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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 AHE64 for Exposure Monitoring in Oklahoma Pecans

FROM: John M. Carley
Human Research Ethics Review Officer

Jeff Evans
Health Effects Division

TO: Jack Housenger, Associate Director
Health Effects Division

REF: Bruce, E. (2008) Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Open Cab Equipment in Oklahoma Tree Nuts. Unpublished protocol dated July 24, 2008, prepared for the Agricultural Handlers Exposure Task Force under Sponsor ID AHE64. 429 p., plus 240 p. scenario design and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.

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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 open-cab airblast scenario appears in Volume 1 of the AHETF submission of August 14, 2008 (V1:7-58)[1]. The IRB-approved protocol and supporting documents specific to study AHE64 appear in Volume 4. Volume 4 does not include procedures for the IIRB, Inc., but these can be found in the documentation of the companion protocols AHE62 and AHE63.

In addition to the final protocol (V4:16-56) Volume 4 includes the following supporting documents:

- Study documents in English approved by IIRB:
  - Informed Consent Form approved 8/05/08 (pp. 58-67)
  - Product-specific risk statements approved 8/05/08 (pp. 69-82)
  - Recruiting flyer approved 8/05/08 (p. 84)
- Study documents in Spanish approved by IIRB:
  - Informed Consent Form approved 8/05/08 (pp. 88-99)
  - Product-specific risk statements approved 8/05/08 (pp. 101-121)
  - Recruiting flyer approved 8/05/08 (p. 123)

- Correspondence between the investigator and IIRB (pp. 11-13; 130-141; 258; 261-262; 314-316; 360-365)
- Protocol and supporting documents as initially submitted to IIRB on 7/25/08 (pp. 140-238)
- Revised SOP AHETF 11.B.2 dated 7/24/08 and submitted to IIRB (pp. 240-255)
- Revised protocol and supporting documents as submitted to IIRB on 7/31/08 (pp. 261-304)
- Revised protocol and supporting documents as submitted to IIRB on 8/08/08 (pp. 314-357)
- Minutes of 8/05/08 IIRB Meeting (pp. 367-372)
- IIRB approval letters of 8/01/08 and 8/08/08 (pp. 11-14; 364)
- Investigator request of 8/01/08 for IIRB approval of recruiting flyers (pp. 261)
- IIRB approval letter of 8/04/08 (p. 319)

The rationale for the proposed sample size and cluster configuration is presented in

[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 Applicable to Three Open Cab Airblast Applicator Studies." "V4" indicates Volume 4 of the AHETF submission, containing "Materials for AHETF Study AHE64." Most pages in both volumes bear more than one page number. All page references in this review to Volume 1 are to "page N of 240"; all page references to Volume 4 are to "page N of 429."

Volume 1, pp. 19-28.

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 are provided in Volume 1, pp. 60-87. Reports of interviews with experts knowledgeable about pesticide use on tree nut crops in Oklahoma are provided in Volume 1, p. 78.

B. Summary Assessment of the Scenario Design[2]

1. **Scenario Definition:** This protocol addresses the handler exposure scenario involving application of liquid pesticides to orchard and trellis crops using conventional airblast sprayers drawn by open-cab vehicles.

   The AHE64 protocol calls for open-cab airblast application of one of two surrogate insecticides to tree nuts (e.g., pecans) in Oklahoma. A total of 15 new Monitoring Units (MUs) are proposed for the open-cab airblast scenario; when the scenario is complete, the five (MUs) to be collected under this protocol will be

[2] Supporting details are in Attachment 1.

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combined in the AHED database with ten more to be collected under field study protocols AHE62 and AHE63, and with 15 others already collected in the 2003 study AHE07-A. 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 open-cab vehicles.

2. **Sampling Design:** The open-cab airblast scenario, as currently proposed, will involve three new clusters of MUs, 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 three new 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 MUs obtained from the earlier 2003 study reflect open-cab application to Georgia peaches, Idaho apples, and Florida citrus. The result of executing the first four steps of the first stage of the diversity selection process was the purposive choice of the following three crop/state combinations for the three proposed new monitoring sites:

   - Trellis crops in California (grapes)
   - Nut crops in Texas or Oklahoma (pecans)
   - Trellis crops in New York (grapes)

   Given the data already collected in AHE07-A, these choices are appropriate to cover the most important regional and agronomic variations in the use of open-cab airblast equipment. Of specific relevance to this protocol, Oklahoma includes 6% of all U.S. acreage where nut crops are grown, and will provide sufficient possible monitoring sites.

   The specific 'site' selected in which to conduct the study is Tulsa County, Oklahoma. According to an extension specialist at Oklahoma State University, Tulsa County and its adjacent counties (i.e., Creek and Okmulgee) are located in production areas where open cab applications are common. These counties are

typical of tree nut producing areas that utilize conventional open cab airblast equipment to maintain the orchards and probably provide enough acreage and growers to locate a suitable pool of eligible growers that can provide 5 MUs for monitoring airblast applicator exposure. The adjacent counties are also tree nut producing counties that can be contacted if suitable test conditions cannot be found in Tulsa County. This is an appropriate choice to efficiently achieve the desired diversity of equipment and scale.

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 the likelihood that samples will contain non-detectable residues. 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 three new 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 in the research and to spray their crop must be identified before their 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”

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Screening of growers for eligibility will continue until the working pool contains somewhat more growers with somewhat more workers than are needed to fill the five defined 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 county)—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 use differing spray equipment, and who expect to make open-cab airblast 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 define the pool of workers from which workers will be recruited to fill each of the five MU slots. If 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.

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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 that the workers actually sampled can be selected randomly.

3. **Choice of Surrogate Materials:** The surrogate chemicals proposed for this scenario are carbaryl and malathion, formulated in any of seven registered products. These pesticides have been successfully used in previous worker/handler exposure monitoring studies, are widely used on pecans, and have well established and reliable analytical methods. These are appropriate choices for this research

C. Summary Assessment of the Scientific Aspects of the Study Design[3]

1. **Statistical design:** This protocol describes collecting five Monitoring Units (MUs) reflecting the exposure of subjects making airblast applications to Oklahoma tree nut crops using open-cab vehicles. This is one of three new clusters defined for the scenario, each of which will include five MUs. The rationale for the 3 x 5 configuration of new clusters is presented in §4 of the scenario design (V1:19-28).

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 will only apply the pesticide; mixing and loading 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 if 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

    Seven registered products containing one of the two 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. All of these products will be mixed with water and loaded into the airblast spray tank by workers not participating in the study.

[3] Supporting details are in Attachment 2.

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During application and when adjusting or repairing equipment subjects will wear all personal protective equipment (PPE) required by the label, in accordance with the Worker Protection Standard (WPS).

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 or branches. However, individual behavior is also expected to affect exposure.

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 Limit of Quantification (LOQ) of the analytical methods, the AHETF is prepared to use half the LOQ or some other statistical method to estimate potential exposures.

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 open 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 and limbs. Residues in socks measured in earlier open-cab airblast studies have been very low (e.g., ≈0.1% of dermal exposure). Exposure to the applicator's feet 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 before 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 outer head patch consists of one layer of inner dosimeter material (fabricated from a one-piece, white, long-underwear union suit constructed of 100% cotton) measuring 50 cm^2, cut oversize to allow use of adhesive tape to hold the patch in place. The patch will be attached to the top of the applicator's chemical resistant

hat and will be worn throughout the monitoring period. At the end of the monitoring period the outer head patch will be carefully removed and trimmed to size (i.e., tape and excess material cut off) using acetone-cleaned scissors. All outer head patch samples will be wrapped in aluminum foil, placed in labelled, plastic bags, and placed into frozen storage.

The inner head patch consists of one layer of inner dosimeter material (same as the outer head patch) measuring 100 cm^2. Extra material is provided for attachment of strings running under the chin of the subject to hold the patch in place. The patch will be worn on the crown of the head, under the chemical resistant hat, throughout the monitoring period. At the end of the monitoring period the patch will be carefully removed and trimmed to size (i.e., strings and excess material cut off) using acetone-cleaned scissors. All inner head patch samples will be wrapped in aluminum foil, placed in labelled plastic bags, and placed into frozen storage.

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 using standard forms and following an established SOP, 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

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covering all monitoring conducted under the open-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 to 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 all applicable scientific standards, including the following elements:

- Scientific objective
- Experimental design for achieving objectives
- Quantification of the test materials
- 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 protocol addresses the technical aspects provided in the applicable exposure monitoring guidelines (i.e., Series 875 Group A and OECD Applicator Guidelines) as well as Good Laboratory Practices (GLPs).

E. Summary Assessment of Ethical Aspects of the Proposed Research[4]

1. **Societal Value of Proposed Research:** The objective of this study is to determine the potential exposure for workers making open-cab airblast applications in Oklahoma nut crops. 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 open-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 of other new field studies proposed for this

[4] Supporting details are in Attachment 2.

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scenario and selected data from an AHETF study completed in 2003 (AHE07-A) 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 growers in Tulsa County and possibly adjacent counties who are identified as "commercial producers [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 open-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 nut crops in Oklahoma.

   Inclusion factors listed in the protocol are appropriate, but reflect careless editing. The fourth criterion is a vague generic version of the study-specific final criterion, and should be deleted. In addition, the reference to "vines" should be removed. The protocol exclusion factors are appropriate, but also reflect careless editing. One of the two duplicate criteria should be deleted. The eligibility factors listed in the Consent Form differ from those in the protocol in possibly important ways—for example, by calling for recent experience in making open-cab airblast application, but not requiring recent experience using the same equipment to be used in the study, as is specified in the protocol. These discrepancies should be harmonized before the research goes forward.

   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 (V4:240:255). 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 either carbaryl or malathion; both are fully tested and well understood. Individual growers will choose from a list of seven 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 nut crops using open-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 FL. 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 (V4:67). As this study will not be conducted in California, inclusion of the Experimental Subject's Bill of Rights is not necessary. EPA assessments of compliance with the requirements of 40 CFR §26.1116 and §26.1117 appear in Attachments 4 and 5 to this review.

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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.

- Harmonize the lists of eligibility factors in the protocol and the consent form.

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.

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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 Open-Cab Airblast Scenario Design dated August 14, 2008
2. Summary Review of Protocol AHE64 dated August 8, 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

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EPA Scenario Review: AHETF Open-Cab Air Blast Scenario

Title: **Open-Cab Airblast Applicator Scenario Sampling Plan:** pp. 8-58 in AHETF Volume 1: General Information Applicable to Three Open-Cab Airblast Applicator Studies

Date: 14 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 open-cab tractors." (V1:11)

"This scenario has some existing exposure data that are suitable for a generic database:

- One cluster of 5 MUs spraying peaches
- One cluster of 6 MUs spraying apples
- One cluster of 4 MUs spraying citrus" (V1:11-12)

"The following three crop type/state combinations and MU numbers are proposed for this scenario that will provide the desired diversity in crop and geography for the entire data set:

- Nut crops in Texas or Oklahoma (e.g., pecans) – 5 MUs
- Trellis crops in California (e.g., grapes) – 5 MUs
- Trellis crops in New York (e.g., grapes) – 5 MUs" (V1:14)

(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?

"Since this scenario contains some existing exposure data that are suitable for a generic database, the scenario design involves examination of the existing data and a proposal to obtain sufficient additional MUs to meet the two standard scenario objectives: for data to provide a 3-fold level of accuracy in normalized exposure estimates and to provide sufficient power to distinguish a proportional from an independent relationship between dermal exposure and the amount of active ingredient handled (AaiH), the normalizing factor.

"The Joint Regulatory Committee (JRC; comprised of EPA, California Department of Pesticide Registration [CDPR], Pest Management Regulatory Agency of Canada

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[PMRA], and the U.S. Department of Agriculture [USDA]) has identified one study (AHE07-A) that includes open cab airblast application data that are suitable for a generic database, consisting of:

- One cluster of 5 MUs (all unique workers) spraying peaches
- One cluster of 6 MUs (all unique workers) spraying apples
- One cluster of 4 MUs (all unique workers) spraying citrus

"Based on the simulation procedures described in Appendix C of the Governing Document (AHETF, 2008), three new clusters with 5 MUs per cluster are needed to supplement the data from study AHE07-A. Since the range in AaiH from this study was narrow, meeting the secondary objective (evaluating the relationship between exposure and AaiH) will require more additional data than the primary objective (accuracy of normalized exposure estimates). This configuration of new MUs slightly exceeds the benchmark objectives for the scenario. As a result, these 15 new MUs in 3 clusters (together with the 15 MUs in the 3 existing clusters) should provide sufficient power to distinguish proportionality from independence for the secondary objective, even if an MU or two are not obtained for some unforeseen reason." (V1:11-12)

"AHETF 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 open cab airblast application of liquid sprays comprise PHED Scenario 11 –Airblast Application, Open Cab (APPL). Data within that scenario were graded by EPA as "High Confidence" for the "No Clothes", "Single Layer, No Gloves", and "Single Layer, Gloves" clothing scenarios. The inhalation exposure data are also graded as "High Confidence". In the AHETF detailed review of these PHED data (Exponent, 2007), one study was found that meets the technical acceptance criteria established by AHETF (identified as Study 460). However, this is part of the same study that AHETF reviewed for acceptability in 2003 (AH502-A). During that review, AHETF and the JRC agreed the entire study (that included data for open and closed cab airblast situations) should not be accepted due primarily to high limits of detection (LODs) and many samples with residues below the LOD. Further examination of that study indicates the open cab data do technically meet the AHETF acceptance criteria. Briefly, that is because the contribution of non-detectable residues (mainly to the hands where all samples were below the high LOD of 40 μg) to total exposure is low (below 3%) due to high residues found on head samples. Nevertheless, the preponderance of such approximated exposure values reduces the value of the data.

"In addition to the large number of non-detectable residues, these data have other limitations:

- The amount of active ingredient handled by workers is quite low and has a very narrow range (2.34-3.75 lbs).

- There is repeated use of the same worker.

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- The examination of dermal exposure values shows extremely large differences between AM-conducted MUs and PM-conducted MUs. Not only does this raise the possibility of experimental problems, but the extreme clustering also reduces the 12 MUs in this study down to an effective sample size of only 2 MUs.

"None of these limitations, in isolation, would necessarily make these data unacceptable. However, when taken together, these 12 MUs are of dubious quality and would result in little, if any, reduction in the number of new MUs needed. As a result, both the AHETF and the JRC agree this study is not useful for a modern generic database.

"AHETF, in conjunction with the JRC, reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that could satisfy current acceptability criteria and qualify for inclusion in a generic database. For this particular scenario, the JRC reviewed seven open cab airblast application studies and agreed that none of the studies should be recommended for the new 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 sufficient additional new data for this open cab airblast application scenario to meet the scientific objectives outlined in the Governing Document. ." (V1:17-18)

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 primarily impacted by airborne aerosols for open cab situations and also believe that overhead spraying will be an important parameter influencing exposure. Another potentially important route of dermal exposure is contact with contaminated equipment such as the sprayer and vehicle. 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 of which are treated with open cab airblast sprayers." (V1:31)

"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

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types can be defined in terms of states that account for 3% or more of the total crop type acreage." (V1:34)

"It is desirable that at least one cluster be located in each of [the five crop-type strata defined in Table 5.] The three existing clusters of MUs from AHE07-A do cover three of the five crop types: citrus (FL), stone fruit (GA), and pome fruit (ID). Note that in the last cluster, Idaho is not a 'predominant state' of the pome fruit growing area. This is not a problem since restriction to the predominant states is only relevant for new clusters. It should also be emphasized that relative crop acreage data are used only as a guide to identifying locations where open cab airblast applications are probably common. Acreages are not 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 open 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. Before specific study sites are chosen, discussions with local agricultural experts are used to delineate those areas of the selected state where the scenario of interest does occur." (V1:36)

"Geographic Stratification: . . . 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." (V1: 36-37)

"The existing data provide diversity that need only be augmented by selection of three new state/crop-types. The diversity selection goal is that the final set of six clusters be different with respect to crop type or region, or both." (V1:38)

"The following combinations were purposively selected to provide open cab airblast scenario MUs for the three new clusters.

1. Nut Crops / Texas or Oklahoma

"This combination was chosen to obtain an unused crop type (nut crops) and to provide additional geographic diversity (note that GA has already been utilized and CA, the state with the most nut production, is being reserved for trellis crops; see below). This cluster will provide MUs characterized by tall orchard crops. Texas and Oklahoma reflect a hot, dry, and often windy climate in the central southern U.S. (EPA Regions VI or VIII).

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2. Trellis Crops / California

"This trellis crop combination was chosen to obtain the remaining unused crop type (trellis crops). California was selected because it has the dominant acreage for trellis crops (77%) and, therefore, will possess an abundance of possible monitoring sites. California reflects a hot and dry climate in the western U.S. (EPA Region X).

3. Trellis Crops / New York

"'Trellis crops' was chosen to be represented by two clusters because it can provide two diverse clusters within the same crop group. There is obvious geographic diversity between California and New York. In addition, juice grape varieties will be selected in New York which are much less common in the western regions. Finally, discussions with local experts indicate the likelihood of finding sufficient open cab sprayers in New York is good. New York reflects a climate that ranges from cool to hot and humid (EPA Region I)." (V1:40)

"**Selection of Specific Monitoring Sites for Each Study:** The final step for selecting new monitoring 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., monitoring 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.

"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 Contract Research Organizations that are hired to conduct the worker exposure monitoring in the field." (V1:41-42)

"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 sections 4.4 and 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 is true). Within-cluster diversification of AaiH will be accomplished by following the standard approach of partitioning the practical AaiH range into strata. Since there will be 5 MUs per new cluster, AaiH will be stratified into the following 5 ranges:

- 5 to 9 pounds ai handled
- 10 to 17 pounds ai handled
- 18 to 30 pounds ai handled

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- 31 to 55 pounds ai handled
- 56 to 100 pounds ai handled

"All five strata are of equal width on the log AaiH scale. Within each new cluster an attempt will be made to obtain a single MU from each of the five strata." (V1:43)

(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: 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).

1. Assemble a list of growers from all of the resources contacted and eliminate any duplicates.

2. Put the list of growers into random order.

3. Contact growers, one at a time, following the random order, and determine whether the grower is 'eligible' to participate. . . .

4. 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. . . .

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"This process results in a random sample of eligible growers and, by association, a random pool of potential workers associated with eligible growers." (V1:44-46)

"AHETF researchers will contact local resources from each of the following categories in Tulsa County and possibly adjacent counties:

- Experts who may serve as Local Site Coordinator (LCS)
- Commercial Applicator Firms that service tree fruit crops
- University Agricultural Researchers / County Extension Agents
- Crop Consultants (e.g., pest control advisors or commercial applicators) that service tree fruit crops
- Chemical Dealers or Sales Representatives
- Tree nut 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 Tulsa County and possibly adjacent counties who are commercial producers of tree nut crops (e.g., pecans) and 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. Over-recruitment will be practiced wherever and whenever possible. This pool will include more growers and more workers than are ultimately needed for the study." (V4:37-39)

(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 be more likely to arise.

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(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 open 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. Nearly all airblast sprayers are fundamentally the same, although a variety of sprayer sizes and configurations exist.

"One of the most important variables affecting worker exposure is the presence or absence of a cab. Airblast sprayers can be pulled or hauled by open or closed cab vehicles and AHETF will address these two situations as separate scenarios. The scenario described in this document addresses only the open cab configuration that is expected to result in higher dermal and inhalation exposures since there is no barrier to protect the worker from exposure during spraying. More specifically, this scenario will include airblast sprayers pulled by tractors with no cab (however, a windshield and/or canopy are acceptable since these are very common, especially in warm climates)." (V1:14)

"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." (V1:49)

"AHETF experts agree that exposure potential will be primarily impacted by airborne aerosols for open cab situations and also believe that overhead spraying will be an important parameter influencing exposure. Another potentially important route of dermal exposure is contact with contaminated equipment such as the sprayer and vehicle." (V1:31)

"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, and do not violate the product label requirements. 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." (V1:48)

(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). Nationwide, the following consensus from experts was clear: In trellis crops, several experts indicated dormant applications are rarely made; others indicated just one

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was made per season. By contrast, several foliar applications are typically made throughout the season depending on disease or insect pressure.

"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." (V1:15)

"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 as much overhead exposure, this plan will restrict MUs involving trellis crops to situations that do not generally 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." (V1:33)

"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. Mist blowers produce droplets that are finer than most other sprayers and are used for low volume applications. The other sprayer types are more similar to ground boom sprayers in that there is no air "blast" that helps force the spray into the foliage. However, they may include small fans or directed airstreams that assist with carrying spray droplets toward the target crop. Discussions with a variety of agricultural experts in several areas of the country indicate 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." (V1:50)

3. Are the proposed test materials appropriate surrogates?

"The following active ingredients are approved for use on orchards and trellis crops, meet the desired PPE requirements listed above, and will be considered for use in this open-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)

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"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." (V1:52-53)

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

"Appendix C of the Governing Document describes the simulation methodology needed to calculate sample sizes when the reference model used is cluster sampling from a lognormal distribution. These simulations determine either accuracy or power given the number and configuration of MUs. When there is no existing data, the simulations only consider new MU configurations. However, for this scenario, the simulations now require that the structure of the existing MUs be held constant and only the number of new MUs is varied. Regardless, it is still the combination of existing and new MUs that must satisfy the benchmark objectives:

1. Primary Objective: Estimates of the geometric mean, the arithmetic mean, and the 95th percentile of normalized dermal exposure generally needs to be accurate to within approximately 3-fold of the actual population value if the reference random sampling model applies.

2. Secondary Objective: There should be at least 80% statistical power to distinguish complete proportionality from complete independence between dermal exposure and AaiH (the normalizing factor for this scenario)." (V1:24-25)

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EPA Protocol Review: AHE64: Open-Cab Airblast Application to Oklahoma Tree Nuts

Title: Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Open Cab Equipment in Oklahoma Tree Nuts

Revision Date: August 8, 2008

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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 open cab airblast applications in Oklahoma tree nuts (e.g., pecans)." (V4:19)

[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.

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

This study will provide a partial answer to the question of what dermal and inhalation exposures are likely for applicators using conventional airblast equipment and open-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?

In conjunction with the results of study AHE07-A conducted in 2003 and other field studies planned for this scenario, EPA will use the results of this study to estimate the dermal and inhalation exposure likely for future applicator-days for a wide range of agricultural pesticides applied by conventional air-blast sprayers drawn by open-cab tractors.

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

"AHETF 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 addition to the large number of non-detectable residues, these data have other limitations:

- The amount of active ingredient handled by workers is quite low and has a very narrow range (2.34-3.75 lbs).
- There is repeated use of the same worker.
- The examination of dermal exposure values shows extremely large differences between AM-conducted MUs and PM-conducted MUs. Not only does this raise the possibility of experimental problems, but the extreme clustering also reduces the 12 MUs in this study down to an effective sample size of only 2 MUs.

"None of these limitations, in isolation, would necessarily make these data unacceptable. However, when taken together, these 12 MUs are of dubious quality and would result in little, if any, reduction in the number of new MUs needed. As a result, both the AHETF and the JRC agree this study is not useful for a modern generic database.

"AHETF, in conjunction with the JRC, reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that could satisfy current acceptability criteria and qualify for inclusion in a generic database. For this particular scenario, the JRC reviewed seven open cab airblast application studies and agreed that none of the studies should be recommended for the new 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

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(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 sufficient additional new data for this open cab airblast application scenario to meet the scientific objectives outlined in the Governing Document." (V1:17-18)

(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 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 agreed 3-fold accuracy is an appropriate benchmark for this scenario." (V1:23)

"The objective of this study is to develop data to determine the potential exposure for workers making open-cab airblast applications in Oklahoma tree nuts (e.g., pecans)." (V4:19)

No explicit hypothesis is stated, nor is the study 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?

"Table 3 summarizes the results of simulations specifying:

- 3 clusters with the number of MUs and the AaiH levels used in study AHE07-A, plus

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- 2 or 3 additional clusters with 5 MUs per cluster and AaiH levels for each MU selected from different AaiH strata

"The primary objective requires that all relative accuracies be 3-fold or less. This objective appears to be satisfied by two new clusters of 5 MUs each. This is not surprising since this configuration is quite close to the standard sample size configuration when there is no existing data (five 5-MU clusters). Obviously, the use of 3 additional 5-MU clusters will also satisfy the primary objective.

"However, because the existing clusters have limited ranges of AaiH, the secondary objective is more difficult to satisfy. With only 2 new clusters the power of a two-sided test for proportionality is only 0.70. A one-sided test is expected to achieve a power of 0.81. However, most users of these data are more likely to use two-sided regression tests. The use of 3 new clusters with 5-MUs each is expected to achieve a two-sided power of 0.85.

"Consequently, between these two choices, the use of 3 new 5-MU clusters is preferred." (V1:26-28)

(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." (V1:46)

"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

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- No more than 2 MUs from any one grower (this effectively requires at least 3 different growers since 5 MUs are desired)
- No worker may be used more than once
- No piece of equipment (tractor plus sprayer) may be used more than once" (V4:40-41)

(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.'" (V1:55)

(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." (V1:55)

"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 (from both existing and new MUs) 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. Details of these calculations are provided in Appendix C of the Governing Document.

"This primary benchmark objective strictly applies to only dermal exposure. However, for uniformity, the 95 percent bounds on the three parameters will also be computed for inhalation exposure." (V1:55-56)

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

Yes.

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(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 open-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 open 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 β=0. This benchmark objective requires that the number of clusters and the allocation of AaiH levels to MUs should be adequate to ensure that the regression analysis has at least 80% power to reject the hypothesis that β=0 when β is actually equal to one. By symmetry, the mixed model linear regression would also have the same power to reject the hypothesis that β=1 when β=0. This is the precise meaning of being able to 'discriminate between proportionality and independence'." (V1:56)

2.2 How and to what will human subjects be exposed?

The open cab airblast scenario program will monitor instances of worker exposure resulting from the airblast application of pesticides to tree nuts in Oklahoma.

"The short duration of study participation for a subject (generally only one day) limits the risk of toxicity from surrogate chemicals to acute toxic effects (i.e., the potential for chronic effects is negligible). The active ingredients proposed for use in this study have been reviewed to determine the relative acute toxicity risks and status of reregistration at EPA. This study could involve either of two active ingredients: carbaryl or malathion.

"The pesticide products containing these active ingredients and potentially used in this study are currently registered for airblast applications to pecans. AHETF will only monitor workers making applications in accordance with all label and Worker Protection Standard (WPS) requirements." (V4:25)

Calculated Margins of Exposure (MOEs) for combined dermal and inhalation exposure for the highest amount of active ingredient that will be handled in this scenario (100 lb ai/day) range from 152 to 1361. (V4:25)

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(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." (V1:51)

"The following active ingredients are approved for use on orchards and trellis crops, meet the desired PPE requirements listed above, and will be considered for use in this open 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)

"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." (V1:52-53)

(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." (V1:42)

"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

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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" (V1:43)

"A single MU will be conducted in this study from each of the five strata." (V4:45)

(c) What duration of exposure is proposed?

"Duration of monitoring is another parameter that could vary between MUs, especially since the AaiH levels within new clusters 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." (V1:48-49)

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 below and in SOP AHETF-10.E and identified and described in SOP AHETF-8.F." (V4:46)

"For this study, inner dosimeters will be cut into two sections after collection." (V4:46)

"2.1 Upon completion of the monitoring period, the worker shall return to the appropriate staging area. Research personnel collecting dosimetry samples must change their disposable gloves (latex, vinyl, etc...) between each sample collected described as follows.

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"2.2 The research personnel will check the air pump flow rate using equipment and techniques described in SOPs 8.D and 10.A. The air sample will be collected according to SOP 8.D, and the air pump and lines removed from the worker.

"2.3 The worker will then remove their own personal protective equipment (PPE), which may include chemical-resistant (CR) gloves, a respirator, glasses, hat or CR headgear. This headgear may contain head patch samples. If inner head patches were utilized during the study, the researcher will remove the inner head patch according to SOP 8.H.

"2.4 If head patches were utilized in the study, the outer head patch will be collected by research personnel, according to SOP 8.H., after the worker removes their headgear.

"2.5 The worker will then remove any body PPE (e.g., apron, coveralls, or gloves) and their shoes, then the worker may enter the clean, private area where they will remove their outer work clothes and socks.

"2.6 If no sock dosimeters were used on the study, skip to section 2.7 and collect a hand wash sample. Otherwise, upon removal of outer garments (shirt, then pants, then outer socks) by the worker, the researcher will remove the sock dosimeters, according to SOP 8.I.

"2.7 Immediately after the worker has removed his outer clothing and if the socks dosimeters (if used) have been collected, the researcher will collect hand wash samples, according to SOP 8.B.

"2.8 After collection of hand washes, the researcher will collect face/neck wipe samples, according to SOP 8.C.

"2.9 After collection of the face/neck wipes, the researcher will remove the inner dosimeter from the worker and process it, according to SOP 8.A."
(SOP AHETF-10.E.2, 3/8/08)

SOP AHETF-8.F.5, 8/31/08, defines procedures to uniquely identify field samples.

(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.

"Full details regarding field recovery evaluation procedures for all sampling media are given in the most recent version of SOP AHETF-8.E. The SOP instructions for

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the "by vial" spiking using active ingredient (ai) in an organic solvent will be followed for all matrices except OVS tubes. The tubes will be spiked at the laboratory with the proper amount of analytical standard.

"In addition, on each fortification day, duplicate samples of the inner dosimeters fortified in the field at the highest level, and duplicate OVS tubes fortified in the laboratory at the next-to-highest fortification level, will be processed in the field for immediate frozen storage and used as travel spikes. These travel spikes will be analyzed only if deemed necessary by the Study Director, for example to help determine the cause of unusually low field fortification recovery results.

"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. All field fortification and untreated control samples will be identified as described in SOP AHETF-11.F" (V4:47)

(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 unit(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." (V4:54)

(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.

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All field fortification and untreated control samples will be identified as described in SOP AHETF-11.F" (V4:47)

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

3. Subject Selection

3.1 Representativeness of Sample

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

"Collectively, the complete open cab airblast scenario data set will include instances of worker exposure resulting from the airblast application of pesticides from existing or new studies. 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 are 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 open cab airblast application-days derived from both selected and constructed conditions." (V1:19)

(b) From what populations will subjects be recruited?

Subjects will be recruited among the employees of growers in Tulsa County and possibly in surrounding counties, who are identified as "commercial producers of tree nuts (e.g., pecans) [who] might utilize airblast equipment in their operations" (V4:37) and who meet AHETF criteria for participation.

(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 open-cab airblast

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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 Oklahoma tree nuts.

(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

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- Are employed by a pesticide manufacturer or a contractor to AHETF" (V4:22-23)

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

None.

(d) 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.

(e) 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 open 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." (V4:40)

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(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." (V4:39-40)

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?

"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." (V4:23)

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

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

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(d) How and when would subjects be paid?

Subjects will be paid in cash, immediately after their participation.

4. Risks to Subjects

4.1 Risk characterization

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

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

"This study could involve either of two active ingredients: carbaryl or malathion. The pesticide products containing these active ingredients and potentially used in this study are currently registered for airblast applications to tree nuts (e.g., pecans). 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." (V4:25)

(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, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation. AHETF has

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adopted an extensive program to minimize these risks. All of the risk minimization procedures, as described in AHETF SOPs, will be followed during the conduct of the study." (V4:23-24)

Each of the six identified kinds of risk is discussed in V4:24-32.

"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/malathion] product is classified as [low/moderate] toxicity for exposure by mouth, by skin, and by breathing. Signs and symptoms of too much short-term exposure include moderate eye irritation, slight skin irritation, [possible allergic skin reaction,] 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." (V4:70, 72, 74, 76, 78, 80, 82 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

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- Ensuring that all tank mix products are used according to approved label(s) and do not require any additional PPE." (V4:31-32)

Additional risk reduction actions specific to each of the six identified kinds of risk are discussed in V4:24-32.

(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 levels 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." (V4:25)

Calculated combined MOEs range from 152 to 1361. (V4:25)

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

"Since open cab workers are exposed to ambient conditions, AHETF will monitor ambient conditions to determine the heat index and base monitoring decisions on the heat index. A heat index of 120^{o}F (adjusted for direct sunlight, if applicable) is the cutoff or stop work point. When the heat index cutoff is reached or exceeded the Study Director or other researcher shall stop the monitoring and move the worker to a cooler environment until monitoring can be resumed. In addition to the procedures discussed above, it is possible that some monitoring will take place at night or early in the morning to avoid excessively hot and humid conditions. AHETF will encourage this if it is a common practice at the field sites selected and when daytime conditions are expected to approach the heat index cutoff of 120º F (adjusted for direct sun, if applicable)." (V4:24-25)

(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." (V4:62)

SOP AHETF-11.H defines procedures to be followed if a subject in an AHETF study requires emergency medical attention.

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(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)." (V4:36)

(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

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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." (V4:62-63)

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." (V4:32)

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 open 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 open-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." (V4:32)
There are, indeed, existing data suitable for use in a generic database describing the exposure of open-cab airblast application workers. Nonetheless, society is likely to benefit from the use of the data generated by the study in EPA risk assessments.

(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." (V4:32)

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

Identified societal benefits are likely to be realized.

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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. A wide variety of experts consulted by AHETF reported that airblast applications are common in both orchard and vineyards across the country. Exposure data for this scenario meeting contemporary standards of reliability and quality will likely provide a significant benefit to society. Because the margins of exposure (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." (V4:32-33)

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.

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(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.)" (V4:21-22)

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. See also Attachment 5.

(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. See also Attachment 4.

(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 candidates who cannot read the consent form in English or Spanish.

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

See §6 of SOP AHETF-11.B.2 (V4:244-247)

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(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; V4:248-249. The form is at V4:253-254)

(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

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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; V4:247-249)

(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." (V4:39-40)

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." (V4:33)

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"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." (V4:63)

(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)." (V4:33)

"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." (V4:64)

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

"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 duties on the day of the study. Your alternative is to not take part." (V4:64)

"If you withdraw, the long underwear, head patch, 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." (V4:64)

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§ 26.1111 Criteria for IRB approval of research
AHETF Protocol AHE64: Oklahoma Pecans: 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	

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§26.1116 General requirements for informed consent
AHETF Protocol AHE64: Oklahoma Pecans: 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 AHE64: Oklahoma Pecans: 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	

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40 CFR 26.1125 Prior submission of proposed human research for EPA review
AHETF Protocol AHE64: Oklahoma Pecans: 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 • 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	V4:16-56; 143-195; 264-304; 317-357 V4:58-84
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y Y Y N n/a	V4:367-372 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	V4: 11-14; 130-141; 258; 261-262; 314-316; 360-365
	(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y	IIRB roster and credentials on file with EPA.
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		Y	V2: 269-310; V3:265-306
	(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	V4:23-32
		(2) The measures proposed to minimize risks to the human subjects;	Y	V4:23-32
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	V4:32-33
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	V1:15
		(5) The balance of risks and benefits of the proposed research.	Y	V4:32-33
	§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 V4:197-221, 307-311 Approved V4:58-84, 88-124
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	V1:39-40; V4:23, 39-41; 84; 123; 240-255; 307; 309
	§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	V4:39-41; 240-255
	§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	V4:11-14

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