59 at its October 2008 meeting, in each instance concurring with the Agency's assessment (Sherman 2011) that these five proposed closed-cab airblast field study protocols, if revised as suggested by the Agency and the HSRB, would meet the applicable requirements of 40 CFR part 26, subparts K and L.

    b. *Responsiveness to HSRB and Agency Recommendations.* The initial ethics review by the Agency and by the HSRB provided 26 recommendations with regard to these five protocols. All of those recommendations, and the responses made with regard to them, are detailed in Attachment 4, on pages 42 and 43, of the Agency's Review (Sherman 2011, 42-3). The HSRB agrees with the Agency that the comments by the Agency and HSRB were satisfactorily addressed.

2. The Board also concluded that this study, as conducted, met all applicable ethical requirements for research involving human participants, in accordance with the following criteria.

    a. Acceptable risk-benefit ratio.

        1) The risks to study participants were minimized appropriately and were justified by the potential societal benefits, particularly data on the dermal and inhalation exposure of professional pesticide applicators to the liquid pesticides they apply to orchard and trellis crops using an airblast sprayer drawn by a vehicle with an enclosed cab. These data could be used to develop mechanisms to protect future persons who apply these liquid pesticides.

        2) Minors and pregnant or lactating women were excluded from participation, with pregnancy confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential of stigma resulting from study exclusion was also appropriately minimized.

        3) Clear stopping rules and medical management procedures were in place, and no adverse events or other incidents of concern related to product exposure were reported, except as described in section 3, below.

4) The study was designed to minimize the risks of exposure to the test compounds, subject to being able to accomplish the purposes of the study.

b. Voluntary and informed consent of all participants.

1) The study protocol included several mechanisms designed to minimize coercive recruitment and enrollment.

2) Monetary compensation was not so high as to unduly influence participation.

3. Twenty-two minor protocol deviations were reported by the sponsor. The Agency's Ethics Review also notes thirteen minor protocol deviations that were unreported. All of these are documented in some detail in Table 2 of the Ethics Review (Sherman 2011, 18). The Board agrees with the Agency's evaluation of these deviations, and the fact that they do not require any changes in the Board's determinations described above.

However, one category of protocol deviation is given special attention in the EPA Ethics Review and merits discussion here. These deviations involved the fact, on multiple occasions in three of the five CCAB studies, subjects failed to wear gloves while touching a contaminated surface, usually part of the airblast cab or attached machinery.

As the Agency notes, according to the protocols, these protocol violations involved a safety issue (exposure to the pesticide). In each instance the person who observed these violations of safety standards should have reminded the workers to wear their gloves and reported the behavior to the study director. There is no record that these steps took place. However, given the nature of these exposures to the pesticides, and the pesticides that were chosen for use in these protocols, the actual increased risk to the subjects appears minimal. The Board agrees with the Agency's determinations in that regard (Sherman 2011, 29).

Beyond these completed studies, however, these deviations raise an issue that the Agency and sponsors may wish to consider with regard to the design of future protocols. That 25% of the subjects in these five studies engaged in this behavior suggests that it is probably not uncommon. Although experienced pesticide applicators are told of the need to wear gloves before touching certain pieces of equipment, it appears that they commonly fail to do so. If indeed this is a common behavior, and EPA wants to collect data from such exposures, then Agency and the sponsors may want to consider an approach that specifies safety standards in the informed consent form but indicates that observers will not necessarily remind participants of the standard each time they are observed violating these standards. In addition to or as an alternative to this approach, it may be desirable to write an SOP that is referenced in future protocols.

The purpose of the SOP would be to clarify for study observers the safety-related interventions, if any, that observers should make when participant's engage in behaviors that are inconsistent with either the protocol or the label. In such an SOP, it would be necessary to clearly spell out which safety-related deviations are "acceptable" (meaning they would not require an intervention such as a reminder to the subject to alter their behavior each time that

behavior is observed), and which are not (meaning they would require an intervention, such as a reminder or warning). Acceptable deviations should only be those that involve very low risks to subjects. Observers should receive guidance on safety violations that would merit reminders or warnings to subjects, reports to the study director, and immediate interventions to correct inappropriate behavior, including the most common examples of behaviors that are and are not acceptable. In addition to potentially reducing participant risk, this guidance would also help to standardize observations by removing variation introduced when observers are required to make their own subjective evaluations of risk in determining when and how to intervene.

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