UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 8, 2009

MEMORANDUM

SUBJECT: Science and Ethics Review of AHETF Scenario Design and Protocol AHE120 for Exposure Monitoring of Workers during Mixing and Loading of Pesticide Products in Water Soluble Packets in Five Regions of the United States (submitted to EPA on January 16, 2009)

FROM: Jeff Evans
Health Effects Division

Kelly Sherman
Human Research Ethics Reviewer

TO: Steve Knizner, Associate Director
Health Effects Division

REF: Bruce, E. (2009) Determination of Dermal and Inhalation Exposure to Workers during Mixing/Loading of Pesticide Products in Water Soluble Packets in the United States. Unpublished protocol dated December 11, 2008, prepared for the Agricultural Handlers Exposure Task Force under Sponsor ID AHE120, 552 p.

We have reviewed the referenced proposal from both scientific and ethics perspectives. Scientific aspects of the proposed research are assessed in terms of the recommendations of the EPA Guidelines Series 875 and of the EPA Human Studies Review Board. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board. Below is a summary of the conclusions reached in our science and ethics reviews.

Science Review

- The protocol addresses the technical aspects of applicable exposure monitoring guidelines and is likely to produce scientifically valid and useful data.

Ethics Review

- The protocol meets the applicable ethical requirements of 40 CFR part 26, subparts K and L.
- Before the research is conducted, the protocol should be revised as follows and re-submitted for review by the approving IRB:
    - The Local Site Coordinator, the Principal Field Investigator, the Analytical Facility, and the Principal Analytical Investigator must be identified in the protocol.
    - The page headings on the English Language Research Participant Bill of Rights should be changed from Spanish to English.
- In addition, please provide the following information to the Agency. If a protocol revision is necessary to address these comments (or for any other reason), please also re-submit for review by the approving IRB:
    - Collect information on growers who do not respond or who decline to participate, such that the representativeness of participating growers can be evaluated.
    - Provide more information about how individual level exposure data will be presented to subjects upon request. In particular, please explain how the data will be framed and how the AHETF will work to prevent workers from changing future behavior to their own detriment if their individual risk levels are lower than the average of all workers.
    - Verify the appropriateness of, or make necessary improvements to, the Spanish translations of the consent form, product risk statements, and recruitment materials. Spanish translations should be written in common, simple Spanish, appropriate to the reading ability of potential Spanish-speaking subjects.

A. Completeness and Contents of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. All required elements are present. EPA's checklist is appended to this review as Attachment 6.

The following two documents comprise the protocol submission and were considered in EPA's review:

- Water Soluble Packet Mixer/Loader Scenario Submission (January 16, 2009) (552 pages); and
- Supplemental Submission of Final Versions of 12 SOPs (February 24, 2009) (78 pages).

The monitoring unit selection and scenario construction plan appear on pages 10-47.[1] The rationale for the proposed sample size and cluster configuration is presented on pages 15-21. The IRB-approved protocol and supporting documents (consent forms, product-specific risk statements, and recruitment flyers) appear on pages 85-147 (English) and pages 148-163 (Spanish). Documentation of all interactions between the investigators and the Independent Investigational Review Board, Inc., of Plantation FL appears on pages 177-552.

The following documents are included in the submission:

- Monitoring Unit Selection and Construction Plan for Scenario (pp. 10-47)
- Background Information from Experts (pp. 48-79)
- IIRB Approval Letter and Approved Supporting Documents (pp. 80-176)
- IIRB Approval Letter (pp. 81-84)
- IIRB-approved Protocol (pp. 85-125)
- Study Documents in English approved by IIRB:
    - Informed Consent Form (pp. 126-136)
    - Product Risk Statements (pp. 137-143)
    - Recruiting Flyer (pp. 144-145)
    - Research Participant Bill of Rights (pp. 146-147)
- Spanish translations of study documents approved by IIRB:
    - Informed Consent Form (pp. 148-160)
    - Product Risk Statements (pp. 164-173)
    - Recruiting Flyer (pp. 174-176)
    - Research Participant Bill of Rights (pp. 161-163)
- SOPs Referenced in the protocol (pp. 395-538)
- Records of IRB Review (pp. 177-552)

The SOPs listed below are cited in the scenario and protocols. The eight SOPs marked by a single asterisk have been revised since the October 2008 HSRB meeting to address EPA and HSRB comments. The four SOPs marked by a double asterisk are new SOPs written since the October 2008 HSRB meeting to address EPA and HSRB comments. Final versions of the twelve new or revised SOPs are provided in the 78-page supplemental submission that was provided to EPA by the AHETF on February 24, 2009.

Final versions of the SOPs that are unchanged since the October 2008 HSRB meeting, plus draft versions of the twelve new or revised SOPs, are provided on pages 395-538 of the main submission, as part of the materials submitted for IRB review.[2]

---

[1] Unless otherwise noted, all page references in this review are to "p. N of 552" of the main submission. If pages within the supplemental submission of the twelve new and revised SOPs are referenced, the page reference will indicate "SOP Supplemental Submission, p. N of 78."

[2] When the protocol was submitted for IRB review in December 2008, the twelve new or revised SOPs were still in draft form. Since that time, the twelve SOPs have been finalized, and the final versions of the twelve SOPs are contained in the 78-page Supplemental Submission of SOPs (dated February 24, 2009).

AHETF-1.B.4*	Personnel Responsibilities
AHETF-1.F.0	Potential Referable Findings
AHETF-1.H.0**	Procedure for Recruiting Study Participants
AHETF-2.C.2	Protocol Design and Preparation
AHETF-6.B.1	Access to Archived Data
AHETF-6.D.0	Access to Confidential Worker Info
AHETF-8.A.3	Whole Body Sampling – Inner Dosimeters
AHETF-8.B.4	Hand Wash Samples
AHETF-8.C.6*	Dermal Face/Neck Wipe Samples
AHETF-8.D.4*	Collection of Air Samples Using OVS Tubes
AHETF-8.E.5*	Fortification of Matrix Samples
AHETF-8.F.5	Sample Identification
AHETF-8.G.2	Worker Clothing Acceptability Criteria
AHETF-8.K.0	Sample Quality
AHETF-9.J.0	Analytical Quality Control and Statistics
AHETF-10.C.4	Worker and Study Observations
AHETF-10.E.2	Worker Sample Collection Sequence
AHETF-10.G.1	Personal Air Sampling Pump Calibration
AHETF-11.A.1	Ethical Requirements for AHETF Studies
AHETF-11.B.4*	Recruiting Study Volunteers
AHETF-11.C.1	Worker Health Status
AHETF-11.D.1	Pregnancy Testing
AHETF-11.E.1	Pesticide Safety Instructions
AHETF-11.F.1	Adverse Events Reporting for Institutional Review Boards
AHETF-11.G.1	Identification and Control of Heat Stress
AHETF-11.H.2*	Emergency Procedures for Human Subjects
AHETF-11.I.1*	Language Requirements and Considerations for Study Volunteers
AHETF-11.J.1*	Seeking Informed Consent from Study Volunteers
AHETF-11.K.0**	Compiling Lists of Potential Growers
AHETF-11.L.0**	Compiling Lists of Potential Commercial Applicators
AHETF-11.M.0**	Recruiting Potentially Eligible Growers and Commercial Applicators

B. Summary Assessment of the Scenario Design[3]

1. **Scenario Design:** This proposal addresses the handler exposure scenario involving mixing/loading of pesticides enclosed in water soluble packets (WSP). The mixing/loading activities will involve a variety of application equipment such as ground boom and airblast sprayers. EPA's Worker Protection Standard (WPS) at 40 CFR 170.240(d)(4) states that WSP products, when used correctly, qualify as a closed mixing/loading system.

[3] Supporting details are in Attachment 1.

Mixers and loaders using water-soluble packets must:

- Wear a long-sleeved shirt, long pants, shoes, socks, chemical-resistant gloves and a chemical-resistant apron.
- Be provided with chemical-resistant footwear, immediately available in an emergency (such as a broken package, spill or equipment breakdown), and wear it in such an emergency.
- If a respirator is required for open mixing/loading, then the respirator must be provided and worn also in case of emergency.

The AHE120 protocol calls for mixing/loading one of two surrogate pesticides into a variety of tanks containing water in a variety of agricultural spraying operations. A total of 25 Monitoring Units (MUs) are proposed for this scenario; when the scenario is complete, the 25MUs will be added to the AHED database. EPA intends to use these data to estimate daily dermal and inhalation exposures of pesticide handlers mixing/loading pesticides in water soluble packets (WSPs) for a variety of mixing and loading scenarios.

2. **Sampling Design:** The proposed mixing/loading of water soluble packets scenario will involve five clusters purposively selected to reflect a diverse range of agronomic practices, geographic regions and likelihood of use of one or both surrogate pesticides (acephate and carbaryl). Each cluster is referred to as a monitoring 'site;' at each site five workers will be monitored.

   The AHETF diversified the five clusters for this scenario by surrogate pesticide usage and geographic region through a purposive five-step process:

   - Identifying geographic areas associated with the use of water soluble packets
   - Stratifying WSP use areas by EPA growing regions
   - Identifying the predominant surrogate pesticide-using states in the EPA growing regions
   - Selecting one major producing state for each major crop, with no more than one state per region
   - Selecting a site—a county or group of adjacent counties— in which to conduct each field study, likely to support an efficient study and to have an ample supply of handlers

   The result of executing these steps was the purposive choice of the following five states for the five proposed monitoring sites:

   - New York (EPA Region I)
   - Louisiana (EPA Region IV)
   - Michigan (EPA Region V)
   - California (southern portion of EPA Region X)
   - Washington (eastern portion of EPA Region XI)

These choices are appropriate to cover the most important regional and agronomic variations and likelihood of use of WSP containing either acephate or carbaryl.

New York (Region I) represents a cool climate having a wide variety of orchard, trellis and field crops. According to the annual use data from the National Agricultural Statistical Service (NASS), approximately 29,000 pounds of carbaryl active ingredient (AI) were reportedly used on apples and 26,000 pounds AI being used on grapes.

Louisiana (Region IV) represents a hot and humid climate where higher acreages of cotton and soybeans are available that are treated with acephate. According to the annual use data from NASS, approximately one million and 400,000 pounds of acephate AI were applied to cotton and soybeans respectively.

Michigan (Region V) represents a cool climate in the upper Midwest having a wide variety of orchard crops such as cherries apples and peaches. Trellis and field crops are also represented in this state. According to the annual use data from NASS, approximately 67,000 pounds AI of carbaryl and 11,000 pounds AI of acephate were applied to a variety of crops.

California (central/southern portion of Region X) represents a region having high usage of both carbaryl and acephate on a wide variety of orchard, trellis and field crops. According to the annual use data from NASS, approximately 74,000 pounds AI of carbaryl and 68,000 pounds AI of acephate were applied to a variety of crops. California also represents a hot and dry climate in the western U.S.

Washington (eastern portion of Region XI) also represents a hot and dry climate but situated in the northwest U.S. According to the annual use data from NASS, approximately 1.6 million and 53,000 pounds of carbaryl AI were applied to apples and cherries respectively.

In the next stage of the diversity selection process, the practical range of amount of active ingredient handled (AaiH) for the water-soluble packet scenario is divided into five bands ranging from 5 to 2000 pounds AaiH. Past studies have shown that AaiH is strongly associated with exposure and is a meta-factor associated with differences in equipment and spraying practices. The AHETF selected the 2000 pound AaiH value as the practical upper limit based on experience in other mixer/loader studies. This limit was also selected to reduce the burden on subjects in the studies, and to avoid long monitoring periods. AHETF has set a lower limit at 5 lbs, to minimize non-detects. AHETF has partitioned the practical AaiH range into five strata:

- 5 to 17 lbs AI handled
- 18 to 55 lbs AI handled
- 56 to 182 lbs AI handled
- 183 to 603 lbs AI handled
- 604 to 2,000 lbs AI handled

This is a reasonable approach to stratification, and it should be possible to fill all strata in all five region field studies defined for this scenario within the range of standard agronomic practices.

The next stage of sample selection results in identifying the growers whose crops will be treated and the workers whose exposure will be monitored. As with other agricultural pesticide application scenarios, growers who agree to cooperate with the research and to spray their crop must be identified before workers can be recruited.

The AHETF process for identifying handler subjects recruited from growers or commercial pesticide application firms includes five steps:

- Contacting local resources to identify growers of the crops of interest
- Assembling a list of growers from all resources contacted and suppressing duplicates
- Putting the list of growers into random order
- Contacting growers, one at a time, in the sequence of the randomized list, to determine whether the grower is 'eligible' to participate
- Placing eligible growers into a "working pool"

Screening of growers for eligibility will continue until the pool contains somewhat more growers with somewhat more workers than are needed to fill five MUs in each cluster. From each grower in the working pool, the following range of information will be compiled:

- The grower is willing to cooperate with the AHETF
- The grower has the necessary mixing/loading equipment
- The grower has at least one worker with experience in the mixing/loading of water soluble packets
- The grower has sufficient acreage that the minimum AaiH can be mixed/loaded
- The grower is willing to use a least one of the surrogates (acephate or carbaryl)

This process of identifying cooperating growers is basically sound. EPA has accepted this approach.

When constructing MUs, three additional restrictions will be enforced to increase diversity within the cluster:

- No handler may be used more than once
- No piece of equipment may be utilized more than once
- No more than one MU may be obtained from one grower or commercial pesticide applicator company

The growers and/or commercial pesticide applicator companies in the chosen configuration provide the pool of handlers from which handlers will be recruited to fill each of the five MU slots. If selected growers or handlers drop out as the time of the field study approaches, additional handlers appropriate to fill out the MU design may be recruitable from among those employed by growers and commercial firms already in the working pool of eligible entities. If there are too few handlers available in the pool to complete a revised efficient configuration, the working pool can be expanded by approaching more growers or commercial firms from the original randomized list. If the original randomized list is exhausted without finding enough interested handlers to complete the field study design, another list will be generated.

3. **Choice of Surrogate Materials:** The surrogate chemicals proposed for this scenario are carbaryl and acephate, formulated in water soluble packets as one of three registered products: Acephate 90 WSP, Acephate 75 WSP, or Sevin® 80 Solupak. These pesticide active ingredients have been successfully used as surrogates in previous worker/handler exposure monitoring studies and have well established and reliable analytical methods. These are generally appropriate choices for this research. However, due to risk estimates for acephate, we recommend that no more than 700 pounds AI be handled by any worker on any given day.

C. Summary Assessment of the Scientific Aspects of the Study Design[4]

1. **Statistical design:** This protocol describes collecting 25 Monitoring Units (MUs) reflecting the exposure of subjects mixing/loading formulations of acephate or carbaryl enclosed in water soluble packets, to support a variety of applications to field, orchard or trellis crops. These MUs will be collected in five separate clusters diverse in geographic location and climate. Each cluster or study site will include five MUs. The general rationale for the 5 x 5 cluster configuration is presented in Appendix C of the revised AHETF Governing Document; details specific to the mixing/loading of water soluble packets scenario are in the scenario design. No characteristics of this scenario have been identified which would justify a departure from the 5 x 5 configuration.

[4] Supporting details are in Attachment 2.

2. **Proposed pattern of exposure:** The proposed minimum exposure duration for each MU will be at least 4 hours, involving the mixing/loading of at least 3 tank-loads. Subjects will only mix and load the surrogate pesticide; applying the finished spray solution/suspension will be done by others not participating in the study. Over the course of a day each subject will apply the surrogate active ingredient in one of the following five strata of AaiH:

    - 5 to 17 pounds AI handled
    - 17 to 55 pounds AI handled
    - 56 to 182 pounds AI handled
    - 183 to 603 pounds AI handled
    - 604 to 2000 pounds AI handled

    Three registered products containing one of the two designated surrogate pesticide active ingredients have been identified, and a cooperating grower may choose to use any of them for a specific MU. All of these products will be mixed with water and loaded into the various sprays tanks in one of three possible ways:

    - Loading individual WSPs directly into the tank associated with the application equipment (e.g., groundboom or airblast sprayers)
    - Loading individual WSPs into holding or nurse tanks before the finished spray solution/suspensions are transferred to the application equipment tanks (e.g., fixed wing aircraft). The pesticide concentrate in this situation is the same concentration that will be applied using the spray equipment to which it will be transferred
    - Loading individual WSPs into slurry tanks or other tanks to make more concentrated solutions/suspensions that must be diluted with water before being transferred to the final spray tank

    The AHETF will ensure that at least one MU in each cluster will reflect each of the mixing/loading situations described above.

    For this scenario the duration of the monitoring period is expected to vary considerably because of the wide range of AI to be handled by the different subjects. Furthermore, some subjects may perform other tasks between episodes of mixing and loading, and others may simply wait at the mixing site between episodes. The AHETF acknowledges that some scripting may be needed for subjects assigned to the lower AI strata to ensure at least 3 mixing/loading events are measured for each worker.

3. **Endpoints and Measures:** The study will measure dermal and inhalation exposure for each MU. These data will contribute to development of Unit Exposures (exposure per unit of pesticide active ingredient applied) or other exposure metrics, and to estimates of dermal and inhalation exposure to other pesticides for workers mixing and loading pesticides formulated in water soluble

packets. EPA believes that the proposed measures are appropriate and sound for the study design.

Dermal exposure will be measured by a whole body dosimeter (WBD) worn beneath the subject's outer clothing. After the monitoring event, the inner dosimeter will be removed from the subject and sectioned into six pieces: the front torso (above the waist); rear torso (above the waist); right and left upper arms (shoulder to elbow); right and left lower arms (elbow to cuff); right and left upper legs (waist to knee) and the right and left lower legs (knee to cuff).

Before beginning work, subjects will wash their hands in 500 mL of 0.01% Aerosol® OT-75 solution (AOT solution) to remove any source of contamination and to practice the method of hand-washing. These samples will be discarded. Hand wash samples will be collected before toilet and lunch breaks, before water breaks if required by the label or requested by the subject, and at the end of each exposure period.

Before beginning work, each subject's face and neck will be wiped with a cotton gauze swab to remove any contamination not associated with the monitoring event. This wipe sample will be discarded. Subjects will undergo another face/neck wipe sampling prior to the break and again at the end of the exposure period; both these samples will be retained for analysis. As required by AHETF SOP 10.C.4, the study team will record what type of personal protective equipment (PPE), including respirators, was worn at any time during the monitoring event.

Airborne concentrations of the surrogate will be monitored in the subject's breathing zone using an OSHA Versatile Sampler (OVS) tube sample collector connected to a personal sampling pump. The unit will be calibrated prior to the monitoring event using a rotameter. The OVS tube will be clipped to the subject's shirt collar with the intake facing downward. The air sampling pump will be connected to the OVS tube and will be operated for the total monitoring period including any breaks.

Additional measures will record environmental conditions at the time of monitoring. Observers will make field notes of subject activity throughout the monitoring event, and photographs or videos may be taken selectively to illustrate events.

4. **QA/QC Plan:** The study will be monitored by three different quality assurance units: one from the exposure monitoring contractor that conducts the study in the field, one from the analytical laboratory that determines the level of pesticide residues in field samples, and one contracted directly by AHETF.

   Analytical and field sampling quality control procedures include complete validation of all analytical methods, field fortification and control samples,

laboratory fortification and control samples, and guidelines on the use of calibration curves to determine chemical residues found on all sample matrices.

Field fortifications will be conducted in the field under the same conditions as the field samples. They will be transported and stored in a similar manner as the field samples, and will be analyzed in the laboratory concurrently with the field samples. Samples collected from the subjects will be corrected based on the results of the recovery of the field fortified samples.

5. **Statistical Analysis Plan:** The results of physical sample analysis will be provided in the final report of this field study and in the scenario monograph covering all monitoring conducted under the mixing/loading of water soluble packets scenario, and will be posted to the AHED® database, where they will be available to regulatory agencies for later statistical analysis. The documentation will report a confidence-interval-based approach to determine the relative accuracy for the arithmetic mean and 95th percentile of unit exposures. The AHETF will not otherwise statistically analyze the monitoring data.

D. Compliance with Applicable Scientific Standards

This protocol itself adequately addresses the following elements according to applicable scientific standards:

- Scientific objective
- Experimental design for achieving objectives
- Quantification of the test materials
- Data collection, compilation and summary of test results
- Justification for selection of test substances
- Justification for sample size
- Fortification levels and number of samples for laboratory, field, and storage stability samples

Additionally, the proposal has addressed the technical aspects provided in the applicable exposure monitoring guidelines (i.e. Series 875 Group A and OECD Applicator Guidelines) as well as Good Laboratory Practices (GLPs).

E. Summary Assessment of Ethical Aspects of the Proposed Research[5]

1. **Societal Value of Proposed Research:** The objective of this study is to develop data to determine the potential exposure for workers who mix and load solid pesticide products packaged in water soluble packets. This mixing/loading method is widely used and applicable to a large variety of commercially important crops, and the existing exposure data are inadequate. EPA will use the results of this study to estimate the dermal and inhalation exposure likely for a wide range of agricultural pesticides applied under this exposure scenario.

2. **Subject Selection:** Subjects will be recruited among the employees of commercial growers who utilize solid pesticides packaged in water soluble packets, who are willing to use at least one of the surrogate active ingredients for this study (acephate and carbaryl), and who meet AHETF criteria for participation. Eligible growers will be identified from a complete list of growers in the target area, processed in random sequence. Subjects will be recruited who are employees of eligible growers (or of pesticide application service companies used by eligible growers), with experience within the past year mixing and loading water soluble packets using the particular equipment to be used in the study, and who meet the eligibility requirements of the study. If more employees are available and interested than are needed, qualified participants will be selected randomly. Although the design is purposive, and thus participants are not representative in a statistical sense, they are expected to be typical of those who mix and load pesticide products packaged in water soluble packages.

   Subjects will be recruited according to the standard procedures set forth in SOP AHETF-11.B.4 (SOP Supplemental Submission, pp. 29-34 of 78). The Study Director or designated researcher will seek permission from the eligible grower to approach his/her employees to recruit volunteers for the study. Depending on the number of employees and size of the grower's facility, the Study Director or researcher may contact employees using an informational recruitment flyer posted in a common work area. Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the grower's employees who express interest in participation. Such recruitment meetings will always occur without the grower or supervisors being present. The Study Director or researcher will describe the AHETF Exposure Monitoring Program, the goals of this specific study, the procedures to be used in exposure monitoring, and the risks and benefits to participants.

   The subject eligibility factors listed in the consent form and SOP AHETF-11.B.4 are appropriate. However, the page headings on the English Language Research Participant Bill of Rights (p. 147) should be changed from Spanish to English.

[5] Supporting details are in Attachment 2.

Candidates who attend an individual interview will be paid $20 whether or not they agree to participate; enrolled subjects who put on the whole-body dosimeter will be paid $80 in addition to their usual pay, whether or not they complete participation.

3. **Risks to Subjects:** Five kinds of risks to subjects are discussed in the protocol, along with specific steps proposed to minimize them:

    - The risk of heat-related illness
    - The risk of exposure to surrogate chemicals
    - The risk associated with scripting of field activities
    - Psychological risk
    - The risk of exposure to surfactants used for hand washing and face wipes

    The surrogate chemicals used will be acephate or carbaryl; both are fully tested and well understood. Individual growers will choose from three registered products (two containing acephate as the active ingredient and one containing carbaryl as the active ingredient), for each of which a product-specific supplement to the consent form describes the specific risks identified on the approved label. Margins of Exposure (MOEs) calculated for the highest levels of exposure proposed in the protocol meet or exceed EPA's target MOEs, and therefore the exposures are not of concern to EPA.

    Appropriate provision is made for safety and medical monitoring. At the end of the test day, subjects will be reminded that they have a copy of the consent form with phone numbers to call if they think they have any adverse effects resulting from participation.

4. **Benefits:** This research offers no direct benefits to the subjects, but subjects may request their individual results. If they are told only their own results, little benefit would result, but if they are told how their exposure compared to that of others, it could be of potential indirect benefit to them. The principal benefit of this research is likely to be reliable data about the dermal and inhalation exposure of workers mixing/loading water soluble packets of pesticide formulations, usable by EPA and other regulatory agencies to support exposure assessments for a wide variety of pesticides with similar use patterns.

5. **Risk/Benefit Balance:** Risks to subjects have been minimized in the design of the research. The low residual risk is reasonable in light of the likely benefits to society from new data supporting more accurate applicator exposure assessments for a wide range of agricultural pesticides.

6. **Independent Ethics Review:** The proposed research has been reviewed and approved by the Independent Investigational Review Board, Inc., (IIRB, Inc.) of Plantation, Florida. The submitted materials include a full record of correspondence between the investigators and the IIRB.

7. **Informed Consent:** Informed consent will be obtained from each prospective subject and appropriately documented. Subjects will sign both the consent form and the product-specific supplement describing the surrogate material chosen by the grower. If participating in the study in California, subjects will also receive the California Research Participant Bill of Rights. Oral fluency in English or Spanish is a criterion for inclusion, but literacy is not required. The reading level of the English language consent form is appropriate. Adequate provision is made to meet the needs of subjects who do not read either language. EPA assessments of compliance with the requirements of 40 CFR §26.1116 and §26.1117 appear in Attachments 4 and 5 to this review.

8. **Respect for Subjects:** Subject identifying information will be recorded only once; all subsequent data records and reports will refer to individual subjects only by a code. Provision is made for discrete handling of pregnancy testing, required of all female subjects on the day of testing. Candidates and subjects will be repeatedly reminded that they are free to decline to participate or to withdraw at any time for any reason, without penalty.

F. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

A detailed evaluation of how this proposal addresses applicable standards of ethical conduct is included in Attachments 2-5 to this review.

The following specific deficiencies in the protocol should be addressed before the research is initiated:

- The Local Site Coordinator, the Principal Field Investigator, the Analytical Facility, and the Principal Analytical Investigator must be identified in the protocol.

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

> EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

The protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA to rely on a study executed according to this protocol.

If the deficiencies noted above are addressed and the amended protocol is approved by the overseeing IRB, this research should meet the ethical standards of FIFRA §12(a)(2)(P) and 40 CFR 26 subparts K and L.

Attachments:

1. EPA Scenario Review: AHETF Mixing/Loading of Wettable Powder in Water Soluble Packets (AHE120)
2. EPA Protocol Review: AHETF Mixing/Loading of Wettable Powder in Water Soluble Packet (AHE 120)
3. §26.1111 Criteria for IRB approval of research
4. §26.1116 General requirements for informed consent
5. §26.1117 Documentation of informed consent
6. §26.1125 Criteria for Completeness of Proposals for Human Research
7. **Responsiveness to Recommendations in the Final Report of the October 2008 HSRB Meeting**

EPA Scenario Review: AHETF Mixing/Loading of Wettable Powder in Water Soluble Packets (AHE120)

Title: **Monitoring Unit Selection and Construction Plan for Scenario: Mixing/Loading of Water Soluble Packets**

Date: December 4, 2008

Sponsor: Agricultural Handlers Exposure Task Force

1. Scope of Scenario Design

"This scenario includes the mixing/loading of water soluble packets into various types of farm equipment and dilution with water for future application as liquid sprays. This is accomplished by mixing/loading the packets directly into the tank to be used for the application or into a pre-mix tank where the contents will later be transferred to the spray tank used for the actual application." (p. 12)

"…the following states are proposed for this scenario to provide the desired diversity in geography and likely use of one or more surrogates:

- New York
- Louisiana
- Michigan
- California (the southern portion in EPA Region X)
- Washington (the eastern portion in EPA Region XI)" (p. 152)

(a) Is the scenario adequately defined?

The scenario is clearly and appropriately defined.

(b) Is there a need for the data? Will it fill an important gap in understanding?

"AHETF has identified the WSP mixing/loading scenario as being within the scope of the task force goals and one for which data are lacking. A number of AHETF member products are labeled for this use pattern. This mixing/loading scenario is applicable to a wide variety of commercially important crops (e.g., orchards, row crops, grains, field crops, trellis crops, greenhouse and nursery plants, forestry, etc.). Therefore, it is necessary to have data in AHED for the mixing/loading technique described by this scenario…

"AHETF (in conjunction with EPA, PMRA, and CDPR, collectively the Joint Regulatory Committee (JRC)) reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that satisfy current acceptability criteria and

qualify for inclusion in a generic database. For this particular scenario, the JRC reviewed three studies (AH508, AH520, andAH608) involving mixing/loading only with water soluble packets; however, none of these studies were deemed appropriate for a generic database.

"AHETF also conducted a detailed review of the data in PHED (EPA, 1998a) for this scenario to determine if any of the data were suitable for a modern generic database. Data for mixing/loading of water soluble packets comprise PHED Scenario 5 – Wettable Powder, Water Soluble Bags (MLOD). Data within that scenario were graded by EPA as "Low Confidence" for the "No Clothes", "Single Layer, No Gloves" and "Single Layer, Gloves" clothing scenarios. The inhalation exposure data are also graded as "Low Confidence". The low confidence ratings were primarily due to low numbers of measurements…

"Finally, EPA examined data from existing water soluble packet mixing/loading exposure studies or exposure assessments that were not available to the AHETF and concluded that none of the exposure data should be included in the AHETF database (meeting, November 3, 2008)." (pp. 16-17)

2. Rationale for Scenario Sampling Design

(a) Are the variables in the scenario design likely to capture diverse exposures at the high-end?

"Exposure experts within the AHETF have identified equipment type as a potentially important parameter that might impact exposure. Factors such as the design of the equipment affect the spatial relationship of the worker to the opening where loading occurs (e.g., a short tank at chest height versus a taller tank where loading may be slightly overhead). Equipment design can also affect the amount of contact the worker has with contaminated surfaces and other factors such a whether or not diluted product is transferred to another tank. Therefore, equipment type will be informally diversified within clusters of MUs.

Experts identified several general types of equipment and procedures used with WSPs that are identified below (Honeycutt, 2008):

- Direct mixing WSPs into tanks that are used directly for application (e.g., groundboom, airblast, chemigation, etc., tanks)
- Mixing WSPs into tanks not directly used for the application but which serve as holding tanks and contain the spray mix solution in the final concentration at which it will be applied (e.g., these tanks go by various names such as holding, nurse, pre-mix, etc. tanks)
- Mixing WSPs in tanks not directly used for the application (e.g., slurry tank or bucket) and which contain a concentrated spray mix solution that must be further diluted and transferred to a final tank used for the application…

Consequently, it is proposed that the possible equipment types used for this scenario be grouped into the following 3 general categories:

1. Mixing of WSPs directly into the tank used for the application
2. Mixing of WSPs into a "pre-mix" tank in which the solution is at the same concentration as that applied to the crop
3. Mixing of WSPs into a tank (or other container) to make a concentrated solution that must be diluted & transferred to the final application tank," (pp. 38-40)

"Geographic Stratification: . . . the use of water soluble packets can be found throughout the United States and can involve a wide variety of crops, including field crops, trellis crops, and orchard crops. Geographic diversity between clusters of monitoring units is expected to provide some variability in agronomic conditions and of other factors, such as equipment type, work practices, weather, etc. That is, it is viewed as a meta-factor that is associated with both known and unknown effects usually classified as simply 'study effects'. . . .

EPA has established 13 U.S. Growing Regions. The 12 regions of the continental U.S. are shown below in Figure 1. Growing Region XIII consists of Hawaii and Puerto Rico and is not being considered for this scenario. These Growing Regions provide a convenient basis for geographic stratification. These Regions have been used when planning and conducting pesticide residue trials for various crop types. The regions were based on natural geography and climatic boundaries (ACPA, 1992) and are therefore useful for indicating when locations selected for exposure monitoring are geographically diverse. . . ." (pp. 24-25)

"Predominant Surrogate Use: Although water soluble packets may be used in all 12 EPA Growing Regions, not all are expected to have wide use of the two AHETF surrogate active ingredients (acephate and carbaryl). Thus, for practical reasons, the distribution of surrogate use will be considered when selecting the five monitoring sites.

Table 2 illustrates this surrogate distribution with chemical usage data obtained from USDA on (NASS 2003 and 2006). The total usage for acephate and carbaryl (in thousands of lbs per year) are shown for the top seven crops for each chemical. For acephate, these seven crops account for more than 99% of acephate usage reported by NASS. For carbaryl, the top seven crops account for 77% of reported usage. …The set of predominant states accounts for at least 90% of the total surrogate usage in the listed crop, or are the only states listed in the USDA database for that crop." (p. 26)

"**Selection of a Geographically Diverse Set of Clusters:** Five new monitoring sites need to be selected that are geographically diverse. Such a diverse configuration can be obtained by simply locating each site in a different EPA Growing Region. In theory, five growing regions could be selected at random from among the 12 regions that stratify the

continental U.S. A state (or portion of a state) could be randomly or purposively chosen from within the selected Region. . . . However, such undirected selection of states would be quite inefficient…Locating sites near crop areas where the surrogates have wide use over a wide variety of crops increases the likelihood that surrogates will be in use at the particular monitoring site ultimately chosen….the following states were purposively selected to contain the following five monitoring sites.

1. **New York (Region I)**

New York involves usage of carbaryl on a variety of crops including orchard, trellis, and field crops. This state reflects a cool climate in the northwestern U.S.

2. **Louisiana (Region IV)**

Louisiana involves by far the highest usage of acephate, including cotton and soybeans. Louisiana reflects mostly a hot and humid climate in the southern U.S.

3. **Michigan (Region V)**

Michigan involves usage of acephate and carbaryl and a variety of crops including orchard, trellis, and field crops. This state reflects a cool climate in the upper Midwestern U.S.

4. **California (the central/southern portion in Region X)**

California involves significant usage of acephate and carbaryl and a variety of orchard, trellis, and field crops. The central and southern portions of California generally reflect a hot and dry climate in the western U.S.

5. **Washington (the eastern portion in Region XI)**

Washington involves the highest usage of carbaryl, primarily on apples and cherries, but also some on grapes. Eastern portions of Washington reflect a hot and dry climate in the northwestern U.S." (pp. 28-30)

"**Selection of Specific Monitoring Sites for Each Study:** The final step for selecting sites is to choose a specific area within each selected state(s) identified above where growers and workers can be recruited to conduct a study in a reasonable amount of time. This involves selecting the sites in a reasonably limited geographic area so that MU identification and selection operations can be conducted efficiently in one local area. This will facilitate the logistics of the field research team and keep the costs of study conduct reasonable so a sufficient number MUs can be obtained in the AHETF monitoring program.

"Choosing a cost-effective configuration of MUs is necessary since costs escalate rapidly when a research team makes multiple visits to a location in order to monitor the desired five MUs. Cost-effectiveness is obviously maximized when all MUs are collected during

the same visit so researcher salary, travel, food, lodging, and field fortification expenses are minimized.

"Therefore, for each cluster, a particular area of each target state will be selected and identified in the study protocol. The actual site location within this general growing region will be determined by discussions with local resources to indicate counties that are most likely to apply the surrogate product and have sufficient growers, equipment, and workers to allow an efficient design." (pp. 30-31)

(b) How have random elements been incorporated into the scenario sampling design?

All choices in the first stage of the proposed diversity selection process, and stratification by AaiH in the second stage, are purposive choices.

"AHETF has determined that a method of randomly choosing a working pool of growers is practical for this scenario. This pool of growers will provide the workers and mixing/loading conditions needed to construct MUs for the cluster. Random selection of growers is preferable, when feasible, to reduce the possibility of selection bias that might arise from the LSC (i.e., a local agricultural researcher) purposively choosing which growers to contact. Therefore, a procedure for generating a list of available growers for each cluster (i.e., associated with each local monitoring site), and randomly selecting a pool of growers from that list, will be established in the protocol for that study. The general procedure to be followed is described in the following steps:

1. "Contact local resources from each of the following groups and ask for a list of growers that might utilize water soluble packets at the identified site (generally about one to three counties):
    - Farm Market ID
    - Commercial list providers
    - State and local government entities
    - Grower associations
    - Grower Publication subscription lists

2. "Assemble a reasonably sized and randomly selected list of growers from all of the resources contacted and eliminate any duplicates.

3. "Contact all the growers on the list and determine whether the grower is 'eligible' to participate. Eligibility generally means all of the following are true:

    - The grower is willing to cooperate with AHETF, including the ethical aspects of the research
    - The grower has the necessary mixing/loading equipment
    - The grower has at least one worker with experience in the mixing/loading of water soluble packets
    - The grower is willing to allow AHETF to recruit his/her worker(s)

- The grower has sufficient acreage that the minimum AaiH can reasonably be handled by a worker in one day
- The grower is willing to use at least on of the surrogate active ingredients listed in this protocol

"Growers who indicate they use commercial pesticide application companies to mix/load their product will also be considered. Those growers will be asked to identify their preferred commercial companies and AHETF will contact them to screen them for willingness to cooperate ….The important consideration with this step is that the first the appropriate equipment is identified and the workers associated with that equipment are identified…

4. "Each grower identified as eligible (sometimes along with an associated commercial pesticide application company) is placed into a working pool along with information on:

    - Specific location of mixing/loading sites
    - Description of equipment available (e.g., number, type, and size)
    - Surrogate chemical(s) that might be utilized
    - Approximate timing of surrogate applications
    - Number of workers available
    - AaiH those workers might be able to handle in a day. (pp. 35-36)

(c) What feasible opportunities to incorporate random elements in the design—if any—have been overlooked?

By constructing an "efficient configuration" of MUs such that more handlers and growers are in the recruiting pool in a given geographical area, it is likely that the opportunity will often arise to select randomly from among interested workers.

(d) What typical patterns of exposure will likely be included by the sampling design?

"The workers will be allowed to follow their normal procedures as long as they fit the scenario definition and do not conflict with EPA's Worker Protection Standard (WPS) regulations. The duration of the work activity will be partially determined by the amount of AaiH but will involve the mixing/loading of at least three loads and a minimum duration of four hours.

"A parameter that might impact exposure is the number of loads prepared since each mixing/loading event might require transferring diluted product from tank to tank and potential contact with contaminated surfaces (e.g., water soluble packets, tanks, hoses, etc.)…If other functions are also associated with the mixing/loading event (e.g., transferring from a slurry tank to an application tank) then these events are also included as part of the monitoring." (p. 40)

(e) What typical patterns of exposure will likely be excluded by the sampling design?

"While other factors were considered that might potentially affect exposure potential, they will not be purposively diversified. For example, size of packets or concentration of the product in the packet might possibly impact exposure. However WSPs are generally packaged in relatively small packets of 1 to 5 pound product. Therefore, in this instance, variability in packaging is not considered a parameter for purposive diversification. Other factors such as the crop being treated are no expected to directly affect exposure, but might lead to selection of various equipment set-ups that could impact exposure potential." (p. 41)

3. Are the proposed test materials appropriate surrogates?

"The following active ingredients are available in water soluble packets and will be considered for use in this mixing/loading scenario. The commercial products of the active ingredients that might be used in particular will be listed in the study protocol.

- Acephate
- Carbaryl

"These surrogate active ingredients also typically have high use rates for the potential crops of interest that enables measurements at the high end of AaiH per day. Additionally, cooperating growers who will use these products are likely to be available. Finally, these active ingredients have been used as surrogates in other studies and are known to have the required stability under field study conditions." (p. 42)

4. What is the rationale for the proposed cluster design and sample size?

"Appendix C of the Governing Document describes the methodology to calculate sample sizes when the reference model used is cluster sampling from a lognormal distribution. For the purposes of determining sample sizes, the default variation structure for normalized dermal exposure derived in Appendix C is also assumed applicable to the water soluble packet mixing/loading scenario. AHETF and the Joint Regulatory Committee agreed there is no evidence to suggest otherwise and no strong opinion to the contrary (meeting with AHETF, June 27, 2007). It is therefore appropriate to use the default relative variation structure consisting of a geometric standard deviation (GSD) of 4.0 and intra-cluster correlation (ICC) of 0.3. Appendix C shows that under these conditions (and where no suitable MUs exist) a sample of 5 clusters (N_C =5) with 5 MUs per cluster (N_M=5) is the most cost effective design configuration that meets the 3-fold accuracy requirement. This accuracy is possible with a variable number of MUs/cluster as long as the total number of MUs is at least 25 and no cluster has more than 5 MUs. Each cluster (i.e. monitoring site) will be addressed by a separate study protocol.

"Appendix C of the Governing Document also shows that when the benchmark accuracy requirement above is met there may also be sufficient power to permit users of the database to perform a limited examination of the relationship between the normalizing factor (e.g.,

AaiH) and exposure. This is true provided: (1) the practical range of the normalizing factor is at least an order of magnitude and (2) there is adequate within-cluster variation in the normalizing factor. When these conditions occur, the MU sample will be of sufficient size and diversity to provide at least 80% statistical power to distinguish complete proportionality from complete independence between exposure and the normalizing factor used in the primary benchmark. Since these conditions can be satisfied for the reference sampling design, then the purposive diversity design for the water soluble packet scenario should provide adequate power for the minor (i.e., secondary) objective: the ability to conduct limited examinations of the relationship between AaiH and exposure." (p. 23)

EPA Protocol Review: AHE120: Water Soluble Packet Mixer/Loader Scenario

Title: Determination of Dermal and Inhalation Exposure to Workers during Mixing/Loading of Pesticide Products in Water Soluble Packets in the United States

Revision Date: December 11, 2008

Study Director and Sub-Investigators:
Eric D. Bruce
Brian Lange[6]
Tami Belcher[5]
Aaron Rotondaro[5]

Local Site Coordinator: TBD[7]

Field Facility: TBD[6]

Analytical Facility: TBD[6]

Sponsor: Agricultural Handlers Exposure Task Force, LLC
c/o David R. Johnson, Ph.D.
1720 Prospect Drive
Macon MO 63552

Reviewing IRB: Independent Investigational Review Board, Inc.
6738 West Sunrise Blvd Suite 102
Plantation FL 33313

1. Societal Value of Proposed Research

(a) What is the stated purpose of the proposed research?

"The objective of this study is to develop data to determine the potential exposure for workers who mix and load solid pesticide products packaged in water soluble packets in five regions of the United States." (p. 89)

[6] One of these three will be the "Principal Field Investigator" for this study. When the choice is made it will be reflected in the protocol and consent document.

[7] The Local Site Coordinator, Field Facility, Analytical Facility, and Principle Analytical Investigator must all be identified.

(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?

This study will provide a partial answer to the question of what dermal and inhalation exposures are likely for workers who mix and load solid pesticide products packaged in water soluble packets. This is a widespread method of mixing and loading solid pesticide products, for which existing data are inadequate.

(c) How would the study be used by EPA?

EPA will use the results of this study to estimate the dermal and inhalation exposure likely for mixing and loading agricultural pesticides formulated in water soluble packets.

(d) Could the research question be answered with existing data? If so, how?

"AHETF (in conjunction with EPA, PMRA, and CDPR, collectively the Joint Regulatory Committee (JRC)) reviewed handler exposure measurements in existing studies (mostly not included in PHED to identify those that satisfy current acceptability criteria and qualify for inclusion in a generic database. For this particular scenario, the JRC reviewed three studies (AH508, AH520, and AH608) involving mixing/loading with water soluble packets; however, none of these studies were deemed appropriate for a generic database.

"AHETF also conducted a detailed review of the data in PHED for this scenario to determine if any of the data were suitable for a modern generic database. . . . Thus there are no data currently in PHED for this scenario that are useful for a modern generic database. (p. 16)

(e) Could the question be answered without newly exposing human subjects? If so how? If not, why not?

There is no alternative to monitoring handlers as they mix/load pesticides for measuring their dermal and inhalation exposure.

2. Study Design

(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?

"The goal of conducting a water soluble packet mixing/loading study is to develop a set of generic dermal and inhalation exposure data which regulators and other potential users of the generic database can utilize to characterize a predicted distribution of future exposures and perform exposure assessments for this scenario." (p. 44)

"The primary benchmark objective for this scenario is that a sample from the hypothetical reference sampling distribution above be of adequate size to describe selected measures of the (normalized) exposure distribution with a pre-determined level of accuracy…The current consensus is that estimates of the geometric mean, the arithmetic mean, and the 95th percentile generally need to be accurate to within approximately 3-fold of the actual population value. AHETF and the Joint Regulatory Committee (EPA, California Dept. of Pesticide Registration, Pest Management Regulatory Agency [Canada], and the U.S. Department of Agriculture) agreed 3-fold accuracy is an appropriate benchmark for this scenario (meeting with AHETF, November 3, 2008)." (p 21 of 552)

No explicit hypothesis is stated, nor is the study explicitly designed to test one.

(b) Can the study as proposed achieve that objective or test this hypothesis?

It is likely that the objective can be achieved by the proposed study.

2.1 Statistical Design

(a) What is the rationale for the choice of sample size?

"Appendix C of the Governing Document describes the methodology to calculate sample sizes when the reference model used is cluster sampling from a lognormal distribution. For the purposes of determining sample sizes, the default variation structure for normalized dermal exposure derived in Appendix C is also assumed applicable to the water soluble packet mixing/loading scenario. AHETF and the Joint Regulatory Committee agreed there is no evidence to suggest otherwise and no strong opinion to the contrary (meeting with AHETF, November 3, 2008). It is therefore appropriate to use the default relative variation structure consisting of a geometric standard deviation (GSD) of 4.0 and intra-cluster correlation (ICC) of 0.3.

"Appendix C shows that under these conditions (and where no suitable MUs exist) a sample of 5 clusters (N_C=5) with 5 MUs per cluster (N_M=5) is the most cost effective design configuration that meets the 3-fold accuracy requirement. This accuracy is possible with a variable number of MUs/cluster as long as the total number of MUs is at least 25 and no cluster has more than 5 MUs." (pp. 22-23)

(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

No positive or negative controls are proposed. This is appropriate for the study design and statistical analysis plan.

(c) How is the study blinded?

The study is not blinded, nor could it be.

(d) What is the plan for allocating individuals to treatment or control groups?

"After the randomly-selected pool of eligible growers is assembled, researchers (e.g., LSC and Study Director) will examine the details of potential MUs and identify a configuration of MUs (i.e., growers, chemicals, workers, AaiH, timing) that will result in an efficient cluster design." (p. 36)

"When constructing MUs, three restrictions will be enforced to ensure diversity within the cluster of MUs:

- No worker may be used for more than one MU in the cluster. Worker-related behaviors are also viewed as a meta-factor since individual practices might be associated with exposure potential.
- No piece of equipment may be used more than once and each of the three general equipment types must be used at least once per cluster (see section 6.1 below)
- No more than 1 MU may be obtained from any grower or commercial pesticide application company (so a grower with several workers and several pieces of equipment can contribute one MU)." (p. 37)

(e) Can the data be statistically analyzed?

"As has always been the case, any statistical conclusions based on such data imply the qualification: 'to the extent that the data can be viewed as deriving from a true random sample.'" (p. 44)

(f) What is the plan for statistical analysis of the data?

"As detailed in the Governing Document, the data collected from the studies for this scenario will only be statistically evaluated with respect to the benchmark measures of adequacy. These two categories of data adequacy are:

1. The relative accuracy of selected statistics characterizing the distribution of exposure normalized by amount of active ingredient handled (AaiH).

2. How well the data can be expected to describe a relationship between exposure and AaiH, if one existed." (p. 44)

"The primary benchmark objective is that selected lognormal-based estimates of normalized dermal exposure distribution be accurate to within 3-fold, at least 95% of

the time. The benchmark estimates specified are those for the geometric mean, arithmetic mean, and the 95th percentile.

"To evaluate how well the collected data conform to this benchmark, the 95 percent bound on relative accuracy will be calculated from the confidence interval for each of the three parameters given above." (p. 45)

"This secondary benchmark objective [Adequacy of the Data for Distinguishing a Proportional from an Independent Relationship between Exposure and AaiH] applies to the water soluble packet mixing/loading scenario because the practical range in the amount of active ingredient handled (AaiH) exceeds an order of magnitude. In this case it is reasonable to consider the linear regression of log dermal exposure on log AaiH. Such a regression would use a mixed model formulation in order to incorporate random cluster effects." (p. 45)

(g) Are proposed statistical methods appropriate to answer the research question?

Yes.

(h) Does the proposed design have adequate statistical power to definitively answer the research question?

Since the primary objective of the research is to characterize the distribution of exposure normalized by the amount of active ingredient handled (AaiH), statistical power does not relate to this objective. However, EPA believes the resulting data will reliably characterize the distribution of exposures for the individuals monitored during the mixing/loading using water soluble packets in this study, and that these exposures can inform assessments of the likely exposures for individuals in similar future situations.

Regarding the secondary objective, distinguishing a proportional from an independent relationship between exposure and AaiH, statistical power is relevant.

"This secondary benchmark objective applies to the water soluble scenario because the practical range in the amount of active ingredient handled (AaiH) exceeds an order of magnitude. In this case it is reasonable to consider the linear regression of log dermal exposure on log AaiH. Such a regression would use a mixed model formulation in order to incorporate random cluster effects. As described in the Governing Document, in such a model the true slope, β, would be equal to one if dermal exposure were directly proportional to AaiH. If exposure were independent of AaiH, then β=0. This benchmark objective requires that the number of clusters and the allocation of AaiH levels to MUs should be adequate to ensure that the regression analysis has at least 80% power to reject the hypothesis that β=0 when β is actually equal to one. By symmetry, the mixed model linear regression would also have the same power to reject the hypothesis that β=1 when β=0. This is the precise meaning of being able to 'discriminate between proportionality and independence'." (p. 45)

2.2 How and to what will human subjects be exposed?

"The water soluble packet mixing/loading program will monitor instances of worker exposure resulting from the mixing/loading the packets of pesticide." (p. 17)

"The test substances approved for use in this study are listed in Section 2.3.2 above. The most appropriate test substance, based largely on the preference of the grower, will be used at each of the individual sites. A different test substance may be used at each site and by each worker within a site if appropriate." (pp. 112-113)

(a) What is the rationale for the choice of test material and formulation?

"The AHETF has developed several pesticide active ingredient compounds for use as surrogates . . . . Since the AHETF is developing a generic database that will be applicable to nearly all pesticide products and uses, any of the AHETF surrogates can be used for generating exposure data for this scenario. The choice of surrogate at each location will depend largely upon the preference of the grower and pest pressure on his crop at that time…

"The following active ingredients are available in water soluble packets and will be considered for use in this mixing/loading scenario. The commercial products of these active ingredients that might be used in particular studies will be listed in study protocol.

- Acephate
- Carbaryl

"These surrogate active ingredients also typically have high use rates for the potential crops of interest that enables measurements at the high end of AaiH per day. Additionally, cooperating growers who will use these products are likely to be available. Finally, these active ingredients have been used as surrogates in other studies and are known to have the required stability under field study conditions." (pp. 41-42)

(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?

"Since the number of pounds of active ingredient handled is the normalizing factor and indirectly influences many other handling conditions, efforts will be taken to generate data in as wide a range of AaiH as practical within each cluster of MUs. AaiH is selected since AHETF feels it is the most reasonable measure of active ingredient contact potential for this scenario. . . . In addition, EPA currently normalizes water soluble packet mixing/loading exposure by AaiH during pesticide product exposure assessments and there is no other factor identified as being more appropriate.

"In addition to its potential direct relationship to exposure, the amount of active ingredient handled is also viewed as a meta-factor affecting parameters such as tank size, number of loads applied, etc. Thus, diversification of AaiH induces diversification of such associated factors as well.

"AHETF has calculated a practical range in AaiH for this scenario taking into account such factors as typical use rates of products, types of products available on the market, types of crops on which the products are used, number of acres that can be treated in a day, etc. AHETF has selected a range of 5 to 2,000 lbs active ingredient to be handled per day for this scenario." (pp. 31-32)

"[I]t is important that the AaiH levels be well diversified within each cluster. This allows the data for this scenario to be used to discriminate a completely proportional relationship from a completely independent relationship between exposure and AaiH (if one of those two relationships were true). Within-cluster diversification of AaiH will be accomplished by following the standard approach of partitioning the practical AaiH range into five logarithmically-spaced strata. These strata are:

- 5 to 17 pounds AI handled
- 18 to 55 pounds AI handled
- 56 to 182 pounds AI handled
- 183 to 603 pounds AI handled
- 604 to 2,000 pounds AI handled

"…[A]n attempt will be made within each cluster to obtain a single MU from each of the five strata." (p. 34)

(c) What duration of exposure is proposed?

"Duration of monitoring is another parameter that could vary between MUs, especially since the AaiH will be varied by more than two orders of magnitude. Mixer/loaders might spend several hours per day at the staging site but can also spend long intervals performing other tasks (or just sitting around) between actual mix/load events (i.e., while the applicator is making the application). So MUs will be monitored during their entire work day since many other unknown factors might contribute to exposure. All monitoring periods for this scenario must meet the general rule of being at least 4 hours. This is designed to overcome the criticism of early exposure studies where many of the sampling regimes monitored workers for only a few minutes. Avoiding very short monitoring intervals will ensure that daily exposure estimates are not biased by unusual conditions during that short interval. If necessary, some minor scripting of worker activities will be done to ensure the lowest levels of AaiH are handled and/or a minimum of four hours are monitored. For example, a worker might be asked to use a smaller tank, make smaller loads, or increase the spray volume slightly in order to mix 3 loads in four hours." (pp. 40-41)

2.3 Endpoints and Measures

(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?

At the completion of the monitoring period, exposure samples will be taken in the following order to minimize cross contamination: inhalation samples (discussed in the next section), then hand washes, then face/neck wipes, and finally inner dosimeters as described in SOP AHETF-10.E.2 (pp. 465-466) and SOP AHETF-8.A.3 (pp. 422-426).

For this study, inner dosimeters will be cut into six sections.

Full details of the personal air-sampling method, attachment of pumps, monitoring of workers, and pump calibration are presented in AHETF-8.D.4 (SOP Supplemental Submission, pp. 11-14).

(b) What steps are proposed to ensure measurements are accurate and reliable?

Please see SOP AHETF-8.E.5, Fortification of Matrix Samples (SOP Supplemental Submission pp. 15-23).

"This SOP describes the methods by which agricultural worker exposure monitoring matrices, (i.e., inner dosimeters, hand washes, face/neck wipes, inner socks, outer head patches, inner head patches [inner socks and inner and outer head patches are not monitored in this study] and OVS tubes) are to be spiked.

"Field fortification samples are exposure matrix samples that are fortified (or spiked), generally in the field, with known amounts of active ingredient and subsequently analyzed to determine the amount of active ingredient recovered. Field fortification samples are subjected to the same environmental, handling, shipping and storage conditions as worker samples. Because these conditions are similar, and because field fortification samples are analyzed along with worker samples, recovery values calculated from analysis of fortification samples are applicable to worker exposure samples. Field fortification recoveries are therefore used to adjust residue levels found in worker samples for residue losses that might have occurred during collection, handling, shipping and storage." (p. 438)

(c) What QA methods are proposed?

"AHETF intends that all regulatory studies are conducted in accordance with the FIFRA GLP Standards (40 CFR part 160). Field and analytical aspects of this study will be monitored by the relevant quality assurance units(s) (QAU) while this study is in progress to ensure compliance with the FIFRA GLP regulation and adherence to this protocol and relevant SOPs. The QAU(s) will submit copies of its/their

inspection reports to the Study Director and AHETF Sponsor Representative (40 CFR part 160.35(4)). The final report will be audited by the QAU specified in Section 1.15 to ensure that the contents of the report accurately describe the conduct and findings of the study.

"The final report will contain a Quality Assurance Statement from the QAU of each contributing laboratory conducting QA audits, and from the QAU specified in section 1.15." (p. 123)

(d) How will uncertainty be addressed? Will reported point values be accompanied by measures of uncertainty?

Uncertainty in field measurements will be addressed via fortification samples.

"Sample matrix fortifications designed to assess the stability of the active ingredient during field, storage and transit conditions in or on the sampling materials (inner dosimeters, hand wash solutions, face/neck wipes, and air sampling matrices) will be conducted on a minimum of one day of exposure monitoring at each location, or more days as appropriate for environmental conditions. . . . On each fortification day, two untreated control samples of each matrix will be processed similar to the field fortification samples (i.e., some are weathered). Packaging, storage and shipment of the field fortification samples will be the same as for the worker exposure samples." (pp. 116-117)

In general, field measurements are adjusted based on the recovery from the fortification sample. For example, a field measurement for an inner dosimeter of 300 ug would be adjusted based on the applicable fortification sample for the inner dosimeter matrix. If the recovery from that matrix was 80%, the reported measurement for that sample would be 300 ug/80% = 375 ug.

3. Subject Selection

3.1 Representativeness of Sample

(a) What is the population of concern? How was it identified?

"The water soluble packet mixing/loading scenario program will monitor instances of worker exposure resulting from the mixing/loading the packets of pesticides. Each instance is termed a monitoring unit (MU). Each MU consists of a set of mixing/loading conditions (including the particular worker) that are intended to represent the scenario activities for a single workday. In many cases monitoring units will be selected from 'naturally occurring' water soluble packet mixer/loader-days. However, the selected application conditions are sometimes modified or scripted slightly to ensure that the sample of MUs reflects the expected diversity in the entire population of future water soluble mixer/loader-days. . . .Thus, MUs are technically

not 'sampled' from a population. More correctly, they should be viewed as synthetic water soluble mixing/loading-days derived from both selected and constructed conditions." (pp. 17-18)

(b) From what populations will subjects be recruited?

"The growers and/or commercial pesticide application companies in the chosen configuration provide the pool of workers from which cluster participants will be recruited." (p. 37)

(c) Are expected participants representative of the population of concern? If not, why not?

"AHETF has determined that a method of randomly choosing a working pool of growers is practical for this scenario. This pool of growers will provide the workers and mixing/loading conditions needed to construct MUs for the cluster. . . .a procedure for generating a list of available growers for each cluster (i.e., associated with each local monitoring site), and randomly selecting a pool of growers from that list will be established in the protocol. The general procedure to be followed is described in the following steps:

1. "Contact local resources such as those listed below to obtain a list of growers that might utilize water soluble packets at the identified site (generally about one to three counties)
    - Farm Market ID
    - Commercial list providers
    - State an local government entities
    - Grower associations
    - Grower Publication subscription lists

2. "Assemble a reasonably sized and randomly selected list of growers from all of the resources contacted and eliminate any duplicates

3. "Contact all the growers on the list and determine whether the grower is 'eligible' to participate. Eligibility generally means all of the following are true:

    - The grower is willing to cooperate with AHETF, including the ethical aspects of the research
    - The grower has the necessary mixing/loading equipment
    - The grower has at least one worker with experience in the mixing/loading of water soluble packets
    - The grower is willing to allow AHETF to recruit his/her worker(s)
    - The grower has sufficient acreage that the minimum AaiH can be reasonably be handled by a worker in one day

- The grower is willing to use at least one of the surrogate active ingredients listed in the study protocol." (pp. 35-36)

"The growers and/or commercial pesticide application companies in the chosen configuration provide the pool of workers from which cluster participants will be recruited. (p. 37)

(d) Can the findings from the proposed study be generalized beyond the study sample?

Yes, within the limits imposed by the purposive design of the study.

3.2 Equitable Selection of Subjects

(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?

"[A]ll AHETF Study participants must meet these inclusion criteria:

- Have experience within the past year with the work activity being monitored in the study (including the particular equipment to be used during mixing/loading or application)
- Handle pesticides as part of their job
- Be trained in safe pesticide handling practices in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training
- Provide proof of being at least 18 years old with a government-issued photo ID
- Confirm they do not work for a pesticide company or a contractor of the AHETF
- Consider their general health status to be good and tell researchers they have no medical conditions that affect their ability to participate in the study (See SOP AHETF-11.C.1 for health status determination)
- Not be pregnant or nursing (See SOP AHETF-11.D.1, pp. 481-483)
- Confirm they do not normally wear personal protective equipment that is not required by the label and that might impact the objectives of the study, such as chemical-resistant clothing. Confirm they will follow label directions.
- Have a private meeting with a researcher to review and discuss the consent form
- Understand English or Spanish (See SOP AHETF-11.I.1 for a detailed discussion of this topic)
- Understand and sign the consent form, Product Risk Statement, and if in California, the California Experimental Research Subject's Bill of Rights" (SOP AHETF-11.B.4)

"For this mixing/loading of water soluble packets study, the following inclusion criteria also apply:

- Have experience within the past year with mixing/loading water soluble packets (including the particular equipment to be used) (p. 92)

(b) What, if any, is the relationship between the investigator and the subjects?

None

(c) If any potential subjects are from a vulnerable population, what is the justification for including them?

Potential subjects are of necessity agricultural workers, and could potentially be subjected to undue influence either to participate or not to participate by their employers. This possibility is minimized through methods of recruiting growers and by requiring growers to promise in writing not to influence their employee's decisions.

(d) What process is proposed for recruiting and informing potential subjects?

"For each selected site, AHETF will follow standard procedures (see SOP AHETF-11.B.4) to recruit potential participants for this water soluble packet mixing/loading study. Individual workers will be recruited during an initial site inspection or subsequent visit(s) to a potentially eligible grower facility.

"The Study Director or designated researcher will seek permission from the eligible grower to approach his/her employees to recruit volunteers for the study. Depending on the number of employees and size of the grower facility the Study Director or researcher may contact employees using an informational recruitment flyer posted in a common work area. Such a flyer will briefly describe the research study and provide a toll-free phone number for employees to express an interest in participating in the study. The flyer shall have been previously reviewed and approved by an IRB.

"Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the grower's employees who express an interest in participation. Such recruitment meetings will always occur without the grower or supervisors being present (SOP AHETF-11.B.4). The Study Director or researcher shall make a presentation describing the AHETF Exposure Monitoring Program, the goals of the research study, the procedures used in exposure monitoring, and the risks and benefits to participants. A toll-free phone number will be provided, and individuals will be encouraged to contact AHETF if they desire additional information about the study or are interested in participating in the study. All presentation materials, such as handouts or visual aids, shall be reviewed and approved by an IRB prior to use in recruiting subjects." (pp. 109-110)

(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?

"In accordance with SOP AHETF-11.B.4, the individual growers will be asked to sign a non-coercion statement (Employer Cooperation Statement) affirming to their workers and AHETF that they will not coerce or unduly influence their workers to either participate or not participate in the study. Growers must also certify that alternate work will be provided on study days for workers who choose not to volunteer; and that the employee's decision to participate or not will have no impact on their employment." (p. 109)

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for the subjects?

"During recruitment, workers will be offered an opportunity to take part in a recruitment meeting with the Study Director or other designated member of the study team (but without the workers' supervisors) to learn about participating in this study. No remuneration is offered for this introductory meeting. Workers who are still interested in participating in the study will attend a private consent meeting with a researcher who will obtain the informed consent of the worker. Workers will be paid $20 for their attendance right after the consent meeting, whether or not they decide to participate in the study. Workers who decide to participate in the study will be paid an additional $80 each time they suit up (i.e., put on the long underwear) to participate in the study. Usually, workers will participate in the study on only one day unless their participation is terminated due to weather or other unexpected occurrences. The additional $80 is provided in cash at the end of the monitoring period or at the time the volunteer withdraws from the study. All workers who participate will receive the payment, even if they withdraw or their participation is terminated by the study team." (pp. 208-209)

(b) Is proposed remuneration so high as to be an undue inducement? No.

(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects? No.

(d) How and when would subjects be paid?

In cash, immediately after their participation

4. Risks to Subjects

4.1 Risk Characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?

The potential surrogate materials are registered with EPA, are well understood, and have been fully tested.

This study could involve either of two active ingredients: acephate or carbaryl. "The pesticide products containing these active ingredients and potentially used in this study are currently registered for agricultural use. AHETF will only monitor workers making applications in accordance with all label and Worker Protection Standard (WPS) requirements." (p. 94)

For both of the active ingredients that may be used in this study, the calculated MOEs meet or exceed the required MOE for both the individual dermal and inhalation routes of exposure, as well as for the combined exposure, and their use is acceptable for this scenario.

(b) What is the nature of the risks to subjects of the proposed research?

"Five kinds of risks are associated with the conduct of the current exposure monitoring study. These are:

- The risk of heat-related illness
- The risk of exposure to surrogate chemicals
- The risk associated with scripting of field activities
- Psychological risks
- The risk of exposure to detergents

"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. In particular, this study involves the use of chemicals (pesticides, fertilizers, additives, etc.) that present a risk of adverse health effects. In addition, AHETF believes the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation." (p. 93)

Each of these five kinds of risk is discussed in the protocol (pp. 93-100) and the consent form (p. 131).

(c) What is the probability of each risk associated with the research? How was this probability estimated?

Quantitative probabilities are not estimated.

4.2 Risk Minimization

(a) What specific steps are proposed to minimize risks to subjects?

"The following practices, designed to minimize these risks and respond to injuries, will be followed during this study:

- Selecting only experienced pesticide handlers who consider themselves to be in good health
- Requiring experience with the mixing/loading equipment to be used
- Reminding workers of safe chemical handling practices
- Practicing the face wipe and hand wash procedures with each participant before pesticide handling begins
- Identifying nearby medical treatment facilities in case of emergency
- Monitoring the heat index and stopping the study if conditions warrant
- Providing transportation to medical treatment and covering the costs of treatment
- Having a medical professional on site to observe the workers and provide urgent care
- Observing study participants throughout the monitoring period
- Ensuring that all tank mix products are used according to approved label(s) and do not require any additional PPE that could adversely affect the study objectives (for example, chemical-resistant coveralls)." (pp. 98-99)

Risk reduction actions specific to each of the six identified kinds of risk are discussed in the protocol (pp. 93-99).

(b) How do proposed dose/exposure levels compare to established NOELs/NOAELs for the test materials?

For both of the active ingredients that may be used in this scenario, the Margins of Exposure (MOEs) calculated for the highest level of exposure in this protocol "meet or exceed the minimum required MOE, or level of concern, for the individual dermal and inhalation routes of exposure, as well as for the combined exposure." (p. 95)

(c) What stopping rules are proposed in the protocol?

"AHETF will monitor ambient conditions outside the cab 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 120^{o} 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." (p. 94)

(d) How does the protocol provide for medical management of potential illness or injury to subjects?

"As a safety measure, AHETF will have a medical professional on site during the study. This may be a paramedic, physician's assistant, nurse, or emergency medical technician. This professional will also observe you for signs of illness. They will provide medical attention as needed." (p. 131)

SOP AHETF-11.H.2 (SOP Supplemental Submission, pp. 35-38) defines procedures to be followed if a subject in an AHETF study requires emergency medical attention.

(e) How does the protocol provide for safety monitoring?

The protocol refers to various SOPs which define procedures for safety monitoring:

- SOP AHETF-11.E.1 (pp. 484-486) calls for researchers to monitor worker compliance with label and Worker Protection Standard requirements, and permits the Study Director to remove from the study a worker who engages in unsafe work practices.
- SOP AHETF-11.G.1 (pp. 489-503) calls for the Study Director, the on-site medical professional, and all researchers and observers to monitor subjects for any indication of heat-related illness.
- SOP AHETF-11.H.2 (SOP Supplemental Submission, pp. 35-38) defines procedures to be followed if a subject in an AHETF study requires emergency medical attention.

(f) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

"During the consenting process each volunteer will be provided the opportunity to request a summary of their personal results from the study. This will require the worker to provide a name and address (mail or e-mail). The results will include the distribution of chemical exposure among the various body areas measured so the worker can be aware of where most dermal exposure occurs and a comparison to the results for other workers performing the same task. Results are typically available six to nine months after monitoring occurs. The personal information related to this follow-up will be retained as described in SOP AHETF-6.D.0.

"Just prior to the completion of the worker's participation in the study, a researcher will remind the participant he/she should bathe or shower as soon as practical and that they have received a copy of the signed consent form with phone numbers for reporting any health changes they think might be related to participation in the study.

Post-study inquiries will be forwarded to the Study Director who will deal with the situation as appropriate and notify AHETF management (SOP AHETF-11.B.4)." (p. 103)

(g) How and by whom will medical care for research-related injuries to subjects be paid for?

"If you are injured or get sick because of your participation in this study, medical treatment will be available at your workplace and at a nearby health care facility. If necessary, AHETF will arrange transportation for you to receive medical attention. You may refuse medical treatment *unless* you get sick from too much exposure to pesticides or from getting too hot, or if we believe you are too sick to make a rational decision about getting medical treatment.

"AHETF will cover the cost of reasonable and appropriate medical attention for a study-related injury or illness that is not covered by your own insurance or insurance provided through your employer. This includes deductible costs and any out-of-pocket expenses, including co-payments, you might have. The Study Director, in consultation with the on-site medical professional, will decide if you have an illness or injury that is due to your participation in this study." (p. 132)

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

"There are no personal benefits to the study participants." (p. 99)

Although there are no direct benefits to study participants, a potential indirect benefit is knowledge about how their exposure compares to that of others doing similar work; this is not addressed in the protocol.

(b) What benefits to society are anticipated from the information likely to be gained through the research?

"Since there are not sufficient existing data suitable for use in a generic database describing the exposure to workers from mixing/loading water soluble packets, society will likely benefit from data generated by this study through the improved risk assessments by EPA and other regulatory agencies." (p. 99)

"Data from the AHETF exposure monitoring program has the potential to improve the ability of EPA and other regulatory agencies to accurately assess occupational risks associated with mixing/loading pesticides packaged in water soluble packets. Water soluble packets are considered an engineering control designed to reduce exposure potential for mixer/loaders. The knowledge likely to be obtained from this study is

generalizable and will contribute to assessments of the risks of both new and existing pesticides." (p. 99)

(c) How would societal benefits be distributed? Who would benefit from the proposed research?

"Growers who allow the study to be conducted using their equipment, crops and facilities will be reimbursed for the pesticides used for the study. While this is beneficial to the grower, it is considered a minor benefit when compared to the costs of running their businesses. The AHETF member companies will likely realize a benefit by addressing regulatory data requirements generically, at lower cost (and using fewer human subjects), than if they conducted similar studies for individual pesticide ingredients." (p. 99)

(d) What is the likelihood that each identified societal benefits would be realized?

Identified societal benefits are likely to be realized.

6. Risk/Benefit Balance: How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

"By monitoring exposure to professional agricultural handlers who follow their normal practices, but wear an additional layer of clothing (as an inner dosimeter which traps chemical that penetrates the work clothing), this study presents a greater than minimal risk to participants. Participating in this study increases the risk of heat-related illness, but this risk is mitigated by a medical management program which emphasizes prevention measures and guidelines for stopping participation when warranted based on environmental conditions.

"The likely benefit to agricultural workers as a whole and to society in general, in the form of more accurate measurements of potential exposure to pesticides, must be weighed against the risks to participants. Pesticide products packaged in water soluble packets are becoming more common for many agricultural uses across the country and a variety of experts consulted by AHETF reported their use occurs widely throughout the country. Exposure data for this scenario meeting contemporary standards of reliability and quality will likely provide a significant benefit to society. Because the margins of exposure are acceptable for the products proposed for use in this research study, subjects are very unlikely to experience acute toxic effects, and because extensive procedures will be in place to minimize these and other risks to participants, the likelihood of serious adverse effects is very small. In summary, AHETF believes the risks to study participants from participating in this study are reasonable in light of the likely benefit to society of the knowledge to be gained." (p. 100)

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Independent Investigational Review Board, Inc., of Plantation FL

(b) Is this IRB independent of the investigators and sponsors of the research? Yes

(c) Is this IRB registered with OHRP? Yes

(d) Is this IRB accredited? No.

(e) Does this IRB hold a Federal-Wide Assurance from OHRP? No.

(f) Are complete records of the IRB review provided as required by 40 CFR 26.1125?

Yes.

(g) What standard(s) of ethical conduct would govern the work?

"This study will be conducted in accordance with EPA's final regulation published at 40 CFR Part 26 that establishes requirements for the protection of subjects in human research (see SOP AHETF-11.A.1). The protocol, informed consent form(s), California Experimental Research Subject's Bill of Rights, and other required documentation for this study will be approved by an institutional review board (IRB) and the California Department of Pesticide Regulation, and submitted to the EPA as required by 40 CFR 26.1125. The report of the completed research is subject to 40 CFR 26.1303 requirements to document its ethical conduct.

"The IRB for the proposed research shall be the Independent Investigational Review Board Inc. (IIRB) of Plantation, Florida. Complete records of the IIRB review as required by 40 CFR 26.1125 will be submitted to EPA for review along with this protocol and other documents.

"Researchers that participate in the study and interact with study participants must undergo ethics training (SOP AHETF-1.B.4). The training shall include successful completion of the course from the National Institutes of Health (Protecting Human Research Participants (PHRP)) and/or the Basic Collaborative IRB Training Initiative Course (CITI; The Protection of Human Research Subjects). Copies of the certificates of completion for the ethics courses will be submitted to the IRB and stored in the respective personnel files (maintained by the AHETF and all contract facilities.)" (p. 92)

8. Informed Consent

(a) Will informed consent be obtained from each prospective subject? Yes

(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR §26.1117? Yes

(c) Do the informed consent materials meet the requirements of 40 CFR §26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research? Yes

(d) What is the literacy rate in English or other languages among the intended research subjects?

Not addressed in protocol. Appropriate provision is made for informing English or Spanish-speaking candidates who cannot read the consent form.

(e) What measures are proposed to overcome language differences, if any, between investigators and subjects?

See SOP AHETF-11.I.1 (SOP Supplemental Submission, pp. 39-44)

(f) What measures are proposed to ensure subject comprehension of risks and discomforts?

"In all situations, the SD (or designee) will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential workers that would require a response that indicates understanding of key issues. The form in Attachment 11.J.1 will be used to ascertain general understanding." (SOP AHETF-11.J.1 §3.10, SOP Supplemental Submission, p. 47)

(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

"The SD (or designee) will be responsible for obtaining informed consent from all study workers prior to their participation in the study. Any materials used during the consent meeting will be approved by the IRB before use.

"Informed consent discussions will be conducted by the person obtaining consent in private with each worker. The worker may have a friend, family member, or advisor with them during the meeting. Witnesses may also be present as described in SOP AHETF-11.I.1.

"The person obtaining consent will inform the worker that he/she will receive $20 for participation in the consent meeting, or the amount specified in the protocol, even if he/she decides not to participate in the study.

"During the private consent meeting the person obtaining consent will provide each worker with a full explanation of the study, its requirements, any potential risks, its benefits, alternatives to participation, *etc*. Workers will be advised of their right to withdraw from the study at any time and for any reason without jeopardizing their normal position with their employers or their daily wages. Workers will be told they will receive an additional $80, or the amount specified in the protocol, if they decide to participate (don the dosimeters) even if they withdraw before the end of the monitoring period.

"The person obtaining consent will provide information about the risk of the surrogate chemical in the study, including signs and symptoms of acute overexposure. This information will be presented as an attachment to the Consent Form (referred to as Product Risk Statement {PRS}). WPS requirements, especially proper use of clothing, personal protective equipment, *etc*., will be discussed. Refer to SOP AHETF-11.E.1 for details.

"Information will be provided about the risk of heat stress, including signs and symptoms, and ways to prevent it. Information will also be provided about the availability of medical attention during the study. Details on heat stress and its presentation are outlined in SOP AHETF-11.G.1, while details on emergency medical procedures are outlined in SOP AHETF-11.H.2.

"During the discussions between potential participants and the person obtaining consent, ample time will be provided for questions and the person obtaining consent will provide any additional information or clarification that is requested.

"The IRB-approved Consent Form (and all supporting documents) will be presented in the preferred language (English or Spanish) of the worker. All sections of the Consent Form will be explained in detail. When the person obtaining consent is satisfied that the worker understands the requirements and risks of the study, and if the worker still wants to participate, he/she will be asked to sign and date the Consent Form and the person obtaining consent will provide a copy of the signed form to the worker.

"An additional IRB-approved document, "Product Risk Statement", will be attached to the Consent Form. If the study is conducted in California, the IRB-approved "California Experimental Research Subject's Bill of Rights" will also be attached. These documents (in the appropriate language) will be reviewed, signed and dated by the worker, and copies will be provided.

"In all situations, the person obtaining consent will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking

questions of the potential workers that would require a response that indicates understanding of key issues. The form in Attachment 11-J-1 will be used to ascertain general understanding.

"The person obtaining consent will not sign the Consent Form unless he/she believes that the process has been free of any element of coercion or undue influence and the witness (when required) has signed the consent form." (SOP AHETF-11.J.1 §3.2-3.11, SOP Supplemental Submission, pp. 46-47)

(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

"In accordance with SOP AHETF-11.B.4 the individual growers will be asked to sign a non-coercion statement (Employer Cooperation Statement) affirming to their workers and AHETF that they will not coerce or unduly influence their workers to either participate or not participate in the study. Growers must also certify that alternate work will be provided on study days for workers who choose not to volunteer; and that the employee's decision to participate or not will have no impact on their employment." (p. 109)

9. Respect for Subjects

(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?

"The AHETF employs many procedures to protect subject privacy during recruitment, consent, study conduct, and maintenance of study records. The consent form also summarizes important confidentiality issues for subjects. These procedures are described in SOPs AHETF-6.B.1, 6.D.0, 11.B.4, 11.D.1, and 11-J.1." (p. 100)

"Your name will only appear on the consent form, the Product Risk Statement, an optional form for you to request your personal study results, and if in California the California Experimental Research Subject's Bill of Rights. In all other parts of the study you will be identified by a code. Records with your name will be stored in a secure place with limited access.

"Information about you taking part in this study will not be given to your employer.

"A study report will be written by AHETF and will be available to member companies. It will be sent to the US Environmental Protection Agency (EPA). It may also be sent to state government agencies and to governments in other countries. Your name will not be in the study report.

"We cannot promise you total confidentiality. There may be a need to give information to some organizations or to parties in legal actions, as required by law. Records which identify you may be looked at or copied by the AHETF and any consultants working with

the AHETF, by EPA or other government agencies, and by the Independent Investigational Review Board, Inc., (IIRB). IIRB is a group of people who review and monitor research to make sure the people who take part are protected.

"You may ask the Study Director for a copy of your personal results from this study. You will need to provide your name and a mail or e-mail address." (pp. 132-133)

(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

"The absolute right for subjects to withdraw from the research is the cornerstone of protection of human subjects. Prospective and enrolled subjects will be informed of their right to withdraw without consequence prior to and during the conduct of the research.

"Any volunteer expressing a need or desire to withdraw from the research after exposure monitoring begins will be paid $80 and allowed to return to their normal work duties for their employer. If a participant withdraws while being monitored, the long underwear and air sampling pump will be removed, and the hand and face/neck samples will be collected with the worker's consent. The Study Director will decide whether these samples will be analyzed (SOP AHETF-8.K.0)." (pp. 100-101)

"Your employer has agreed to let us do the research and has confirmed that he/she does not care whether you take part in this study or not. Your decision to be in this study is voluntary. This decision is entirely up to you. If you decide to take part, you may change your mind and drop out of the study at any time and for any reason. A decision not to take part, or to withdraw from the study after it starts, will have no effect on your job or pay or include any penalty or loss of benefits you are owed." (p. 133)

(c) How will subjects who decline to participate or who withdraw from the research be dealt with?

"If you decide to take part, you may change your mind and drop out of the study at any time and for any reason. A decision not to take part, or to withdraw from the study after it starts, will not affect your job or pay or include any penalty or any loss of benefits you are owed.

"If you withdraw, the long underwear and air sampling pump will be removed. The hand and face/neck samples may be collected if you agree.

"Your part in this study may be stopped at any time by the researchers or the AHETF. The long underwear and air sampling pump will be removed. The hand and face/neck samples may be collected if you agree.

"If you withdraw or are removed from the study, you can go back to your usual work activities. If the study does not last an entire workday, you can go back to your usual work activities.

"No one can force you to take part in this study. Taking part is totally voluntary. If you choose not to take part in this study you will perform your ordinary activities on the day of the study. Your alternative is to not take part." (pp. 133-134)

§ 26.1111 Criteria for IRB approval of research
AHETF Protocol AHE120: Mixing/Loading of Wettable Powder in Water Soluble Packets

Criterion	Y/N	Comment/Page Reference
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	n/a	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	Y	
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	Y	

§26.1116 General requirements for informed consent
AHETF Protocol AHE120: Mixing/Loading of Wettable Powder in Water Soluble Packets

Criterion		Y/N	Comment/Page Reference
No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative		OK	
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		OK	
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		OK	
No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence		OK	
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	OK	
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	OK	
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	OK	
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	n/a	
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	OK	
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	OK	Although research doesn't involve more than minimal risk, compensation and treatment of injuries are provided for
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	OK	
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	OK	
(b) When appropriate, one or more of the following elements of information shall also be provided to each subject	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	OK	
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	OK	
	(3) Any additional costs to the subject that may result from participation in the research	OK	
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	OK	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	n/a	
	(6) The approximate number of subjects involved in the study	OK	
(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		OK	

§26.1117 Documentation of informed consent
AHETF Protocol AHE120: Mixing/Loading of Wettable Powder in Water Soluble Packets

Criterion	Y/N	Comment/Page Reference
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.	OK	
(b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or	OK	
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	n/a	

40 CFR 26.1125 Prior submission of proposed human research for EPA review
AHETF Protocol AHE120: Mixing/Loading of Wettable Powder in Water Soluble Packets

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

	Requirement		Y/N	Comments/Page Refs
All information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	pp. 180-538 pp. 127-136, 149-158
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		 Y Y Y N n/a	 pp. 550-552 The only required changes were minor typographical changes to the ICF No controverted issues
	(3) Records of continuing review activities.		n/a	
	(4) Copies of all correspondence between the IRB and the investigators.		Y	pp. 80-84, 180, 182-183, 541, 543, 545, 548
	(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y	IIRB roster and credentials on file with EPA.
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		Y	Separately submitted to EPA under confidentiality claim
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	
The following Information, to the extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 93-99
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 93-99
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 99
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	pp. 16-17 and AHETF Governing Document (reviewed at June 2008 HSRB meeting)
		(5) The balance of risks and benefits of the proposed research.	Y	p. 100
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Original pp. 243-252 Approved pp. 127-136
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 34-38, 92-93, 105-111, 145, 175
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	pp. 100-103
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 80-84, 180, 182-183, 541, 543, 545, 548
	§1125(f): Official notification to the sponsor or investigator…that research involving human subjects has been reviewed and approved by an IRB.		Y	pp. 82-84

Responsiveness to Recommendations in the Final Report of the October 2008 HSRB Meeting[8]

Recommendations in the Oct. 2008 HSRB Final Report about the AHETF Closed Cab and Open Cab Airblast Protocols		Addressed in the M/L WSP Proposal?	How/Where Addressed
1	5 monitoring units in each cluster, each from a different farm, is needed to ensure that the design and analyses are scientifically sound.	YES	
2	Information should be collected about growers who do not respond or who decline to participate, such that the representativeness of participating growers can be evaluated.	NO	
3	The Local Site Coordinator, the Principal Field Investigator, the Field Facility, the Analytical Facility, and the Principal Analytical Investigator must be identified in the protocol	NO, but will be addressed prior to study initiation	
4	Any key members of the research team who will have contact with the research subjects or their identifiable data must receive and document their recent (not expired) training in human subjects' protection	YES	Revised SOP AHETF-11.J.1 (SOP Supplemental Submission, pp. 45-52)
5	Revise subject recruitment plan to specifically address the probability that subjects may also be growers.	YES	Revised SOP AHETF-11.B.4, Sec. 4.2 (b) and (c) (SOP Supplemental Submission, p. 31)
6	Remove risks of agricultural work from the listing of risks related to the research.	YES	Section removed from risk discussion in protocol
7	Identify risks of pesticide products that are due to scripting.	YES	p. 97
8	Revise the IRB application to indicate expected ethnic/racial distribution specific to the location in which the study will be conducted.	YES	p. 194
9	Complete a Data and Safety Monitoring Plan	YES	pp. 196-197
10	Revise the description of the consent process to indicate how bilingual witnesses are going to be recruited and the amount of remuneration, as referenced in the recruitment standard operating procedures.	YES	Revised SOP AHETF-11.I.1, Sec. 2.3 and 2.4 (SOP Supplemental Submission, pp. 40-41)
11	Revise the section of the recruitment SOP that relates to recruitment and enrollment of illiterate or low literacy subjects.	YES	Revised SOP AHETF-11.I.1, Sec. 2.2, 2.3. 2.4, 2.5 (SOP Supplemental Submission, pp. 40-43)

[8] HSRB recommendations that are specific to the closed cab and open cab airblast protocols reviewed in October, but which are not applicable to the M/L WSP protocol being reviewed herein, are not included in the table.

Recommendations in the Oct. 2008 HSRB Final Report about the AHETF Closed Cab and Open Cab Airblast Protocols		Addressed in the M/L WSP Proposal?	How/Where Addressed
12	Describe how individual level data will be presented to the subject upon request.	YES	Revised SOP AHETF-11.J.1, Sec. 4.1, 4.2 (SOP Supplemental Submission, p. 48)
13	Explain how the AHETF will work to prevent workers from changing future behavior to their own detriment if their individual risk levels are lower than the average of all workers.	NO	
14	Harmonize enrollment criteria (inclusion, exclusion) between the protocol and consent form.	YES	pp. 92, 128; Revised SOP AHETF-11.B.4, Sec. 5.0 (SOP Supplemental Submission, pp. 32-33)
15	In the consent form, replace "regular working hours" with the specific hours for the time zone in which the research will take place.	YES	p. 134
16	Revise the consent form with the underlined word: "you may refuse medical treatment. However, you cannot refuse medical treatment if you get sick from too much exposure to pesticides….."	YES	p. 132
17	Verify the appropriateness of, or make necessary improvements to, the Spanish translations of the consent form, product risk statements, and recruitment materials.	NO	
18	Revise the consent form to identify who makes the determination that an injury is study-related.	YES	p. 132
19	Revise attestation statement for witness on consent form to eliminate subject's understanding or accuracy of the consent process.	YES	p. 136
20	Revise consent form's attestation statement of person obtaining consent to "I conducted the private consent meeting with the worker named above and confirm that consent was given voluntarily after the participant was fully informed of all of the information stated above, *including the procedures, risks, and benefits of the research."*	YES	p. 136
21	Confirm and clarify in informed consent that compensation for research-related injury includes any co-pay.	YES	p. 132
22	Consider revising Product Risk Statements to indicate which sign and symptoms are due to use that follows the product label, and which are due to overdose or massive spills or excessive exposure beyond what is expected to occur in the research.	YES	pp. 139, 141, 143

Recommendations in the Oct. 2008 HSRB Final Report about the AHETF Closed Cab and Open Cab Airblast Protocols		Addressed in the M/L WSP Proposal?	How/Where Addressed
23	Define the term "sufficient" when used in the inclusion criterion "sufficient experience".	YES	Inclusion criteria now state that eligible participants must "Have mixed and loaded pesticide products packaged in water soluble packets, and used the particular mixing/loading equipment you will use in this study, within the last year."
24	Revise wording of eligibility criterion that states "Confirm that you normally wear the personal protective equipment (PPE) listed on the Product Risk Statement. Confirm that you will follow label directions."	YES	p. 128
25	Add to the protocol some provisions for counting and reporting the number of potentially eligible workers linked to each grower, the number of potential subjects attending initial group meetings, number attending individual consent interviews, number consenting to participation, number subsequently withdrawing or being withdrawn (with the reason for withdrawal) and number completing the study.	YES	pp. 107, 110