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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 23, 2008

MEMORANDUM

SUBJECT: Science and Ethics Review of AHETF Scenario Design and Protocol for Exposure Monitoring in Michigan Stone Fruit

FROM: Jeff Evans
Health Effects Division

Kelly Sherman
Human Research Ethics Reviewer

TO: Jack Housenger, Associate Director
Health Effects Division

REF: Smith, L. (2008) Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment in Michigan Stone Fruits. Unpublished protocol dated August 14, 2008, prepared for the Agricultural Handlers Exposure Task Force under Sponsor ID AHE57. 357 p., plus 343 p. scenario design and supporting documents.

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.

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 scenario design for the closed-cab airblast scenario appears in Volume 1 of the AHETF submission of August 14, 2008 (V1:7-51)¹. The IRB-approved protocol and supporting documents (consent forms, product-specific risk statements, and recruitment flyers in both English and Spanish) appear in Volume 2 of the AHETF submission (V2:9-153). Documentation of all interactions between the investigators and the Independent Investigational Review Board, Inc., of Plantation FL also appears in Volume 2 of the AHETF submission (V2:154-357).

In addition to the final protocol (V2:16-57), Volume 2 includes the following supporting documents:

- Study documents in English approved by IIRB:
 - Informed Consent Form approved 8/05/08 (pp. 59-68)
 - Product-specific risk statements approved 8/05/08 (pp. 70-95)
 - Recruiting flyer approved 8/05/08 (p. 97)

- Spanish translations of study documents approved by IIRB:
 - Informed Consent Form approved 8/05/08 (pp. 99-109)
 - Product-specific risk statements approved 8/05/08 (pp. 112-150)
 - Recruiting flyer approved 8/05/08 (pp. 151-153)

- Correspondence between the investigator and IIRB (pp. 11-14, 156-167, 288, 291-292, 345-349)
- Protocol and supporting documents as initially submitted to IIRB on 7/24/08 (pp. 168-285)
- Revised SOP AHETF 11.B.2 dated 7/24/08 and submitted to IIRB on 7/24/08 (pp. 269-285)
- IIRB response to 7/24/08 submission (pp. 286-288)
- Revised protocol and recruiting flyers as submitted to IIRB on 7/31/08 (pp. 289-342)
- IIRB approval letter of 8/05/08 (pp. 11-14)
- Minutes of 8/05/08 IIRB Meeting (pp. 350-356)

¹ This convention will be used for all page number references in this review and its attachments. For example, "V1" refers to Volume 1 of the AHETF submission, which contains the "General Information and Scenario Sampling Plan" for the Closed-Cab Airblast scenario. "V2" indicates Volume 2 of the AHETF submission. Volume 1 and Volume 2 together document the protocol for Michigan stone fruit. Many pages in the two volumes bear more than one page number. All page references in this review to Volume 1 are to "page N of 343", and page references to Volume 2 are to "page N of 357."

The rationale for the proposed sample size and cluster configuration is presented in Volume 1 (pp. 15-21).

The following SOPs are cited in the protocol. Those marked by an asterisk have been revised since the HSRB meeting of June 2008 to address EPA and HSRB comments.

AHETF-1.B.3*	Personnel Responsibilities
AHETF-1.F.0	Potential Referable Findings
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.4	Dermal Face/Neck Wipe Samples
AHETF-8.D.2	Collection of Air Samples Using OVS Tubes
AHETF-8.E.4	Fortification of Matrix Samples
AHETF-8.F.5*	Sample Identification
AHETF-8.G.2	Worker Clothing Acceptability Criteria
AHETF-8.H.2	Head Patch Samples
AHETF-8.K.0	Sample Quality
AHETF-10.C.4*	Worker and Study Observations
AHETF-10.D.0	Application Equipment Operation Verification
AHETF-10.G.1	Personal Air Sampling Pump Calibration
AHETF-11.B.3*	Recruitment of Study Volunteers and Informed Consent
AHETF-11.C.1*	Worker Health Status
AHETF-11.D.1*	Pregnancy Testing
AHETF-11.F.1*	Adverse Events Reporting for IRBs
AHETF-11.G.1*	Identification and Control of Heat Stress

Reports of interviews with experts knowledgeable about the use of airblast application equipment in orchard and trellis crops are provided in Volume 1, pp. 52-80.

B. Summary Assessment of the Scenario Design²

- 1. Scenario Design:** This protocol addresses the handler exposure scenario involving application of liquid pesticides to orchard and trellis crops using conventional airblast sprayers drawn by closed-cab vehicles. EPA's Worker Protection Standard (WPS) at 40 CFR 170.240(d)(5) requires enclosed cabs to completely surround occupants with a nonporous barrier that prevents contact with pesticides outside the cab. Limitation to use with an enclosed cab is a risk/exposure mitigation option EPA may exercise in its regulatory decision-making.

² Supporting details are in Attachment 1.

According to the WPS, in an enclosed cab that *does not* provide respiratory protection, handlers need not wear all the PPE listed on the pesticide labeling, but must wear at least:

- long-sleeved shirt and long pants,
- shoes and socks, and
- any respirator of a type listed on the label
- protective eyewear (chlorothalonil).

In an enclosed cab that *does* provide respiratory protection equivalent to that provided by respirators identified on the pesticide label, handlers must still wear a long-sleeved shirt and long pants, shoes and socks, but need not wear a respirator.

The AHE57 protocol calls for closed-cab airblast application of one of three surrogate insecticides to stone fruit trees (e.g., cherries) in Michigan. A total of 25 Monitoring Units (MUs) are proposed for the closed-cab airblast scenario; when the scenario is complete, the five (MUs) to be collected under this protocol will be combined in the AHED database with twenty more to be collected under other field study protocols. EPA intends to use these data to estimate daily dermal and inhalation exposures of pesticide applicators applying liquid pesticides to orchard and trellis crops using conventional airblast equipment drawn by closed-cab vehicles.

- 2. Sampling Design:** The closed-cab airblast scenario, as currently planned, will involve five clusters, each defined as a separate field study. Clusters have been purposively selected to create a diverse range of orchard/trellis crops, agronomic practices, and geographic regions. Each cluster is referred to as a monitoring 'site.'

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

- Identifying the principle crop types associated with airblast application, based on consultation with experts
- Identifying the states where each principle crop is grown from NASS statistics
- Grouping the states by EPA's growing regions
- Selecting one of the major producing states for each major crop, but no more than one state/crop pair per region
- Selecting a county or counties for each state/crop pair in which to conduct each field study

The result of executing the first four steps of this first stage of the diversity selection process was the purposive choice of the following five crop/state combinations for the five proposed monitoring sites:

- Citrus crops in Florida (oranges)
- Nut crops in Georgia (pecans)
- Pome fruit in Washington (apples)
- Stone fruit in Michigan (cherries)
- Trellis crops in California (grapes)

These choices are appropriate to cover the most important regional and agronomic variations in the use of airblast equipment. A review of protocols addressing citrus crops in Florida (AHE55) and nut crops in Georgia (AHE56) were presented to the Board during the June 2008 HSRB meeting. Of specific relevance to this protocol (AHE57), Michigan is a major cherry producing state and represents a logical choice for a cluster representing stone fruit crops grown in the Upper Midwest (EPA Region V).

The specific 'site' selected in which to conduct the cherry study is Leelanau and/or Grand Traverse Counties. These counties are located in the northwestern region of Michigan's Lower Peninsula, along Lake Michigan. Of the ~8,000 acres of bearing sweet cherries produced in Michigan, ~6,500 are grown in these two counties. These counties are also reportedly counties having large farms likely to utilize enclosed cab tractors for making airblast applications. Approximately 14,000 acres of tart cherries are also grown in these two counties. According to USDA's Agricultural Chemical Usage 2005 Fruit Summary, 39% of the sweet cherry production area is treated with carbaryl (9,600 pounds a.i.) and 71% with chlorothalonil (27,000 pounds a.i.).

In the next stage of the diversity selection process the practical range of amount of active ingredient handled (AaiH) for the airblast scenario is divided into five bands, of equal width on the log AaiH scale. Past studies have shown that AaiH is strongly associated with exposure and is a meta-factor associated with differences in equipment and spraying practices. Although the AHETF calculates the maximum amount an applicator may handle as 200 lbs AI/day, a more practical upper bound is 100 lbs AI/day. AHETF has set a lower limit at 5 lbs, to minimize non-detects. AHETF has partitioned the practical AaiH range from 5 to 100 lbs AI/day into five strata:

- 5 to 9 lbs AI handled
- 10 to 17 lbs AI handled
- 18 to 30 lbs AI handled
- 31 to 55 lbs AI handled
- 56 to 100 lbs AI handled

This is a reasonable approach to stratification, and it should be possible to fill all strata in all five crop/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 growers includes five steps:

- Contacting local resources to identify growers of the crop 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. From each grower in the working pool, the following range of information will be compiled:

- Crop and acreage that might be treated
- Specific location of crop(s) that might be treated
- Number, type, and size of airblast sprayers available
- Surrogate chemical(s) that might be used
- Estimated timing of applications
- Number of experienced workers available
- Range of AaiH those workers might be able to handle in a day

This process of identifying cooperating growers is basically sound, but represents a changed practice for the AHETF and its research cooperators. The AHETF has promised to document all steps taken and assess how well they worked in early field studies, and then to develop an SOP governing this process. EPA has accepted this approach.

From the identified pool of potential cooperating growers—correctly characterized as a random sample of growers (of the purposively selected crop in the purposively selected state and counties)—the Study Director and the Local Site Coordinator will purposively construct an “efficient configuration” of potential Monitoring Units (MUs). An efficient configuration will involve a group of growers in the same geographic area who can provide workers for all five strata of AaiH, who would involve some diversity in spray equipment, and who expect to make applications at approximately the same time. When constructing MUs, three additional restrictions will be enforced to increase diversity within the cluster:

- No worker may be used more than once
- No airblast sprayer may be utilized more than once
- No more than 2 MUs may be obtained from one grower or grower/commercial applicator pair

The growers and/or commercial applicators in the chosen configuration provide the pool of workers from which workers will be recruited to fill each of the five MU slots. If selected growers or workers drop out as the time of the field study approaches, additional workers appropriate to fill out the MU design may be recruitable from among those employed by growers already in the working pool of eligible growers. If there are too few workers available in the pool to complete a revised efficient configuration, the working pool can be expanded by approaching more growers from the original randomized list. It is not clear what steps would be taken if the original randomized list were exhausted without finding enough cooperating growers and interested workers to complete the field study design. The process for selecting workers is defined to include over-recruiting growers, so that there are likely to be more interested and qualified workers than MU slots, so the workers actually sampled can be selected randomly.

- 3. Choice of Surrogate Materials:** The surrogate chemicals proposed for this scenario are carbaryl, chlorothalonil and malathion, formulated in any of 13 registered products. These pesticides have been successfully used in previous worker/handler exposure monitoring studies and have well established and reliable analytical methods. These are generally appropriate choices for this research, and although malathion is widely used for other uses within this scenario, it does not appear to be widely used in the area of the study site. Formulations of carbaryl and chlorothalonil are more likely to be used.

C. Summary Assessment of the Scientific Aspects of the Study Design³

- 1. Statistical design:** This protocol describes collecting five Monitoring Units (MUs) reflecting the exposure of subjects making airblast applications to stone fruits (cherries) using closed-cab vehicles. This is one of five clusters in the scenario, each of which 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 closed-cab airblast 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.
- 2. Proposed pattern of exposure:** The proposed exposure duration for each MU will be at least 4 hours, involving application of at least 3 tank-loads. Subjects

³ Supporting details are in Attachment 2.

will only apply the pesticide; mixing and loading of the spray solution 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 9 pounds
- 10 to 17 pounds
- 18 to 30 pounds
- 31 to 55 pounds
- 56 to 100 pounds

Thirteen registered products containing one of the three designated surrogate pesticides have been identified, and a cooperating grower may choose to use any of them for a specific MU. Carbaryl formulations include wettable powders enclosed in water-soluble bags and liquid flowable concentrates. Malathion formulations include emulsifiable concentrates or liquid flowable concentrates. Chlorothalonil formulations are flowable concentrates. All of these products will be mixed with water and loaded into the airblast spray tank by workers not participating in the study.

During application subjects may need to leave their enclosed cab to adjust or repair equipment or for other reasons. Whenever they leave the cab applicators will wear all personal protective equipment (PPE) required by the label, in accordance with the Worker Protection Standard (WPS), which requires that in any enclosed cab where reduced PPE is worn handlers must:

- Keep immediately available all PPE listed on the labeling for the type of task being performed
- Wear the PPE if it is necessary to leave the cab and contact pesticide treated surfaces in the treated area,
- Take off PPE that was worn in the treatment area before reentering the cab, and
- Store all PPE in a chemical-resistant container, such as a plastic bag, to prevent contamination of the cab.

The exposure pattern of open-cab airblast applicators is generally to the upper body as a result of falling aerosolized sprays or brushing into treated foliage/branches; the enclosed cab is meant to mitigate this exposure potential. However, individual behavior is also expected to affect exposure.

In many of the existing closed-cab studies in PHED, the exposure contact values are based on many measurements that were below the Limit of Quantification (LOQ). Current analytical methods for the surrogate chemicals are more sensitive than those used in earlier studies populating PHED, but if the results of this study are measurements below the LOQ, the AHETF is prepared to use half the LOQ or some other statistical method to estimate potential exposures. The

investigators also need to record what type of PPE are worn when exiting enclosed cabs so that face/neck wipe samples can be adjusted for the area covered by a respirator or other PPE.

- 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 applied to orchard or trellis crops with conventional airblast sprayers drawn by vehicles with closed cabs. 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 two pieces representing the upper and lower torso. Residues in socks measured in earlier open-cab airblast studies have been very low (e.g., $\approx 0.1\%$ of dermal exposure). Exposure to the applicator's feet in a closed-cab scenario is expected to be insignificant; socks will not be collected as dosimeters.

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 prior to restroom 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 each subject begins work his/her face and neck will be wiped with a cotton gauze swab to remove any contamination not associated with the monitoring event. This face/neck 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 samples will be retained for analysis. The study team needs to record what type of respirator 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 QAUs: 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 closed-cab airblast 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

The scenario sampling design is generally sound, but would be strengthened by increasing the numbers of growers and workers in the working pool, so that individual workers no fill each MU slot can be selected randomly from among qualified, interested volunteers. In addition, provision is needed for the possibility that the MUs cannot all be filled from among workers employed by growers on the original randomized list.

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 Research⁴

- 1. Societal Value of Proposed Research:** The objective of this study is to develop data to determine the potential exposure for workers making closed cab airblast applications in Michigan stone fruit. This study will provide a partial answer to the question of what dermal and inhalation exposures are likely for applicators using conventional airblast equipment and closed-cab tractors. This is a widespread pattern of pesticide application in orchard and trellis crops, for which existing applicator exposure data are inadequate. EPA will use the results of this study, in conjunction with the results from one field study conducted in August 2008 and three other field studies planned for this scenario, to estimate the dermal and inhalation exposure likely for future applicator-days 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 of stone fruit (e.g., cherries) in Leelanau and/or Grand Traverse County (and possibly adjacent counties) who are identified as commercial growers who “might utilize airblast equipment in their operations” 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 recent experience using the closed-cab airblast application equipment to be used in the study, who meet the eligibility requirements of the study. If more employees are available and interested than are needed, 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 use airblast equipment to treat stone fruit crops in Michigan.

Inclusion factors listed in the protocol are appropriate, but the fourth criterion should be deleted because it is essentially a duplicate of the final criterion. In addition, the last criterion should be revised to delete the reference to “vines.” The protocol exclusion factors are appropriate, but one of the two duplicate criteria should be deleted. The eligibility factors listed in the Consent Form (V2:60) differ from those in the protocol (V2:22-23) in possibly important ways, and should be harmonized.

⁴ Supporting details are in Attachment 2.

The description of the process for recruiting subjects relies heavily on references to AHETF SOP 11.B, which has been extensively revised since the June 2008 HSRB meeting and has been appended to the protocol (V2:269-285). Appropriate steps are proposed to protect candidates and subjects from coercion or undue influence to participate. Candidates who attend an individual interview will be paid \$20 whether or not they agree to participate; enrolled subjects who once 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: Six 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 background risk of injury associated with agricultural work

The surrogate chemical used will be carbaryl, chlorothalonil, or malathion; all three are fully tested and well understood. Individual growers will choose from a list of thirteen registered products containing one of these ingredients, 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 this protocol substantially exceed the target MOE for occupational dermal and inhalation exposure.

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 applying pesticides to stone fruit crops using closed-cab airblast equipment, 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. 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, but witnesses should not be asked to attest to the subject's understanding of the material (V2:68). 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 Field Facility, the Analytical Facility, and the Principal Analytical Investigator must be identified in the protocol.
- Add to the protocol provision for counting and reporting the number of potentially eligible workers linked to each grower, and the numbers attending initial group meetings, attending individual consent interviews, signing consent forms, subsequently withdrawing or being withdrawn, and completing participation.

- The lists of eligibility factors in the protocol and the consent form must be harmonized.
- Chlorothalonil was omitted from some portions of Section 2.3.2 of the protocol – for example, the last sentence of the first paragraph. This section must be revised to properly reflect that there are three surrogate chemicals.

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. Summary Review of Closed-Cab Airblast Scenario Design dated August 14, 2008
2. Summary Review of Protocol AHE57 dated August 14, 2008
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

EPA Scenario Review: AHETF Close-Cab Air Blast Scenario

Title: Closed Cab Airblast Applicator Scenario Sampling Plan: pp. 8-51 in AHETF Volume I: General Information and Scenario Sampling Plan

Date: Revised 7 August 2008

Sponsor: Agricultural Handlers Exposure Task Force

1. Scope of Scenario Design

“This scenario includes application of liquid sprays to actively growing, foliated crops using conventional airblast equipment and closed-cab tractors.” (V1:3)

“The following five crop type/state combinations are proposed for this scenario that will provide the desired diversity in crop and geography:

- Citrus crops in Florida (e.g., oranges)
- Nut crops in Georgia (e.g., pecans)
- Pome fruit in Washington (e.g., apples)
- Stone fruit in Michigan (e.g., cherries)
- Trellis crops in California (e.g., grapes)” (V1:4)

(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 closed cab airblast application 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 application scenario is applicable to a wide variety of commercially important crops (e.g., fruit trees, nut trees, and trellis crops). Therefore, it is necessary to have data in AHED for the application 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 two closed cab airblast application studies and did not identify any data from existing studies that were deemed useful 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. Data for closed cab airblast application of liquid sprays comprise PHED Scenario 12 –Airblast Application, Closed Cab (APPL). Data within that scenario were graded by EPA as “Low Confidence” for the “No Clothes” and “Single Layer, No Gloves” clothing scenarios. The inhalation exposure data are also graded as “Low Confidence”. The “Single Layer, Gloves” clothing scenario in PHED was graded as “High Confidence” but it was noted that there are a large number of non-quantifiable residues for this clothing scenario. In the AHETF detailed review of these PHED data, one MU from one study was found that possibly met the acceptance criteria established by AHETF. However, several issues associated with this MU make it of dubious quality and the logistical problems of obtaining a single MU from a single study provides sufficient rationale for not further pursuing these data (Exponent, 2007). Thus, there are no data currently in PHED for this scenario that are useful for a modern generic database.

“Finally, EPA examined data from 13 existing airblast exposure studies or exposure assessments (for open and/or closed cabs) that were not available to the AHETF and concluded that none of the exposure data should be included in the AHETF database (correspondence from EPA on July 3 as a follow-up to a June 27, 2007 meeting with AHETF). This MU selection plan therefore proposes to collect a full set of new data for this closed cab airblast application scenario to meet the scientific objectives outlined in the Governing Document.” (V1:7-8)

2. Rationale for Scenario Sampling Design

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

“AHETF experts agree that exposure potential will be considerably less for closed cab situations than for open cab situations and believe that overhead spraying, exiting the cab, and contacting surfaces (e.g., while making adjustments or repairs) may be the most important parameters influencing exposure in closed cab situations. . . . AHETF believes the best way to get diversity in these various parameters is to vary the crop type, especially for crop height and foliage density. This will ensure the collection of MUs includes some overhead exposure and a variety of equipment configurations and settings (see Section 6 for more details).

“Crop conditions are therefore considered an important parameter that should be formally diversified. Consequently, any stratification should distinguish orchard and trellis crops, both commonly treated with closed cab airblast sprayers. . . .” (V1:17)

“. . . Five crop categories encompass approximately 97% of all the acreage that might be treated by airblast applications. This suggests the possibility of stratifying the crops treated by airblast into these five crop types:

- Nut crops

- Citrus
- Pome fruit
- Stone fruit
- Trellis crops

“The ‘other orchard’ category will be restricted from the target population because overall acreage is relatively low and agricultural experts did not indicate there were fundamental differences in how these crops are treated by airblast. These orchard crops include avocados, dates, figs, guavas, olives, and papayas.

“Trellis crops will be considered as a group with one exception – tall hops. Hops are treated with conventional airblast equipment like other trellis crops, but unlike grapes and caneberries they can grow very tall and involve overhead exposure similar to orchard situations. Since trellis crops are purposively included in the sampling plan because they are shorter than orchard crops and don’t involve overhead exposure, this plan will restrict MUs involving trellis crops to situations that do not involve overhead exposure (i.e., tall hops will not be included).

“However, exposure potential for workers who use airblast sprayers in tall hops will still be covered within AHED by data from orchard applications.” (V1:18-19)

“**Crop Type Growing Areas:** Acreage by state for each of the five crop types is readily available from USDA . . . and provides a convenient way to identify where important crop types are commonly grown. A ‘predominant growing area’ for each of the five crop types can be defined in terms of states that account for 5% or more of the total crop type acreage.” (V1:19)

“One state will ultimately be selected from each of these five crop type strata. It should be emphasized, however, that relative crop acreage was used only to delineate states associated with where most of the crops are grown. Acreages cannot be used to guide a “representative” sample of airblast application conditions. This is because information on the number of sprays performed per year by airblast with enclosed cabs in particular areas and for particular crops would be needed. This information is not readily available and it varies from year to year based on the amount and type of pest pressure in each crop in each area. Therefore, acreage data are used only as a guide to indentifying locations where enclosed cab airblast applications are probably common. Discussions with local agricultural experts are then used to verify that the scenario of interest is common and then specific study sites can be chosen.” (V1:21)

“**Geographic Stratification:** . . . Closed-cab airblast applications are made almost exclusively to orchard and trellis crops and these crops are grown in many regions of the country. . . . For this reason, geographic diversity between sites is also desired. Geographic diversity between clusters of monitoring units is . . . viewed as a meta-factor that is associated with both known and unknown effects usually classified as simply ‘study effects’

“The 13 U.S. Growing Regions established by EPA (Figure 2) 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. . . . The goal in diversity selection is to obtain no more than a single state from each EPA growing region.” (V1:21-22)

“Selecting States from Crop Type and Geographic Strata: . . . The diversity selection goal is to choose one state for each crop type with the proviso that no two states are in the same EPA growing region. Guided by this rule and the information in Table 5, the following five combinations . . . were purposively selected.

1. Citrus / Florida

“This citrus combination was chosen because of the dominant acreage for citrus crops in Florida (66%) and because it is the only combination in Region III. Florida was selected over California (the only other combination involving citrus) since California will be chosen for another crop type (see below). Florida reflects a hot and humid climate in the peninsular southeastern US (EPA Region III).

2. Trellis Crops / California

“This trellis crop combination was chosen because of the dominant acreage for trellis crops in California (77%). California was selected over Washington (the number two acreage state) so that Washington could be selected for pome fruits due to its dominance in that crop type (see below). California reflects a hot and dry climate in the western US (EPA Region X).

3. Nut Crops / Georgia

“This nut crop combination was chosen because California (the highest nut crop acreage) is already selected and because AHETF has a qualified Local Site Coordinator in Georgia that will likely result in a localized and efficient study. This state reflects a hot and humid climate in the southeastern US (EPA Region II).

4. Pome Fruit / Washington

“This pome fruit combination was chosen because of the dominant acreage available for pome fruits (84%) and because it provides good geographic diversity. This state reflects a cool climate in the Pacific Northwestern US (EPA Region XI or XII).

5. Stone Fruit / Michigan

“This stone fruit combination was chosen because Michigan has the highest acreage for a stone fruit after California. This combination also provides geographic diversity because it reflects a cool climate in the upper Midwestern US (EPA Region V).

“Collectively, these crop type/state combinations cover five different EPA growing regions including the West, Northwest, Southeast, and upper Midwest portions of the US. They also cover all five of the crop types that are desired for diversity. AHETF also has acceptable Local Site Coordinators in each of these states. Finally, local agricultural experts have been contacted from each of these states to confirm airblast applications are common to the crop indicated.” (V1:23-25)

“Selection of Specific Monitoring Sites for Each Study: The final step for selecting sites is to choose a specific area within each selected state identified above where growers and workers can be recruited to conduct a study in a reasonable amount of time. This involves staging the study (i.e., site) in a reasonably limited geographic area so that MU identification and selection operations can be conducted efficiently in one local area within the state. This is necessary primarily to keep the costs of study conduct reasonable so an adequate 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 several 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.” (V1:26)

“Therefore, for each study (i.e., site), a particular area of each state will be selected and identified in the study protocol. This will be determined by discussions with local resources to indicate areas that are most likely to have sufficient growers, equipment, and workers to allow an efficient study. It may also be restricted based on the availability of a Local Site Coordinator who is responsible for providing logistical support to the CROs.” (V1:27)

“The primary considerations for site selection will be the availability of trellis crops sprayed with airblast equipment, suitable growers that are willing to use the AHETF surrogate compounds and are willing to participate in the study, and the availability of a Local Site Coordinator with experience conducting similar studies and a familiarity with agricultural practices in the area. Full details of the site selection process and actual sites will be recorded in the study file.” (V2:22)

(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 application conditions needed to construct MUs for the study. Random selection of growers is preferable, when feasible, to reduce the possibility of selection bias that might arise from the Local Site Coordinator (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 study (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 for the crop type of interest at the identified location (generally about one to three counties)
2. Assemble a list of growers from all of the resources contacted and eliminate any duplicates.
3. Put the list of growers into random order.
4. Contact growers, one at a time, following the random order, and determine whether the grower is 'eligible' to participate. . . .
5. Each grower identified as eligible (sometimes along with an associated commercial applicator) is placed into a working pool along with information on:
 - Crop(s) available, with acreage that might be treated
 - Specific location of crop(s) that might be treated
 - 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

“Screening of the grower list (in random order) continues until a pool of eligible growers (and/or commercial applicators) that is sufficiently large is obtained. . . .

“This process results in a random sample of eligible growers and, by association, a random pool of potential workers associated with eligible growers.” (V1:29-31)

“AHETF researchers will contact local resources from each of the following categories in Leelanau and/or Grand Traverse Counties and possibly adjacent counties:

- Local Site Coordinator (LCS)
- Commercial Applicator Firms that service fruit tree crops
- University Agricultural Researchers / County Extension Agents
- Crop Consultants (e.g., pest control advisors or commercial applicators) that service fruit orchards
- Chemical Dealers or Sales Representatives
- Tree fruit Grower Associations

“The researchers will briefly explain the AHETF Exposure Monitoring Program to the local resources who are then asked for a list of growers in Leelanau and Grand Traverse County and possibly adjacent counties who might utilize airblast equipment in their operations. The list of growers from all of the resources will be compiled and duplicate names eliminated. All local resource contacts shall be documented in a detailed record that shall be maintained in the study file.

“The compiled list of growers from local resources shall be placed in random order for further consideration. The randomization process will be documented and maintained in the study file.

“The growers shall be contacted, one at a time, following the random order, to determine whether the grower is ‘eligible’ to participate in this study.

“Screening of the growers (in the order of the random list) continues until the pool of eligible growers (and/or commercial applicators) contains at least 10 workers who may potentially volunteer for the study, and at least 2 workers are available for each of the AaiH strata. This pool will include more growers and more workers than are ultimately needed for the study.” (V2:22-24)

(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 only 10 workers are in the recruiting pool it is unlikely that the opportunity will often arise to select randomly from among interested workers. If the configuration included a pool of at least 3 or 4 potential workers for each MU, the opportunity to select randomly would arise in nearly all cases.

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

“This is an application scenario defined entirely by the application equipment, i.e., airblast sprayers with closed cabs. Airblast sprayers are used to apply chemicals to orchard trees and trellis crops (e.g., grapes, caneberries, etc.) by delivering pesticides as a liquid carried in a large volume of air. Other crop types, such as row and field crops, are not treated by airblast equipment and are therefore not relevant for this scenario. The air stream functions to move spray into the trees or vines to enhance the uniformity of deposition onto foliage, fruit, and wood. The air stream physically displaces the air space surrounding the foliage and deposits the chemicals on all surfaces of the leaves and branches.” (V1:6)

“Sprayers are commonly drawn by a tractor or vehicle to move the sprayer through the orchard or vineyard, but can also be mounted on a tractor or other vehicle.” (V1:35)

“AHETF experts ... believe that overhead spraying, exiting the cab, and contacting surfaces (e.g., while making adjustments or repairs) may be the most important parameters influencing exposure in closed cab situations.” (V1:17)

“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 application of at least three loads and a minimum duration of four hours.

“For this particular scenario the applicator will be in a closed cab while the actual spraying takes place. The cab enclosure should reduce dermal and inhalation exposure from airborne spray that would otherwise reach the operator. This protection is due to the physical barrier between the pesticide spray and the worker. When doors or windows are opened, however, this barrier is no longer effective and the potential for worker exposure is increased. Opening windows during actual spraying would be contrary to the WPS and a violation of the label. This will, therefore, not be allowed.

“AHETF suspects that exposure potential, especially dermal exposure, may be impacted by how often the applicator gets out of the closed cab, where that exiting occurs, and what the worker does while outside the cab. Exiting the cab might occur to make sprayer adjustments, perform repairs, or prepare a new load. Therefore, exiting might occur within or outside of the treated area. By exiting the cab, the worker might be subjected to lingering airborne sprays and/or surfaces that may have been sprayed with pesticide including the crop itself, the ground, various parts of the sprayer, and the outside of the cab. Exiting the cab is not, however, something that can be predicted or controlled in advance since it depends on factors such as worker preference, number of loads performed, and whether repairs or adjustments are necessary. The agricultural experts consulted by AHETF indicated that exiting the cab is rare. Number of exits, therefore is not amenable to formal diversification, but will likely vary as a result of purposive diversity in AaiH, and other factors such as crop type, equipment, etc.” (V1:33-34)

“Setup of an airblast sprayer can be very complex involving the following factors and others: nozzle type, nozzle size, nozzle placement, number of nozzles, orientation of air director vanes, liquid pressure setting, spray volume per acre (GPA), engine speed, ground speed, etc... Collectively, these factors might also have an impact on exposure potential for airblast applicators, for example by influencing the amount of spray that remains airborne long enough to reach the operator or that contaminates surfaces the operator may later contact.” (V1:36)

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

“Airblast applications are sometimes made to dormant crops (e.g., to control scale), but agricultural experts for orchard and trellis crops indicate that foliar applications (e.g., to control diseases and insects on foliage) are much more common. Overall, dormant applications are estimated to account for 15% or less of all airblast applications (Bruce, 2008). Therefore, because foliar sprays are much more common than dormant sprays, AHETF intends to collect MUs for foliar applications only; dormant applications will be excluded from the target population of conditions for this scenario.” (V1:6-7)

“Figure 1 summarizes U.S. acreage statistics for these important groups of orchard and trellis crops. This chart indicates that five crop categories encompass approximately 97% of all the acreage that might be treated by airblast applications.

“The ‘other orchard’ category will be restricted from the target population because overall acreage is relatively low and agricultural experts did not indicate there were fundamental differences in how these crops are treated by airblast. These orchard crops include avocados, dates, figs, guavas, olives, and papayas.

“Trellis crops will be considered as a group with one exception – tall hops. Hops are treated with conventional airblast equipment like other trellis crops, but unlike grapes and caneberries they can grow very tall and involve overhead exposure similar to orchard situations... this plan will restrict MUs involving trellis crops to situations that do not involve overhead exposure (i.e., tall hops will not be included)... exposure potential for workers who use airblast sprayers in tall hops will still be covered within AHED by data from orchard applications.” (V1:18-19)

“Other application equipment types can sometimes be used as an alternative to conventional airblast sprayers. Agricultural experts indicated the following are sometimes alternatives in orchard or trellis crops: aerial application, directed-spray rigs, wrap-around sprayers, covered boom sprayers (e.g., tunnel or curtain), electrostatic sprayers, and mist blowers... these alternative systems are not nearly as common as conventional airblast sprayers for either trellis or orchard crops. AHETF will therefore limit its MU collection to include exposure to workers operating conventional airblast sprayers.” (V1:36)

3. Are the proposed test materials appropriate surrogates?

“The following active ingredients are approved for use on orchards and trellis crops, meet the minimum PPE requirements listed above, and will be considered for use in this closed-cab airblast application scenario. The commercial products of these active ingredients that might be used in particular studies will be listed in study-specific protocols.

- Carbaryl (insecticide; orchards or trellis)
- Malathion (insecticide; orchards or trellis)
- Chlorothalonil (insecticide; orchards) (V1:37)

“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. Since this scenario involves only applications of liquid sprays, any product with the proper registration that can be added to water and applied as a liquid spray is suitable. The actual product and packaging type has no influence on the potential exposures to these applicators and is, therefore, not an important consideration for this scenario.” (V1:38)

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 closed cab airblast application 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 closed cab airblast 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.” (V1:13-14)

EPA Protocol Review: AHE57: Closed-Cab Airblast Application to Michigan Stone Fruit

Title: Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment in Michigan Stone Fruit.

Revision Date: July 31, 2008

Study Director and Sub-Investigators:

Larry D. Smith, Ph.D.
Brian Lange⁵
Tami Belcher⁵
Aaron Rotondaro⁵

Local Site Coordinator: TBD⁶

Field Facility: TBD⁶

Analytical Facility: TBD⁶

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 making closed cab airblast applications in Michigan Stone Fruit (e.g., cherries).”
(V2:19)

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

⁵ 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.

⁶ The Local Site Coordinator, Field Facility, Analytical Facility, and Principle Analytical Investigator must all be identified.

This study will provide a partial answer to the question of what dermal and inhalation exposures are likely for applicators using conventional airblast equipment and closed-cab tractors. This is a widespread pattern of pesticide application in orchard and trellis crops, for which existing data are inadequate.

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

EPA will use the results of this study, in conjunction with the results from one field study conducted in August 2008 and three other field studies planned for this scenario, to estimate the dermal and inhalation exposure likely for future applicator-days for a wide range of agricultural pesticides.

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

“For this particular scenario, the JRC [Joint Regulatory Committee] reviewed two closed cab airblast application studies and did not identify any data from existing studies that were deemed useful 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. . . . In the AHETF detailed review of these PHED data, one MU from one study was found that possibly met the acceptance criteria established by AHETF. However, several issues associated with this MU make it of dubious quality Thus there are no data currently in PHED for this scenario that are useful for a modern generic database.

“Finally, EPA examined data from 13 existing airblast exposure studies or exposure assessments (for open and/or closed cabs) that were not available to the AHETF and concluded that none of the exposure data should be included in the AHETF database.” (V1:14-15)

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

There is no alternative to monitoring applicators as they apply pesticides for measuring their dermal and inhalation exposure as they apply pesticides.

2. Study Design

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

The objective of the proposed study is to collect exposure monitoring data “to represent future exposures to an arbitrary active ingredient under the closed cab airblast application scenario.” (V1:10)

“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, June 27, 2007).” (V1:19)

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 closed cab airblast application 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.” (V1:13)

(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., Local Site Coordinator 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 study.” (V1:31)

“The Study Director or designated researcher will seek permission from the eligible grower to approach his/her employees to recruit volunteers for the study. . . . The Study Director or researcher shall continue conducting site inspections and potential participant recruitment as described above until an adequate number of eligible growers and potential participants have been secured for an efficient configuration of all MUs in the study. During this process, the following restrictions will be maintained:

- At least 10 workers who may potentially volunteer for the study
- At least 2 workers available for each of the AaiH strata
- No more than 2 MUs from any one grower (this effectively requires at least 3 different growers since 5 MUs are desired)
- No workers may be used more than once
- No piece of equipment (tractor plus sprayer) may be used more than once” (V2:25-26)

(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.’” (V1:40)

(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.” (V1:40)

“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.” (V1:40-41)

“This secondary benchmark objective [Adequacy of the Data for Distinguishing a Proportional from an Independent Relationship between Exposure and AaiH] applies to the closed cab airblast 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.” (V1:41)

(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 closed-cab airblast applications 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 closed cab airblast 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 $\beta=0$. 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 $\beta=0$ 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 $\beta=1$ when $\beta=0$. This is the precise meaning of being able to ‘discriminate between proportionality and independence’.” (V1:41)

2.2 How and to what will human subjects be exposed?

“The closed cab airblast scenario program will monitor instances of worker exposure resulting from the airblast application of pesticides” to stone fruit in Michigan. (V1:15)

“The test substances approved for use in this study are listed in Section 2.3.2 above and Table 1 below. The most appropriate test substance, based largely on the preference of the grower, will be used at each of the individual locations. A different test substance may be used at each location and by each worker within a location if appropriate.” (V2:43)

(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 approved for use on orchards and trellis crops, meet the minimum PPE requirements listed above, and will be considered for use in this closed cab airblast application scenario. The commercial products of these active ingredients that might be used in particular studies will be listed in study-specific protocols.

- Carbaryl (insecticide; orchards or trellis)
- Chlorothalonil (fungicide; orchards)
- Malathion (insecticide; orchards or trellis)

“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.” (V1:45-46)

(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 EPA currently normalizes closed cab airblast 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.

“The MUs for this scenario will span the practical AaiH range of 5 to 100 pounds, just over 1 order-of-magnitude. As noted in Section 4.5 above, it is also 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 strata. These strata are:

- 5 to 9 pounds ai handled
- 10 to 17 pounds ai handled
- 18 to 30 pounds ai handled
- 31 to 55 pounds ai handled
- 56 to 100 pounds ai handled” (V1:27-28)

“A single MU will be conducted in this study from each of the five strata.” (V2:31)

(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 an order of magnitude. Airblast applicators often spend several hours making applications, so all MUs for this scenario must meet the general rule of being at least 4 hours long. 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 apply 3 loads in four hours for the lowest AaiH.” (V1:34)

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.

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

“Full details of the personal air-sampling method, attachment of pumps, monitoring of workers, and pump calibration are given in the most recent versions of SOP AHETF-8.D and 10.G. (V2:31-32)

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

“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.

“All field fortification and untreated control samples will be identified as described in SOP AHETF 11F.” (V2:32-33)

(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. (V2:40)

(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.” (V2:32-33)

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 $300 \text{ ug}/80\% = 375 \text{ ug}$.

3. Subject Selection

3.1 Representativeness of Sample

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

“The closed cab airblast scenario program will monitor instances of worker exposure resulting from the airblast application of pesticides. Each instance is termed a monitoring unit (MU). Each MU consists of a set of airblast application 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’ airblast applicator-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 airblast application-days. Thus, MUs are technically not ‘sampled’ from a population. More correctly, they should be viewed as synthetic closed cab airblast application-days derived from both selected and constructed conditions.” (V1:15)

(b) From what populations will subjects be recruited?

Subjects will be recruited among the employees of commercial growers of stone fruit (e.g., cherries) in Leelanau and/or Grand Traverse County and possibly adjacent counties who might utilize airblast equipment in their operations and who meet AHETF criteria for participation. (V2:38)

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

A ‘working pool’ of eligible growers will be identified from a randomized list of growers in the target area. Based on considerations of equipment type, acreage, anticipated time of treatment, and geographic location the Study Director and LSC

will purposively select growers from this pool to construct an ‘efficient configuration’ of MUs. All employees of eligible growers included in the efficient configuration (or of pesticide application service companies used by eligible growers included in the efficient configuration) who are experienced in the use of closed-cab airblast application equipment and who meet the eligibility requirements of the study will be recruited; if more employees are available and interested than are needed for a specific MU, 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 use airblast equipment to treat Michigan stone fruit crops.

(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?

“Participants in this study must meet the following inclusion criteria:

- Be freely willing to participate and to understand and sign the consent form
- 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.
- Have experience within the past year with the work activity being monitored in this study (including the particular activity to be used during mixing/loading or application).
- Be at least 18 years old with a government-issued ID to verify age.
- Consider themselves to be in good general health with no medical conditions that could impact their ability to participate in the study. See SOP AHETF-11.C for health status determination.
- Be willing to follow all label and WPS requirements
- Understand English or Spanish
- Understand and sign the consent form and the Product Risk Statement for the pesticide they will handle
- Have experience within the past year with making airblast applications to vines using open cab tractors and airblast sprayers (including the particular equipment to be used).

“Exclusion criteria:

- Are pregnant females

- Are nursing mothers
- Normally wear personal protective equipment (PPE) that is not required by the label and might adversely impact the objectives of the study, such as chemical-resistant clothing
- Are employed by a pesticide manufacturer or a contractor to AHETF” (V2:22-23)

(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?

“AHETF will follow standard procedures (see SOP AHETF-11.B) to recruit potential participants for this closed cab airblast application study. Individual workers will be recruited during an initial site inspection or subsequent visit(s) to an 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 through the use of an informational recruitment flyer posted in a common work area. Such a flyer will briefly describe the research study and provide contact information for employees who may have an interest in participation 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 meetings will always occur without the grower or supervisors being present (SOP AHETF-11.B). 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. Contact information 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.” (V2:40-41)

(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, 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.” (V2:40)

If both of the candidate workers identified for a specific MU decline to participate, the investigators would have to repeat several preliminary steps to identify potentially appropriate workers employed by growers in the working pool already identified, or to screen additional growers for inclusion in the working pool. The cost and time associated with repeating these steps could result in some pressure on the second candidate originally identified. This problem could be largely eliminated by identifying a larger pool of candidate workers—at least 3 or 4 for each defined MU—in the first iteration.

3.3 Remuneration of Subjects

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

(b) “During recruitment, workers will be offered an opportunity to take part in a group 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 (Section 6.2). No remuneration is offered for this introductory meeting. Workers who are still interested will attend a private meeting with a researcher who will obtain the informed consent of the worker (Section 2.7). 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.” (V2:23)

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

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

(e) 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 three active ingredients: carbaryl, chlorothalonil, or malathion. “The pesticide products containing these active ingredients and potentially used in this study are currently registered for airblast applications to stone fruit (e.g., cherries). AHETF will only monitor workers making applications in accordance with all label and Worker Protection Standard (WPS) requirements. Margins of Exposure (MOEs) are presented below for the highest amount of active ingredient that will be handled in this scenario (100 lb ai/day). For each of the active ingredients (a.i.) that may be used in this scenario the calculated MOEs 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.” (V2:25-26)

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

“Six 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
- The background risk of injury associated with agricultural work

“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 operation of tractors and airblast sprayers which present risks of accidents and physical injury, as well as the use of chemicals (pesticides, fertilizers, additives, etc.) which presents 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.” (V2:23-24)

Each of these six kinds of risk is discussed in V2:24-32.

“The following signs and symptoms of toxicity from short-term exposure might occur. These effects are not anticipated with normal use, but might occur following a spill or other accidental exposure.

“This [carbaryl/chlorothalonil/malathion] product is classified as [low/low/moderate] toxicity for exposure by mouth, by skin, and by breathing. Signs and symptoms of too much short-term exposure include [slight/moderate] eye irritation, [slight skin irritation,] and inhibition of cholinesterase (cholinesterase is a chemical in our nervous system that allows the nerves to work correctly; when chemicals prevent it from working correctly, there is a stimulation of the nervous system.)

“Inhibition of cholinesterase may result in headache, dizziness, nausea, vomiting, cramps, diarrhea, blurred vision, pinpoint pupils, tightness in the chest, difficulty breathing, nervousness, sweating, watering of the eyes, drooling, muscle spasms, and coma.” (V2:81, 83, 85, 87, 89, 91, 93, 95 Product Risk Statements supplemental to consent form)

(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
- Requiring experience operating the equipment to be used
- Reminding workers of safe chemical handling practices
- Identifying nearby hospitalization 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.” (V2:32)

Risk reduction actions specific to each of the six identified kinds of risk are discussed in V2:24-32.

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

“For each 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] greatly exceeded the required MOE for both the individual dermal and inhalation routes of exposure, as well as for the combined [dermal/inhalation] exposure.” (V2:26)

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

“Since workers may exit the cab, AHETF will monitor ambient conditions outside the cab to determine the heat index and base monitoring decisions on the external heat index. A heat index of 120° F is the cutoff, as measured outside the cab. When the worker is inside an air conditioned closed cab the external heat index will not be applicable to that subject and exposure monitoring will not necessarily stop if the heat index cutoff is reached or exceeded. A worker will be allowed to exit the cab for short periods of time even if the heat index cutoff is exceeded; however, if the duration of exiting becomes prolonged (more than 30 minutes), the Study Director or other researcher shall stop the monitoring and/or move the worker to a cooler environment until monitoring can be resumed.” (V2:25)

(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.” (V2:63)

SOP AHETF-11.H 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 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 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 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.

“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).” (V2:37)

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

“If you are injured or get sick during or after the day of the 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. You cannot refuse medical treatment if 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. The medical treatment records will not become part of the research records. AHETF will make note of the event. The event will be reported in the study report. For further information about this you may call to AHETF Manager (David Johnson) toll free at (866) 925-1421.” (V2:63-64)

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.” (V2:32)

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 no existing data suitable for use in a generic database describing the exposure of closed cab airblast application workers, society will likely benefit from data generated by this study through the improved risk assessments by EPA and other regulatory agencies.

“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 spraying pesticides using airblast equipment and closed-cab tractors. 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.” (V2:33)

(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.” (V2:32-33)

(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?

“This study presents a greater than minimal risk to participants. The primary risk comes from their employment as an agricultural worker where accidents and chemicals contribute to injury and illness. In particular, this scenario involves the use of mechanical equipment that could cause physical injury and handling chemicals that could cause adverse health effects.

However, workers will be experienced with the equipment they will be using and will follow their usual practices while handling pesticides approved for this use pattern.

“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. Airblast applications are common in both orchard and trellis crops across the country and a wide variety of experts consulted by AHETF reported that closed cabs are most common now, and are becoming even more common. 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 (MOEs) calculated for the exposures in this research study indicate that 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.” (V2:33-34)

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. The protocol, informed consent form and other required documentation for this study will be approved by an institutional review board (IRB), 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). 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.)” (V2:21-22)

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 §6 of SOP AHETF-11.B.2 (V2:274-277)

- (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-B-3 will be used to ascertain general understanding.” (SOP AHETF-11.B.2 §7.10.a; V2:278-279. The form is at V2:282-284)

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

“The SD (or a researcher designated by the SD) will be responsible for obtaining informed consent from all study workers prior to their participation in the study. Generally, a PowerPoint presentation will be made that covers all aspects of the study that should be covered during this consent meeting. Any materials used during the consent meeting will be approved by the IRB before use.

“Informed consent discussions will be conducted by the SD (or designee) in private with each worker and others that the worker may want to have present. Witnesses may also be present as described above in Section 6.0. When a bilingual researcher is obtaining consent from a Spanish-speaking worker, the Study Director may also be present during the private meeting to answer study-specific questions.

“The SD (or designee) will inform the worker that he/she will receive \$20, or the amount specified in the protocol, even if he/she decides not to participate in the study.

“During the private meeting the SD (or designee) 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 SD (or designee) 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 (called a Product Risk Statement or PRS) and shall be signed by the worker. WPS requirements, especially proper use of clothing, personal protective equipment, *etc.*, will be discussed. Refer to SOP AHETF-11.E for details.

“The SD (or designee) will discuss the medical management plan with the prospective participants. Information will be provided about the risk of heat stress, including signs and symptoms, and ways to prevent it. Details on heat stress are outlined in SOP AHETF-11.G, while details on emergency medical procedures are outlined in SOP AHETF-11.H.

“During the discussions between potential participants and the SD (or designee), ample time will be provided for questions and the SD 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 SD (or designee) 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 SD (or designee) will provide a copy of the signed form to the worker.

“An additional IRB-approved document, ‘Product Risk Statements,’ will be attached to the Consent Form. If the study is conducted in California, the IRB-approved ‘Experimental 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.”

“The SD (or designee) 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.B.2 §7.2-7.11; V2:277-279)

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

“In accordance with SOP AHETF-11.B 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.” (V2:40)

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, 6.D, 11.B, and 11.D.” (V2:34)

“Your name will only appear on the consent form, the Product Risk Statement, and an optional form for you to request your personal study results. 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.” (V2:64)

(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).” (V2:34)

“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.” (V2:65)

(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.” (V2:65)

**§ 26.1111 Criteria for IRB approval of research
AHETF Protocol AHE57: Michigan Stone Fruit: August 14, 2008**

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 AHE57: Michigan Stone Fruit: August 14, 2008**

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	Ensure bilingual competence among investigators who conduct recruitment and consent interviews
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	Ensure Spanish capability at all listed phone numbers
	(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	

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**§26.1117 Documentation of informed consent
AHETF Protocol AHE57: Michigan Stone Fruit: August 14, 2008**

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 AHE57: Michigan Stone Fruit: August 14, 2008

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 <ul style="list-style-type: none"> 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	V2:16-57; 169-210; 293-335 V2:58-150	
	(2) Minutes of IRB meetings . . . in sufficient detail to show <ul style="list-style-type: none"> 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	V2:350-356 Basis for changes not shown No controverted issues	
	(3) Records of continuing review activities.	n/a		
	(4) Copies of all correspondence between the IRB and the investigators.	Y	V2:11-14,156-167, 288, 291-292, 345-349	
	(5) <ul style="list-style-type: none"> 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	V2:23-32
		(2) The measures proposed to minimize risks to the human subjects;	Y	V2:23-32
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	V2:32-33
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	V1:14
		(5) The balance of risks and benefits of the proposed research.	Y	V2:33-34
	§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 V2:211-248 Approved V2:58-150	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	V1:39-40; V2:23; 34; 39-41; 96-97; 151-153; 269-285; 336-342	
	§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	V2: 40-41; 269-285	
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	See page references above	
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.	Y	V2:11-14	

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