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

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

December 30, 2011

MEMORANDUM

SUBJECT: Science and Ethics Review of AHETF Scenario Design and Protocol AHE600 for Exposure Monitoring of Workers during Mixing, Loading and Application of Pesticides in Managed Horticultural Facilities using Powered Handgun Equipment

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REF: Collier, R. (2011) Mixing, Loading and Application of Pesticides in Managed Horticultural Facilities using Powered Handgun Equipment. Unpublished protocol dated October 24, 2011, prepared for the Agricultural Handler Exposure Task Force under Sponsor ID AHE600, 474 p.

We have reviewed the referenced proposal from both scientific and ethics perspectives. Scientific aspects of the proposed research are assessed in terms of the recommendations of the EPA Guidelines Series 875 and of the EPA Human Studies Review Board (HSRB). 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 HSRB. Below is a summary of the conclusions reached in our science and ethics reviews.

Science Review

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

- Please make the following revision to the protocol before proceeding with the research:

    - EPA anticipates that wettable powder formulations may result in higher inhalation exposures. As such, EPA requests that a wettable powder formulation (e.g., permethrin or sulfur) be used by one participant in each of the clusters for this scenario. SR5 and the formulation sub bullet for SR6 should be revised accordingly.

Ethics Review

- The protocol meets the applicable ethical requirements of 40 CFR part 26, subparts K and L.

- Please make the following revisions in future protocol submissions:

    - In the protocol, please revise the discussion of the "psychological risks" to identify the risk of a breach of confidentiality associated with photographs or video as a potential psychological risk of study participation. Please also clarify that the most significant psychological risk associated with pregnancy testing is the unwanted disclosure of test results, rather than embarrassment associated with administration of the test.

    - In the consent form, please list the risks of breach of confidentiality (related to unwanted disclosure of pregnancy test results, photographs, and videos) in the section titled "Risks and Discomforts."

    - In the protocol, please describe the types of locations where recruitment discussions between researchers and potential subjects will take place. Specifically, please clarify whether these discussions will take place at the work site or at locations that are away from the work site. It is preferable for these discussions to take place away from the work site, to minimize the potential for coercion.

    - As recommended in the HSRB's report dated March 17, 2011, please revise SOP AHETF-11.H.3 to include criteria for decision-making capacity as guidance for medical professionals who will perform this function in AHETF research.

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.

B. Summary Assessment of the Scenario Design[1]

1. **Scenario Design:** Protocol AHE600 is designed to address the dermal and inhalation exposure of handlers using powered (gasoline or electric) handgun/handwand equipment in greenhouses and nurseries. Participants will use the equipment to treat ornamentals and nonbearing fruit trees in nurseries. Participants may also treat ornamentals and vegetables grown in greenhouses. The spray pattern shall include downward, outward and upward directions. The scenario will also include the task of mixing and loading liquid and solid formulations. Aside from the mixing loading component, this scenario is similar to the handgun component of Protocol AHE400 (Rights of Way) reviewed by the Board in October 2010. That is, handlers will apply surrogate pesticides to the foliage of crops in a variety of directions using handguns connected to long hoses. Conceptually, the difference between the two scenarios, with respect to potential impact on exposure (during application) may be due to the organized structure of plants grown in greenhouses and nurseries compared to the unorganized structure of plants growing in Rights of Ways. Another key difference is the degree of openness and enclosure. This scenario will include treatments made in greenhouses and open and quasi-enclosed environments (e.g., shade or lath houses) in nursery settings.

   The handler attire for this scenario is expected to consist of long-sleeved shirts, long pants, shoes plus socks. The minimum amount of PPE worn by participants will be chemical resistant gloves. However, additional PPE may be needed depending on end use product labeling directions for mixing/loading which may require chemical-resistant aprons. Chemical-resistant headgear will be worn when participants make overhead treatments. Patches placed inside and outside of the headgear will be employed to estimate dermal exposure of the protected portions of the body covered by these garments. Some surrogate pesticide labels may require chemical-resistant aprons to be worn by participants during mixing and loading. Since the majority of dermal exposure will result from the application component of this scenario, we do not believe this will adversely impact the results.

   This scenario will consist of all new data because there are no existing data that meet the AHETF's criteria for inclusion in the Agricultural Handlers Exposure Database (AHED). Due to the diversity of application sites, it is expected that handler exposure for this scenario will be highly variable. Therefore, to estimate number of monitoring units (MUs) required, a geometric standard deviation (GSD) of 5 was used rather than a GSD of 4 when running simulations to determine the sample size. The AHETF has selected a ten by three study design (cluster by MUs, respectively) for a total of 30 MUs.

   The definition of the clusters (i.e., monitoring areas) for this scenario can be contiguous counties in portions of states such as southern Florida or contiguous counties in adjoining states such as the proposed Ohio-Pennsylvania monitoring area or non-contiguous

[1] Supporting details are in Attachment 1.

counties having greenhouses and nurseries in a given geographic region (e.g., eastern Texas and Louisiana). The clusters are shown in Figure 1.

Figure 1: Clusters/Monitoring Areas for AHE600

EPA intends to use these data to estimate daily dermal and inhalation exposures of pesticide handlers mixing/loading and applying sprayable pesticides formulated as liquids or solids using powered hand gun equipment. It is EPA's view that dermal exposure will be dominated by the application of the pesticide and that the contribution of the mixing/loading component will be minimal. Thus, the occasional donning of aprons by participants for this task is not likely to impact the dermal exposure measures. However, for the inhalation route, it is possible that the use of the wettable powder formulation may result in increased inhalation exposure. Therefore, the similarity restrictions should account for the use of a wettable powder by at least one participant per monitoring area (i.e., cluster).

EPA anticipates that wettable powder formulations may result in higher inhalation exposures. As such, EPA requests that a wettable powder formulation (e.g., permethrin or sulfur) be used by one participant in each of the clusters for this scenario.

2. Sampling Design:

Ten new clusters (monitoring areas) each having 3 monitoring units (MUs) have been proposed for this scenario. Each monitoring area consists of a distinct group of counties representing a wide variety of geographical and climactic conditions. The monitoring areas were selected by considering the following sources:

- An AHETF-conducted site visit of nurseries and greenhouses (including interviews)
- An AHETF-conducted survey of growers operating ornamental greenhouses and nurseries in six states representing distinct growing areas
- An AHETF-conducted survey of growers operating vegetable greenhouses in important growing areas of US and Canada
- The USDA National Agricultural Statistics Service (NASS): 2007 Census of Agriculture and the Agricultural Chemical Usage 2009, Nursery and Floriculture Summary

The AHETF has purposively selected the following monitoring areas. Specific counties in each region on a state by state basis are presented in Attachment 1 of AHETF's protocol submission.

Proposed Study Monitoring Areas		
		Region/Climatic Description
1	Lower New England	NY, MA, CT and RI/Maritime with warm to cool, humid summers and mild to cold winters
2	Mid-Atlantic	PA, NJ, DE and MD/Warm and humid summers, mild winters
3	North Carolina – South Carolina - Tennessee	Western NC, northwestern SC and eastern TN/warm humid summers and mild winters. Cooler summers and cold winters at higher elevations
4	Northern Florida	Northern 2/3rd of the state/warm and humid summers and mild winters
5	Southern Florida	Southern 1/3rd of the state/moist tropical conditions
6	Ohio – Pennsylvania	Eastern OH and western PA/warm to cool, humid summers, mild to cold winters
7	Indiana - Michigan	Southern MI and northern ID/warm to cool, humid summers and mild to cold winters
8	Illinois – Wisconsin	Northern IL and southern WI/warm to cool, humid summers and mild to cold winters
9	Louisiana – Texas	Eastern TX and western LA/warm humid summers and mild winters
10	Oregon – Washington	Western areas of both OR and WA/Maritime with warm, humid summers and mild winters

EPA agrees that these monitoring areas are likely to provide a wide range of climates and a wide variety of plant materials to be treated. Having such broad areas also increases the likelihood of identifying participants and meeting the AHETFs similarity restrictions. This scenario addresses the exposures of both mixing/loading and making pesticide applications.

After the monitoring areas are identified, the next stage of the diversity selection process involves delineating the practical range of amount of active ingredient handled (AaiH)

that could be handled in a minimum two hour monitoring period. As discussed at the October 2011 HSRB meeting, there is generally no upper limit on the amount AaiH handled by a study participant. While the lower limit is imposed to ensure detectable residues, the upper limit should generally be considered as a guide and as a way to determine sample size and estimate participant exposure. Individuals handling more than 15 pounds would not be excluded from the study. However, for two surrogate chemicals (carbaryl and chlorothalonil), the upper AaiH limit is 4.8 pounds, in the middle stratum, and should not be exceeded based on risk (Margin Of Exposure) estimates. Three AaiH bands (strata) ranging from 0.5 to 15 pounds are proposed. They are as follows:

- 0.5 to 1.6 lbs AaiH
- Greater than 1.6 to 4.8 lbs AaiH
- Greater than 4.8 to 15 lbs AaiH

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 scenarios, growers who agree to cooperate with the research and to have their ornamentals or vegetables treated with any of surrogate pesticides must be identified before study participants can be recruited.

The AHETF process for identifying handler subjects recruited from ornamental and greenhouse (ornamental and vegetable) growers includes five steps:

- Contacting commercial list providers: Meister Media Worldwide, Moose River Media and Dun and Bradstreet
- Assembling a list of growers from all resources contacted and eliminating duplicates
- Putting the list of growers into random order
- Contact a random subsample from the list, one at a time, in the sequence of the randomized list, to determine whether the grower is 'eligible' to participate
- Placing eligible employers into a "working pool"

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

- The employer is willing to cooperate with the AHETF
- The employer has at least one handler with experience with handgun equipment
- The employer will permit AHETF to recruit their employee(s)
- The employer has sufficient acreage such that the minimum AaiH can be mixed/loaded and treated
- The employer can fill an AaiH stratum and is willing to use at least one of the surrogates

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

When selecting MUs, the following the AHETF have developed similarity restrictions (SR) to increase diversity within the cluster. Some SRs are intended to be enforced, others, while desirable, won't be strictly enforced.

- SR1. AHETF **prefers** that no two MUs in the same monitoring area handle AaiH from the same stratum
- SR2. No two MUs obtained for the same scenario can monitor the same worker
- SR3. No two MUs in the same monitoring area can have the same employer
- SR4. Since this scenario includes both greenhouses and nurseries, no two MUs can be based the same conditions in terms of openness or enclosure for each monitoring area.
- SR5. AHETF **prefers** that all three MUs in a given cluster not use the same formulation type (liquid or solid)*****
- SR6. AHETF has the following list of SRs that each pair of MU in a monitoring area **must differ by at least one** of the following by:
  - The facility type such as ornamental greenhouse, vegetable greenhouse or nursery
  - Mixing either directly into the spray tank or pre-mix then transfer to the spray tank.
  - Type of hose attachment (handgun or handwand). [AHETF recognizes that the term 'handgun' can vary but in general distinguishes the term handgun from handwand as follows: A handgun is spray device consisting of single or multiple nozzles in which the operator squeezes a 'trigger'. The handwand, while similar, has a long lightweight extension from the hose ending with a nozzle or cluster of nozzles that can be turned on with a trigger or a valve. In sum, they differ primarily by length]
  - The formulation type mixed (i.e., liquid or solid)*****
  - The predominant direction of spray during the monitoring period (downwards, outwards, or upwards)
  - The size of the surrogate pesticide product container
  - Whether or not equipment clean-up was performed after the application

* The AHETF assert that existing data suggest that mixing/loading a dry/solid formulation like a wettable powder or dry flowable may result in higher inhalation exposures. EPA agrees with the AHETF however our view is that this is particularly true with wettable powder formulations. EPA recommends that wettable powder formulation (e.g., permethrin and sulfur) be used by one participant in each of the clusters selected for this scenario. SR5 and the formulation sub bullet for SR6 should be revised accordingly.

The growers in the chosen configuration provide the pool of handlers from which handlers will be recruited to fill each of the three MU slots. If selected growers or handlers drop out as the time of the field study approaches, additional handlers appropriate to fill out the MU design may be recruitable from among those employed by

growers already in the working pool of eligible entities. If there are too few handlers available in the pool to complete a revised efficient configuration, the working pool can be expanded by approaching more growers from the original randomized list. If the original randomized list is exhausted without finding enough interested handlers to complete the field study design, another list will be generated. Alternatively, the AHETF may consider monitoring as soon as there is an eligible participant if recruitment proves to be difficult.

3. **Choice of Surrogate Materials:** The surrogate pesticides to be used in this study are fungicides and insecticides since the study design is of handlers treating the foliage of desirable crops and not weed control. These pesticides have a wide range of application rates that should help obtain the three AaiH strata in each monitoring area.

Surrogate Pesticide	Type of Pesticide	Restrictions on AaiH handled
Azoxystrobin	Insecticide	No
Carbaryl	Insecticide	Apply no more than 4.8 pounds per day
Chlorothalonil	Fungicide	Apply no more than 4.8 pounds per day
Fosetyl-al	Fungicide	No
Imidacloprid	Insecticide	No
Malathion	Insecticide	No
Permethrin	Insecticide	No
Sulfur	Fungicide/Miticide	No
Thiophanate-Methyl	Fungicide	No

C. Summary Assessment of the Scientific Aspects of the Study Design[2]

1. Statistical design and sample size determination:

There are no acceptable existing data for this scenario. The AHETF will collect 30 MUs based on a 10 cluster by three MU design.

Reference Distribution:
Sample sizes are determined by using a random sampling reference model which is reasonably close to the actual diversity selection process. Sample sizes that would be appropriate under the reference model are then assumed to be reasonable for the study.

The AHETF reference model assumes that:

• Normalized exposure is log-normally distributed with a known geometric standard deviation (GSD). This also means that the logarithm of normalized exposure is normally distributed with a known standard deviation SD=Log(GSD).

[2] Supporting details are in Attachment 2.

• There will be N_C new monitoring areas and N_M new MUs per area. The total number of new MUs in a scenario is, therefore, $N = N_C \times N_M$.

• There may be correlation between the (logarithm of) normalized exposures of MUs if they have been efficiently configured to form a single cluster in a monitoring area. This is referred to as intra-cluster correlation, or simply ICC.

Based on analyses of exposure from a number of available monitoring studies, Appendix C of the AHETF Governing Document derived a default relative variation structure consisting of a geometric standard deviation (GSD) of 4 and an intra-cluster correlation (ICC) of 0.3. AHETF increased the GSD from 4 to 5 based on the expected variability of the handler activities in these highly varied application sites. EPA agrees with this change.

The Number and Configuration of New MUs:

According to the AHETF it is less costly to keep the number of monitoring areas as small as possible and have a large number of MUs per area. However, designs with a smaller number of MUs per monitoring area are more likely to be attainable for all the areas selected. Therefore, the configuration size is restricted to $N_M=3$ for all new MUs.

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 accuracy or power given the number and configuration of MUs that can satisfy the benchmark objectives:

1. **Primary Objective**: Estimates of the geometric mean, the arithmetic mean, and the 95_{th} percentile of normalized dermal exposure generally need to be accurate to within approximately 3-fold of their actual population value assuming the reference random sampling model applies.
2. **Secondary Objective:** If the reference model was true, and AaiH is assumed to be the normalizing factor of interest for each scenario, there should be at least 80% statistical power to distinguish complete proportionality from complete independence between dermal exposure and AaiH.

The AHETF suggest that "for the secondary objective the power to detect proportionality between exposure and AaiH also depends on the particular values of AaiH used." For this scenario the practical AaiH range (0.5 to 15 lb ai/day) was partitioned into the following three strata:

• From 0.5 to 1.6 AaiH
• Greater than 1.6 to 4.8 AaiH
• Greater than 4.8 to 15 AaiH

There is approximately a 3.1 fold difference between the upper and lower bound having roughly equal widths on a log scale (for AaiH). Based on the AHETF's simulations for a

10 by 3 cluster/MU configuration, assuming proportionality as well as the assumed variation structure, 100 percent power was found for meeting the primary objective. Based on those assumptions and values, the secondary objective is expected to be met as well.

EPA is interested in the secondary objective of having enough power to be able to distinguish between independence and proportionality of exposure to AaiH. By incorporating this component of AaiH into AHETFs study designs, AHETF is acknowledging EPA's (and other regulatory agencies) preference to use AaiH as a normalizing factor. Regardless of whether proportionality can be detected in a given study, stratifying AaiH is certainly useful as a meta-factor for diversity selection of MUs.

2. **Proposed pattern of exposure:** The proposed minimum exposure duration for each MU was described as being at least 2 hours in duration involving mixing/loading and applying a maximum of 3 tank-loads. The 2 hour minimum is considered by the AHETF as a guideline rather than a requirement.

   Participants will conduct open mixing of surrogates either directly into the tank to be used for spraying or into a premix tank prior to pouring the premix into the tank to be used for spraying. The tank may be stationary or mobile (in some cases may be mounted on a vehicle). The handguns or handwands will generally be connected by long hoses to the tanks containing the finished spray. It is also possible that some participants will make the applications from a vehicle. The spray orientation for each MU will be directed to the foliage in predominantly downward, outward or upward patterns. Hose management will also be performed by the participant. Minor clean-up consisting of draining, flushing and rinsing the equipment (as well as containers) may be performed if it is the participant's normal work practice to do so.

   There are nine surrogate pesticide active ingredients available for this scenario. A cooperating grower may choose to use any of them for a specific MU. However, only two are reportedly available as wettable powders. EPA recommends that at least one MU use a wettable powder in each of the 10 clusters.

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

   Dermal exposure will be measured by using a whole body dosimeter (WBD) which is to be worn beneath the subject's outer clothing. After the monitoring event, the inner dosimeter will be removed from the subject and sectioned into six sections: right and left upper arms (shoulder to elbow); right and left lower arms (elbow to cuff); front torso (above the waist); rear torso (above the waist); right and left upper legs (waist to knee) and the right and left lower legs (knee to cuff). Inner and outer head patches (100 cm^2 and 50 cm^2 respectively) affixed to the inside and outside of chemical resistant headgear

when worn by participants making overhead sprays. The head patches will be made from the inner dosimeters. Sock dosimeters worn beneath the participant's socks will also be part of the dermal exposure measurements.

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

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

Sectioning WBDs, and measuring the remaining body regions separately will help inform exposure patterns for this scenario. By understanding the exposure patterns (e.g., percent of exposure to lower legs) EPA may be able to develop mitigation strategies (e.g., chemical resistant headgear or chemical resistant footwear) during the risk assessment process.

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

Additional measures will record environmental conditions at the time of monitoring. Observers will make field notes of subject activity throughout the monitoring event, and photographs or videos may be taken selectively to illustrate events. EPA believes that the proposed measures are appropriate and sound for the study design

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

   Analytical and field sampling quality control procedures include complete validation of all analytical methods, field fortification and control samples, laboratory fortification and control samples, and guidelines on the use of calibration curves to determine chemical residues found on all sample matrices.

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

5. **Statistical Analysis Plan:** The results of physical sample analysis will be provided in the final report of this field study and in the scenario monograph covering all monitoring conducted under AHE600, 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

EPA agrees that the AHETF collect MUs for this scenario based on participants using handguns or handwands under a wide range of nursery and greenhouse conditions provided the AHETF adjust its similarity restrictions and monitor at least one MU using a wettable powder formulation per cluster.

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

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

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

E. Summary Assessment of Ethical Aspects of the Proposed Research[3]

1. **Societal Value of Proposed Research:** The objective of this study is to develop data to determine the potential exposure for workers who mix, load, and apply liquid pesticides

[3] Supporting details are in Attachment 2.

using powered handgun equipment in managed horticultural facilities in the United States. This mixing/loading/applying method is applicable to a large variety of commercially important crops associated with the nursery and greenhouse industry across the U.S. and Canada, and the existing exposure data are inadequate. EPA will use the results of this study to estimate the dermal and inhalation exposure likely for a wide range of agricultural pesticides mixed, loaded, and applied under this exposure scenario.

2. **Subject Selection:** Subjects will be recruited among the employees of commercial growers who mix, load, and apply liquid pesticides using powered handgun equipment, who are willing to use at least one of the surrogate active ingredients for this study, and who meet AHETF criteria for participation. Eligible growers will be identified from a complete list of growers in the target area, processed in random sequence. Subjects will be recruited who are employees of eligible growers (or of pesticide application service companies used by eligible growers), with experience within the past year using the piece of hand held application equipment that will be used in the study. If more employees are available and interested than are needed, qualified participants will be selected randomly. Although the design is purposive, and thus participants are not representative in a statistical sense, they are expected to be typical of those who mix, load, and apply liquid pesticides with powered handgun equipment.

   Subjects will be recruited according to the standard procedures set forth in SOP AHETF-11.B.6. The Study Director or designated researcher will seek permission from the eligible grower to approach his/her employees to recruit volunteers for the study. Depending on the number of employees and size of the grower's facility, the Study Director or researcher may contact employees using an informational recruitment flyer posted in a common work area. Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the grower's employees who express interest in participation. Such recruitment meetings will always occur without the grower or supervisors being present. The Study Director or researcher will describe the AHETF Exposure Monitoring Program, the goals of this specific study, the procedures to be used in exposure monitoring, and the risks and benefits to participants. The subject eligibility factors listed in the consent form and SOP AHETF-11.B.6 are appropriate.

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

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

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

In this study, risks to subjects are classified as 'greater than minimal' since the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation. AHETF has adopted an extensive program to minimize these risks. Appropriate provision is made for safety and medical monitoring.

4. **Benefits:** This research offers no direct benefits to the subjects. The principal benefit of this research is likely to be reliable data about the dermal and inhalation exposure of workers mixing/loading/applying pesticides using powered handgun 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 handler exposure assessments for a wide range of agricultural pesticides.

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

7. **Informed Consent:** Informed consent will be obtained from each prospective subject and appropriately documented. 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 English or Spanish. EPA assessments of compliance with the requirements of 40 CFR §26.1116 and §26.1117 appear in Attachments 4 and 5 to this review.

8. **Respect for Subjects:** Subject identifying information will be kept strictly confidential. 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.

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

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

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

If conducted according to the protocol, this research should meet the ethical standards of FIFRA §12(a)(2)(P) and 40 CFR 26 subparts K and L.

Attachments:

1. EPA Scenario Review: Monitoring Unit Selection and Construction Plan for Scenario: Open Pour Mixing/Loading of Pesticides and Application of Liquid Sprays using Powered Handgun Equipment in Managed Horticultural Facilities (AHE600)
2. EPA Protocol Review: Determination of Dermal and Inhalation Exposure to Workers during Mixing, Loading and Application of Liquid Sprays using Powered Handgun Equipment in Managed Horticultural Facilities (AHE600)
3. §26.1111 Criteria for IRB approval of research
4. §26.1116 General requirements for informed consent
5. §26.1117 Documentation of informed consent
6. §26.1125 Criteria for Completeness of Proposals for Human Research

EPA Scenario Review: AHE600

Title: Monitoring Unit Selection and Construction Plan for Scenario: Open Pour Mixing/Loading of Pesticides and Application of Liquid Sprays using Powered Handgun Equipment in Managed Horticultural Facilities

Date: September 27, 2011

Sponsor: Agricultural Handler Exposure Task Force

1. Scope of Scenario Design

"This is a mixing/loading-application (MLA) scenario defined by the activity, equipment, the form of formulated and diluted product, and type of horticultural facility (i.e., nursery or greenhouse). More specifically, this scenario involves the mixing of dry or liquid formulated product with water which can be accomplished by either preparing a pre-mix and transferring to a spray tank where the mixture is diluted with an appropriate amount of water, or the product can be transferred directly to the tank and diluted. Application involves the use of powered handgun equipment in which the liquid spray is applied to the foliage of plants typically grown in commercial horticultural facilities." (p. 13 of 474)

"It is important to note that each of the 10 'regions' shown on the map is merely a convenient boundary that visually circumscribes the extent of a particular monitoring area. In reality, only those counties with 20 operations (i.e. those shaded in grey) actually belong to the monitoring area…

1. Lower New England Monitoring Area
This monitoring area consists of 36 counties in southeastern New York and virtually all of Massachusetts, Connecticut and Rhode Island. The climate is Maritime with warm-to-cool, humid summers and mild-to-cold winters.

2. Mid-Atlantic Monitoring Area
This monitoring area consists of 52 counties in southeastern Pennsylvania and virtually all of New Jersey, Maryland and Delaware. The climate is generally warm and humid in the summer and has mild winters.

3. North Carolina-South Carolina-Tennessee Monitoring Area
This monitoring area consists of 52 counties located in western North Carolina, northwestern South Carolina and eastern Tennessee. The climate generally has warm, humid summers and mild winters, with cooler summers and cold winters at higher elevations.

4. Northern Florida Monitoring Area
This monitoring area consists of 30 counties located in roughly the northern two-thirds of the state. The climate is generally warm and humid in the summer and has mild winters.

5. Southern Florida Monitoring Area
This monitoring area consists of 6 counties in roughly the southern third of Florida. This area has a tropical, moist climate.

6. Ohio-Pennsylvania Monitoring Area
This monitoring area consists of 37 counties in eastern Ohio and western Pennsylvania. The climate generally has warm-to-cool, humid summers and mild-to-cold winters.

7. Indiana-Michigan Monitoring Area
This monitoring area consists of 34 counties in the southern half of Michigan and the northern part of Indiana. The climate ranges from warm-to-cool, humid summers and mild-to-cold winters.

8. Illinois-Wisconsin Monitoring Area
This monitoring area consists of 47 counties in the northern part of Illinois and roughly the southern half of Wisconsin. The climate ranges from warm-to-cool, humid summers and mild-to-cold winters.

9. Louisiana-Texas Monitoring Area
This monitoring area consists of 22 counties in the eastern part of Texas and most of the western portion of Louisiana. The area generally reflects a climate that has warm, humid summers and mild winters.

10. Oregon-Washington Monitoring Area
This monitoring area consists of 30 counties in roughly the western third of both Washington and Oregon. The climate is Maritime with generally warm, humid summers and mild winters." (pp. 32 – 33 of 474)

(a) Is the scenario adequately defined?

The scenario is clearly and appropriately defined.

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

"AHETF has identified the Open Pour Mixing/Loading of Pesticides and Application of Liquid Sprays Using Powered Handgun Equipment in Managed Horticultural Facilities (Powered Handgun Spraying in Horticultural Facilities) scenario as being within the scope of the task force goals and one for which data are lacking. A number of AHETF member products are labeled for this use pattern. These products are important because they help support and maintain commercially important crops associated with the nursery and greenhouse industry across the U.S and Canada. Therefore, it is necessary to have data in AHED for the mixing/loading and application methods described by this scenario." (p. 20 of 474)

"Regulatory Committee (JRC)) reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that satisfy current acceptability criteria and qualify for inclusion in a generic database. Seven studies involving handheld spraying potentially applicable to this scenario were reviewed by the JRC, and are listed below.

AHE04 – This is an AHETF-conducted study in which applicators made handheld applications in greenhouses.
AH102 – This study involved herbicide applications made around almonds using a handheld spray gun attached to tractor-mounted tanks.
AH401 – This study involved handheld applications made in greenhouses.
AH520 – This study involved handheld applications made in greenhouses.
AH705 – This is a mixer/loader-applicator study that involved handheld applications made in greenhouses.
AH903 – This study involved handheld applications in greenhouses.
AH315 – This study involved termiticide applications using truck-mounted handheld application equipment.

Based on these reviews, it was concluded that none of the studies listed above provided MUs that met the acceptance criteria established by AHETF and approved by JRC (did not fit the scenario definition, used double layers of clothing or PPE). Thus, there are no available existing data for this scenario that are useful for a modern generic database. (p. 2 of 474)

2. Rationale for Scenario Sampling Design

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

"…feedback from nursery/greenhouse growers who were interviewed in 2009 (Standart, 2011) also indicated that workers who make applications using handgun equipment usually perform the associated mixing/loading activities as well.

"Therefore, given that a single worker using handgun equipment usually performs both mixing/loading and application activities, this scenario will involve mixing/loading and application. Mixing/loading will be generally accomplished by mixing formulated product directly in the tank to be used for application or into a pre-mix tank where the contents will later be transferred to the actual application tank. Exposure monitoring for this scenario will only include open-pouring situations since open pouring is most common and is expected to represent a higher exposure potential than the use of closed systems (which includes water-soluble packets). Application will be generally accomplished by manually operating the wand or gun and directing spray to foliage while walking along walkways or rows, or in some cases by spraying from a vehicle.

"AHETF also learned that workers often perform some clean-up activities at the end of spraying. Clean-up typically consists of draining and collecting any excess spray mixture;

flushing the sprayer with soapy water and then rinsing with clean water; and triple rinsing containers. These activities will be included in the exposure monitoring whenever the subjects would normally perform them." (pp. 13-14 of 474)

"[T]he ten monitoring areas for this scenario are widely distributed geographically across the U.S., including the Northeast, East, South, Southeast, Northwest, Midwest, and upper Midwest. The wide geographical distribution in turn represents climates ranging from maritime to tropical to mountainous, temperatures ranging from cool/cold to warm/hot, and precipitation from wet or humid to relatively dry conditions." (pp. 33 of 474)

"The following active ingredients will be considered for use in this scenario.

- Azoxystrobin
- Carbaryl
- Chlorothalonil
- Fosetyl-al
- Imidacloprid
- Malathion
- Permethrin
- Sulfur
- Thiophanate-methyl

"Results from the NASS chemical usage survey summary showed that one or more of these AIs are commonly used. They provide a range of use rates that will enable measurements across the desired range of AaiH per day. Prior to sample analysis, analytical methods for each surrogate AI will have been developed and validated for each matrix used in this study. Matrices include: inner dosimeter, hand rinse, face/neck wipe, socks, head patches, OVS tubes, and cassette filters. Finally, these active ingredients will be or have been either tested for stability or used as surrogates in previous studies and are known to have the required stability under field study conditions." (p. 43 of 474)

Selection of a Geographically Diverse Set of Monitoring Areas:

"The Scenario Target Area is the potential geographic extent of this scenario. Horticultural facilities that use powered handguns are likely to be found to some extent or another in any portion of the country. Of the 3,109 counties in the Continental U.S., USDA's National Agricultural Statistical Service's (NASS) 2007 Census of Agriculture reported that 2,636 had at least one operation involved with floriculture, nursery, or greenhouse vegetable production…." (p. 31 of 474)

"The NASS production statistics from the Census were placed on maps of U.S. counties using ESRI's ArcMap 10.0 software. These maps aided in selecting groups of counties from the restricted Target Area that could provide a diverse set of monitoring areas.

"The counties in the restricted Target Area were then grouped into 10 monitoring areas based on their spatial distance to each other. These groupings of counties were examined for having a reasonable number of enclosed square feet and open production acres. To

assure geographic distinctness, a similarity restriction required monitoring areas to be physically separated from each other. That is, counties from one monitoring area could not be interlaced with counties from another monitoring area. Taken together, the set of 10 monitoring areas were constructed to provide diversity in geography and/or climate.

"The resulting set of 10 distinct monitoring areas are shown on the map in Figure 1 and summarized below. It is important to note that each of the 10 'regions' shown on the map is merely a convenient boundary that visually circumscribes the extent of a particular monitoring area. In reality, only those counties with 20 operations (i.e. those shaded in grey) actually belong to the monitoring area. Attachment 1 lists the individual counties in each of the 10 monitoring areas." (p. 31-32 of 474)

"1. Lower New England Monitoring Area
This monitoring area consists of 36 counties in southeastern New York and virtually all of Massachusetts, Connecticut and Rhode Island. The climate is Maritime with warm-to-cool, humid summers and mild-to-cold winters.

"2. Mid-Atlantic Monitoring Area
This monitoring area consists of 52 counties in southeastern Pennsylvania and virtually all of New Jersey, Maryland and Delaware. The climate is generally warm and humid in the summer and has mild winters.

"3. North Carolina-South Carolina-Tennessee Monitoring Area
This monitoring area consists of 52 counties located in western North Carolina, Northwestern South Carolina and eastern Tennessee. The climate generally has warm, humid summers and mild winters, with cooler summers and cold winters at higher elevations.

"4. Northern Florida Monitoring Area
This monitoring area consists of 30 counties located in roughly the northern two-thirds of the state. The climate is generally warm and humid in the summer and has mild winters.

"5. Southern Florida Monitoring Area
This monitoring area consists of 6 counties in roughly the southern third of Florida. This area has a tropical, moist climate.

"6. Ohio-Pennsylvania Monitoring Area
This monitoring area consists of 37 counties in eastern Ohio and western Pennsylvania. The climate generally has warm-to-cool, humid summers and mild-to-cold winters.

"7. Indiana-Michigan Monitoring Area
This monitoring area consists of 34 counties in the southern half of Michigan and the northern part of Indiana. The climate ranges from warm-to-cool, humid summers and mild-to-cold winters.

"8. Illinois-Wisconsin Monitoring Area

This monitoring area consists of 47 counties in the northern part of Illinois and roughly the southern half of Wisconsin. The climate ranges from warm-to-cool, humid summers and mild-to-cold winters.

"9. Louisiana-Texas Monitoring Area
This monitoring area consists of 22 counties in the eastern part of Texas and most of the western portion of Louisiana. The area generally reflects a climate that has warm, humid summers and mild winters.

"10. Oregon-Washington Monitoring Area
This monitoring area consists of 30 counties in roughly the western third of both Washington and Oregon. The climate is Maritime with generally warm, humid summers and mild winters." (pp. 32 – 33 of 474)

Reduction of Monitoring Areas:

"…The Target Area is essentially the entire U.S…However, for efficiency, AHETF normally restricts a scenario's theoretical Target Area to areas likely to provide the best opportunities to obtain the needed MUs. For this scenario, the Target Area was restricted to just those 667 counties that NASS reported had at least 20 operations. The 10 monitoring areas selected are simply large, geographically distinct groups of these counties." (p. 31 of 474)

(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.

"Not all growers will be eligible or willing to participate in the study. AHETF must obtain employer cooperation before it can recruit workers. This includes willingness of the grower to volunteer his facility and application equipment and allow AHETF to recruit his workers.

"For this reason, growers that are both qualified and willing to participate need to be identified within each monitoring area. AHETF has determined that it is practical to list and screen the vast majority of growers within each entire monitoring area for this information. The general procedure to be followed for each area is described in the steps below. A detailed procedure will be described in the study protocol:

1. "Assemble a list of all known nursery and greenhouse growers in the selected monitoring areas. This information will be obtained from multiple sources. The grower lists from all sources will be combined to provide a single list of possible nursery and greenhouse growers. Any duplicate grower names will be eliminated and the order of names on the list randomized. (Alternatively, if the list is very large, a randomly selected subset of the names may be used.)

2. "Contact growers on the list and determine whether the grower is both qualified and willing to participate. Growers found to be both qualified and willing to participate in the study in a manner consistent with AHETF's technical and ethical guidelines are considered 'potentially eligible' for a scenario. For example, the potentially eligible grower will have the appropriate equipment and will allow his workers to be recruited without influencing their participation. Full details about identifying potentially eligible growers are provided in the study protocol.

3. "As an aid to eventual selection of MUs, each grower identified as 'potentially eligible' will also be asked to provide specific information such as the number of their available employees and when their applications are expected to occur. Specific information to be collected from potentially eligible employers is provided in the study protocol. The above screening process will be conducted by one or more task force contractors as specified in the study protocol. (pp. 38-39 of 474)

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

If more handlers and growers are in the recruiting pool in a given monitoring area, it is likely that the opportunity will arise to select randomly from among interested workers.

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

"…. a single worker using handgun equipment usually performs both mixing/loading and application activities, this scenario will involve mixing/loading and application. Mixing/loading will be generally accomplished by mixing formulated product directly in the tank to be used for application or into a pre-mix tank where the contents will later be transferred to the actual application tank. Exposure monitoring for this scenario will only include open-pouring situations since open pouring is most common and is expected to represent a higher exposure potential than the use of closed systems (which includes water-soluble packets). Application will be generally accomplished by manually operating the wand or gun and directing spray to foliage while walking along walkways or rows, or in some cases by spraying from a vehicle. See 'Powered Handgun Equipment' below for more detail.

"AHETF also learned that workers often perform some clean-up activities at the end of spraying. Clean-up typically consists of draining and collecting any excess spray mixture; flushing the sprayer with soapy water and then rinsing with clean water; and triple rinsing containers. These activities will be included in the exposure monitoring whenever the subjects would normally perform them.

"This scenario involves powered handgun prayers (HG). These sprayers are commonly used in nurseries (N) and greenhouses (G) for the control of pests and diseases on a

'scheduled' (preventive) or 'as needed' (curative) basis. Handgun spray equipment is available in various configurations. However, all handgun equipment is similar in that it is comprised of a 'handgun' (or 'hand wand') device which is attached to a hose, which is in turn attached, through a pump, to the spray tank.

"For mixing, the worker prepares the spray mix in a stationary (or fixed spray tank) or in a mobile spray tank (e.g., on a cart or tractor) which can vary in size from a few gallons to several hundred gallons. The tank is usually partially filled with water and the agitator is started. The product is open poured into the tank and agitated until the tank is filled with water. In some situations, such as with wettable powders, the product can be pre-mixed before being added to the spray tank (e.g., in a bucket or pre-mix tank)." (pp. 14 of 474)

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

"…horticultural facilities range from completely open to completely closed, along with 'in-between' structure and/or production area situations. AHETF furthermore recognizes that the structure and/or production area environment in which a worker performs scenario-specific tasks might impact his exposure; therefore, the scenario design will encourage some diversity in the amount of openness (or enclosure) in the set of MUs. In particular, workers that perform scenario activities in any of the types of production areas listed above will be acceptable. However, as specified in Section 5.2.2, all three MUs within the same monitoring area must have monitoring conditions with a different degree of openness or enclosure." (p. 18 of 474)

3. Are the proposed test materials appropriate surrogates?

"The following active ingredients will be considered for use in this scenario.

- Azoxystrobin
- Carbaryl
- Chlorothalonil
- Fosetyl-al
- Imidacloprid
- Malathion
- Permethrin
- Sulfur
- Thiophanate-methyl

"Results from the NASS chemical usage survey summary showed that one or more of these AIs are commonly used. They provide a range of use rates that will enable measurements across the desired range of AaiH per day. Prior to sample analysis, analytical methods for each surrogate AI will have been developed and validated for each matrix used in this study. Matrices include: inner dosimeter, hand rinse, face/neck wipe, socks, head patches, OVS tubes, and cassette filters. Finally, these active ingredients will be or have been either tested

for stability or used as surrogates in previous studies and are known to have the required stability under field study conditions." (p. 43 of 474)

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

"Appendix C of the Governing Document describes the simulation methodology 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. The number and structure of the proposed MUs should be adequate to satisfy the following benchmark objectives discussed in Section 4.4:

1. **"Primary Objective**: Estimates of the geometric mean, the arithmetic mean, and the 95th percentile of normalized dermal exposure generally need to be accurate to within 3-fold of their actual population value assuming 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)." (pp. 27 -28 of 474)

4.5.1. GSD and ICC

"To determine sample sizes, reasonable values for reference model variation parameters are needed. Based on analyses of exposure from a number of available monitoring studies, Appendix C of the AHETF Governing Document derived a default relative variation structure consisting of a geometric standard deviation (GSD) of 4 and an intracluster correlation (ICC) of 0.3. Unless there is other evidence or expert opinion to the contrary, sample sizes are determined using these default values.

"However, the Powered Handgun Spraying in Horticultural Facilities scenario is expected to be quite heterogeneous. Many opportunities for selecting MUs that differ in ways that might impact exposure are expected. Thus, AHETF suspects that diversity selection might result in normalized exposure variation slightly larger than for a typical scenario. For this reason, for sample size determination purposes, a GSD of 5 is considered more likely than the usual value of 4.

"The greater the differences between MUs in the same monitoring area, the closer the ICC should be to zero. Mixer/loader-applicators located in the same area, but working for different, widely dispersed nursery or greenhouse operations, are unlikely to show strong within-cluster correlations in exposure. However, although near zero within-cluster correlation is always the goal of diversity selection, it can never be completely counted upon. Thus, it seems reasonable to continue the conservative default assumption that ICC could be as large as 0.3.

"Because the AHETF and the Joint Regulatory Committee agreed there is no additional evidence to suggest otherwise and no other strong ICC=0.3 opinion to the contrary (meeting, June, 2011) the values of GSD=5 and will be used for determining sample size for the Powered Handgun Spraying in Horticultural Facilities scenario. (pp. 28 -29 of 474)

4.5.2. Required Number and Configuration of New MUs

"In addition to the benchmark objectives described above, a critical issue for this scenario is the likelihood of obtaining a sufficient number of eligible MUs in a monitoring area. In general it is less costly to keep the number of monitoring areas as small as possible and conduct more MUs per area. However, it is expected that designs with a smaller number of MUs per monitoring area are more likely to be attainable for all the areas selected. Therefore, for this scenario, the configuration size is restricted to NM=3 for all MUs. This restriction will necessarily result in the need for a larger number of monitoring areas than would be typical if NM were larger. Although it might be more costly, AHETF believes that configurations with more monitoring areas and fewer MUs per area will be more successful in obtaining the planned number of MUs than configurations with more MUs per monitoring area.

"As noted above, Appendix C of the AHETF Governing Document describes several simulation methods that can be used to determine reasonable sample sizes for MUs. In brief, the simulation procedure for this scenario consists of the following steps:

1. "Given candidate values for number of monitoring areas, NC, numbers of MUs per cluster, NM, and AaiH strata, simulate normalized exposures, AaiH levels, and exposures derived from AaiH levels assuming proportionality, from the two-stage lognormal reference model. For this model, a GSD of 5 and an ICC of 0.3 is assumed.

2. "From these simulated data, estimate the geometric mean, arithmetic mean, and 95th percentile of normalized exposure. Calculate the fold relative accuracy of these estimates compared to their true values.

3. "In addition, from these same simulated data, determine if the slope from a mixed model regression of log exposure on log AaiH is significantly different from zero.

4. "Repeat steps 1 through 3 10,000 times and calculate the 95th percentile of fold relative accuracy for each normalized exposure statistic and determine if it satisfies the primary benchmark objective. Also compute the percentage of simulations yielding a statistically significant slope. This percentage is the power needed to evaluate the secondary benchmark objective.

"Using this approach, it was found that the primary objective can be met with NC = 10 monitoring areas of NM = 3 MUs each. This would provide a total of 30 MUs.

"For the secondary objective, the power to detect proportionality between exposure and AaiH also depends on the particular set of AaiH used. But as noted in step 1 above, AaiH levels must be simulated for the hypothesized MUs. As described in Section 5.2.1 below, diversity selection for new clusters will require that the AaiH levels for MUs extend over the complete practical range expected the scenario. This practical range is 0.5 to 15 lb AI handled per workday and covers two orders of magnitude. Diversity in AaiH levels is achieved by first partitioning the appropriate practical range into 3 strata. Then for each configuration, a single MU is obtained from within each AaiH stratum. The AaiH strata are each designed to have approximately the same upper-to-lower bound ratio, slightly greater than 3-fold.

"An analogous procedure is followed in step 2 above when simulating AaiH levels for MUs: within each simulated new configuration, an AaiH level is simulated log-uniformly from within each of the 3 strata. Then exposure data are simulated assuming proportionality with the AaiH levels and using the assumed variation structure. For each simulated set of data, a regression analysis is performed and the significance of the log-log slope determined (2-sided test). The power is the proportion of the time that the slope was found significant at $p<0.05$.

"When this simulation method is used assuming the 10 3-MU clusters needed to satisfy the primary benchmark, the power was found to be essentially 100%. In other words, the secondary power objective for this scenario is automatically met with the number and configuration of MUs required for the primary benchmark objective." (pp. 29 - 30 of 474)

EPA Protocol Review: AHE600

Title: Determination of Dermal and Inhalation Exposure to Workers during Mixing, Loading and Application of Pesticides in Managed Horticultural Facilities using Powered Handgun Equipment

Revision Date: September 28, 2011

Study Director and Sub-Investigators:
Douglas Baugher
Aaron Rotondaro
Brian Lange

Field Facility: Multiple outdoor agricultural locations; each principal field investigator utilizes a mobile laboratory

Analytical Facility: TBD

Sponsor: Agricultural Handler Exposure Task Force, LLC
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Reviewing IRB: Independent Investigational Review Board, Inc.
6738 West Sunrise Blvd Suite 102
Plantation FL 33313

1. Societal Value of Proposed Research

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

"The objective of this study is to develop data to characterize the potential exposure of workers who perform open pour mixing, loading and application activities using powered handgun equipment in managed horticultural facilities. Specifically, workers will use powered handgun equipment to make foliar applications to plants grown in commercial nurseries or greenhouses. Greenhouses can include both ornamental and vegetable greenhouses. In addition, equipment clean-up activities will be monitored in those situations in which the worker normally performs such activities. Exposure monitoring will be conducted at ten monitoring areas representing a variety of geographical and climatic regions of the United States." (pp. 331 of 474)

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

This study will provide a partial answer to the question of what dermal and inhalation exposures are likely for workers who mix/load and apply pesticide products using handguns and handwands in nurseries and greenhouses.

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

EPA will use the results of this study to estimate the dermal and inhalation exposure likely for handlers using open mixing and loading techniques and making applications with hand-held equipment (handguns and handwands).

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

"AHETF (in conjunction with EPA, PMRA and CDPR, collectively the Joint Regulatory Committee (JRC)) reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that satisfy current acceptability criteria and qualify for inclusion in a generic database. Seven studies involving handheld spraying potentially applicable to this scenario were reviewed by the JRC, and are listed below.

- AHE04 – This is an AHETF-conducted study in which applicators made handheld applications in greenhouses.
- AH102 – This study involved herbicide applications made around almonds using a handheld spray gun attached to tractor-mounted tanks.
- AH401 – This study involved handheld applications made in greenhouses.
- AH520 – This study involved handheld applications made in greenhouses.
- AH705 – This is a mixer/loader-applicator study that involved handheld applications made in greenhouses.
- AH903 – This study involved handheld applications in greenhouses.
- AH315 – This study involved termiticide applications using truck-mounted handheld application equipment.

"Based on these reviews, it was concluded that none of the studies listed above provided MUs that met the acceptance criteria established by AHETF and approved by JRC (did not fit the scenario definition, used double layers of clothing or PPE). Thus, there are no available existing data for this scenario that are useful for a modern generic database.

"AHETF reviewed the data in potentially relevant PHED (EPA, 1998a) handgun (wand) application scenarios to determine if any of the data were suitable for a modern generic database.

"The scenarios were:

- Scenario 18 – Low Pressure Handwand Application (APPL). This PHED scenario contains exposure data for monitoring units making applications only.
- Scenario 19 - High Pressure Handwand Application (APPL). This PHED scenario contains exposure data for monitoring units making applications to indoor (poultry houses) and outdoor (weeds and brush) environments.

- Scenario 21 – Hand Gun (Lawn) Sprayer (APPL). This PHED scenario contains exposure data for monitoring units making handgun applications to lawns.
- Scenario 32 – Liquid / Open Pour / Low Pressure Handwand (MLAP). This PHED scenario contains exposure data for mixing/loading and application activities.
- Scenario 33 – Wettable Powder / Open Pour / Low Pressure Handwand (MLAP) – This PHED scenario contains exposure data for mixing/loading and application activities in crack and crevice situations.
- Scenario 35 – Liquid / Open Pour / High Pressure Handwand (MLAP) – This PHED scenario contains exposure data for mixing/loading and application activities.

"The AHETF is interested in only those PHED MUs corresponding to a single layer of clothing with chemical-resistant gloves. The review found no MUs that met the acceptance criteria established by AHETF and approved by the JRC (incomplete dosimetry, unacceptable data quality). Thus, there are no data currently in PHED for this scenario that are useful for a modern generic database.

"AHETF also reviewed and evaluated several exposure monitoring studies sponsored by the European Crop Protection Association (ECPA) and conducted in Europe within the past 10 years. Seven of those studies, consisting of 105 MUs, involved handheld applications in a variety of greenhouse situations with hose-end sprayers. Four other studies, consisting of 76 MUs, involved handheld applications in orchard crops or vineyards using hose-end sprayers. All eleven of these studies were applicable to this scenario. However, as discussed in the Scenario Definition, AHETF plans to generate data for this scenario that involve individual workers performing both mixing/loading and application activities. Since all of the ECPA MUs evaluated involved application only, none of the ECPA studies are acceptable for the AHETF generic database.

"Finally, EPA examined data from existing handgun MLA exposure studies or exposure assessments that were not available to the AHETF and concluded that none of the exposure data should be included in the AHETF database (Meeting of Joint Regulatory Committee with AHETF, June, 2011). Since no existing data were found that might provide acceptable MUs for this scenario, this selection plan proposes to collect all the MUs necessary to meet the benchmark objectives…." (pp. 20-22 of 474)

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

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

2. Study Design

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

"The goal of conducting MUs for this scenario is to develop a set of generic dermal and inhalation exposure data which regulators and other potential users of the generic database can utilize to characterize the magnitude and likely range of future exposures, and to perform exposure assessments for this scenario. Because the number and types of such analyses will depend on the specific objectives of each future user, there will be no attempt to conduct a comprehensive universal 'analysis' of these data. Rather, the data collected for this scenario will only be statistically evaluated with respect to specific 'benchmark' measures of adequacy. As discussed in the Governing Document, the two categories of benchmark data adequacy considered are:

1. The relative accuracy of selected statistics characterizing the distribution of exposure normalized by amount of active ingredient handled (AaiH).
2. How well the data can be expected to describe a relationship between exposure and AaiH, if one existed." (p. 49 of 474)

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

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

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

2.1 Statistical Design

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

"To determine sample sizes, reasonable values for reference model variation parameters are needed. Based on analyses of exposure from a number of available monitoring studies, Appendix C of the AHETF Governing Document derived a default relative variation structure consisting of a geometric standard deviation (GSD) of 4 and an intracluster correlation (ICC) of 0.3. Unless there is other evidence or expert opinion to the contrary, sample sizes are determined using these default values.

"However, the Powered Handgun Spraying in Horticultural Facilities scenario is expected to be quite heterogeneous. Many opportunities for selecting MUs that differ in ways that might impact exposure are expected. Thus, AHETF suspects that diversity selection might result in normalized exposure variation slightly larger than for a typical scenario. For this reason, for sample size determination purposes, a GSD of 5 is considered more likely than the usual value of 4.

"The greater the differences between MUs in the same monitoring area, the closer the ICC should be to zero. Mixer/loader-applicators located in the same area, but working for different, widely dispersed nursery or greenhouse operations, are unlikely to show strong within-cluster correlations in exposure. However, although near zero within-cluster correlation is always the goal of diversity selection, it can never be completely counted upon. Thus, it seems reasonable to continue the conservative default assumption that ICC could be as large as 0.3.

Because the AHETF and the Joint Regulatory Committee agreed there is no additional evidence to suggest otherwise and no other strong opinion to the contrary (meeting, June, 2011) the values of GSD=5 and ICC=0.3 will be used for determining sample size for the Powered Handgun Spraying in Horticultural Facilities scenario." (pp. 28-29 of 474)

4.5.2. Required Number and Configuration of New MUs

" …Appendix C of the AHETF Governing Document describes several simulation methods that can be used to determine reasonable sample sizes for MUs. In brief, the simulation procedure for this scenario consists of the following steps:

1. Given candidate values for number of monitoring areas, NC, numbers of MUs per cluster, NM, and AaiH strata, simulate normalized exposures, AaiH levels, and exposures derived from AaiH levels assuming proportionality, from the two-stage lognormal reference model. For this model, a GSD of 5 and an ICC of 0.3 is assumed.

2. From these simulated data, estimate the geometric mean, arithmetic mean, and 95th percentile of normalized exposure. Calculate the fold relative accuracy of these estimates compared to their true values.

3. In addition, from these same simulated data, determine if the slope from a mixed model regression of log exposure on log AaiH is significantly different from zero.

4. Repeat steps 1 through 3 10,000 times and calculate the 95th percentile of fold relative accuracy for each normalized exposure statistic and determine if it satisfies the primary benchmark objective. Also compute the percentage of simulations yielding a statistically significant slope. This percentage is the power needed to evaluate the secondary benchmark objective.

"Using this approach, it was found that the primary objective can be met with NC = 10 monitoring areas of NM = 3 MUs each. This would provide a total of 30 MUs.

"For the secondary objective, the power to detect proportionality between exposure and AaiH also depends on the particular set of AaiH used. But as noted in step 1 above, AaiH levels must be simulated for the hypothesized MUs. As described in Section 5.2.1 below, diversity selection for new clusters will require that the AaiH levels for MUs extend over the complete practical range expected the scenario. This practical range is 0.5 to 15 lb AI handled per workday and covers two orders of magnitude. Diversity in AaiH levels is achieved by first partitioning the appropriate practical range into 3 strata. Then for each configuration, a single MU is obtained from within each AaiH stratum. The AaiH strata are each designed to have approximately the same upper-to-lower bound ratio, slightly greater than 3-fold.

"An analogous procedure is followed in step 2 above when simulating AaiH levels for MUs: within each simulated new configuration, an AaiH level is simulated log-uniformly from within each of the 3 strata. Then exposure data are simulated assuming

proportionality with the AaiH levels and using the assumed variation structure. For each simulated set of data, a regression analysis is performed and the significance of the log-log slope determined (2-sided test). The power is the proportion of the time that the slope was found significant at $p<0.05$.

"When this simulation method is used assuming the 10 3-MU clusters needed to satisfy the primary benchmark, the power was found to be essentially 100%. In other words, the secondary power objective for this scenario is automatically met with the number and configuration of MUs required for the primary benchmark objective." (pp. 29-30 of 474)

(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?

"…the within-monitoring-area AaiH diversity for new MUs is imposed by specifying that:

"SR1. It is preferable that no two MUs obtained in the same monitoring area be in the same AaiH stratum

"This similarity restriction results in AaiH levels for all MUs being approximately uniformly located over the entire log AaiH range when log exposure is regressed against log AaiH.

"In addition to the similarity restriction on AaiH (i.e., SR1 above), diversity among MUs is also enhanced by imposing the following mandatory and preferred similarity restrictions on each set of three MUs <u>in the same monitoring area</u>:

"SR2. No two MUs are permitted to utilize the same worker

"SR3. No two workers are permitted to have the same employer (i.e., grower or commercial applicator)

"SR4. All three MUs must have monitoring conditions with a different degree of openness or enclosure

"SR5. When possible, all three MUs should not have the same formulation type (i.e., liquid or solid)

"SR6. Each pair of MUs must differ in at least one of the following characteristics:

- Facility type/sub-type (i.e., N, OGH, or VGH)
- Method of mixing product (example: directly into spray tank or pre-mixed and then added to spray tank)
- Hose attachment (example: handgun-type or hand wand type)
- Predominant spray orientation during monitoring period (i.e., downward, outward, upward, or some combination)
- Formulation type (i.e., liquid or solid)
- Product container size
- Performing equipment clean-up (i.e., yes or no)" (p. 37 of 474)

(e) Can the data be statistically analyzed?

"As has always been the case, any statistical conclusions based on such data imply the qualification: 'to the extent that the data can be viewed as deriving from a true random sample.'" (p. 49 of 474)

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

"As discussed in the Governing Document, the two categories of benchmark data adequacy considered are:

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

"2. How well the data can be expected to describe a relationship between exposure and AaiH, if one existed." (p. 49 of 474)

"The primary benchmark objective is that selected lognormal-based estimates of normalized dermal exposure distribution be accurate to within 3-fold, at least 95% of the time. The benchmark estimates specified are those for the geometric mean, arithmetic mean, and the 95th percentile.

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

"This secondary benchmark objective [Adequacy of the Data for Distinguishing a Proportional from an Independent Relationship between Exposure and AaiH] applies to each of the closed loading of liquids scenarios 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." (pp. 49 - 50 of 474)

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

Yes.

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

Since the primary objective of the research is to characterize the distribution of exposure normalized by the amount of active ingredient handled (AaiH), statistical power does not relate to this objective. However, EPA believes the resulting data will reliably characterize the distribution of exposures for the individuals monitored during closed system liquid loading 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.

"As described in the Governing Document, in such a model the true slope, β, would be equal to one if dermal exposure were directly proportional to AaiH. If exposure were independent of AaiH, then β=0. This benchmark objective requires that the number of clusters and the allocation of AaiH levels to MUs should be adequate to ensure that the regression analysis has at least 80% power to reject the hypothesis that β=0 when β is actually equal to one. By symmetry, the mixed model linear regression would also have the same power to reject the hypothesis that β=1 when β=0. This is the precise meaning of being able to 'discriminate between proportionality and independence'." (p. 50 of 438)

2.2 How and to what will human subjects be exposed?

"AHETF will monitor worker exposure resulting from the mixing/loading and application of a pesticide product using powered handgun equipment in nurseries and greenhouses." (p. 23 of 474)

"The following active ingredients will be considered for use in this scenario:

- Azoxystrobin
- Carbaryl
- Chlorothalonil

- Fosetyl-al
- Imidacloprid
- Malathion
- Permethrin
- Sulfur
- Thiophanate-methyl" (p. 43 of 474)

(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." (pp. 41-42 of 474)

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

"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 spray volume, number of loads sprayed, etc. Thus, diversification of AaiH induces diversification of such associated factors as well. Therefore, in addition to having a wide range, the MUs within the same monitoring area should not have similar AaiH levels.

"A practical AaiH range is first defined for the entire scenario. It encompasses AaiH levels that can be readily found in practice and are expected to produce detectable exposure results. This practical range is then partitioned into three strata of approximately equal width on a logarithmic scale. Then, for each monitoring area, there is an attempt to restrict the MUs to no more than one per AaiH stratum. This similarity restriction imposes AaiH diversity on the MUs and ensures a wide range of AaiH levels within each monitoring area.

"AHETF has developed a practical range in AaiH for this scenario taking into account such factors as the typical use rates of products, types of products available on the market, area that can be treated in a day, etc. The practical range for amount of active ingredient handled per day is 0.5 to 15 lb per day. The lower practical limit of 0.5 pounds of active ingredient per day is selected to avoid an inordinate number of non-quantifiable residues on worker exposure matrices and to allow for at least 2 hours of work time with the high output handgun equipment being used in this scenario." (p. 35 of 474)

"This practical AaiH range was partitioned into the following three strata:

- Stratum 1 – From 0.5 lb to 1.6 lb
- Stratum 2 – Greater than 1.6 lb to 4.8 lb

- Stratum 3 – Greater than 4.8 lb to 15 lb" (pp. 36 of 474)

(c) What duration of exposure is proposed?

"Work Duration

"Monitoring duration will be largely driven by the amount of AaiH. However, AHETF strives to monitor workers that represent a full workday with a desired minimum monitoring duration of half the workday. This helps to insure that daily exposure estimates are not biased by unusual conditions during short intervals. However, the typical workday for this scenario is generally shorter than in other scenarios studied by AHETF. That is, survey results indicate that, depending on equipment and facility type, roughly 55 to 90% of workers make their applications in less than four hours. Therefore, for purposes of this scenario design, a typical workday is assumed to be 4 hours, which will result in a desired minimum duration of two hours. Minor scripting may be involved in order to achieve the desired monitoring duration such as spraying from partially filled tanks resulting in more tank fillings than normal.

"Number of Loads Handled

"The number of loads handled could have an impact on exposure. AHETF's standard guideline is that each MU will handle a minimum of three tank loads (i.e., mixing/loading and application). This ensures the generic database will contain exposure data generated from work periods that represent a full day and from repeated application cycles that increase the opportunity for exposure (and therefore will not underestimate exposure potential). However, handling three loads may, in some cases, not be practical to achieve because of the large spray tank sizes, the overall relatively low amounts of AaiH involved, and the potentially short monitoring periods. However, scripting will be done if needed and practical under the application conditions of the particular operation in order to meet this desired minimum." (p. 41 of 403)

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 inner head patches after worker removes the chemical-resistant headgear, then inner socks, then hand washes, then face/neck wipes, and finally inner dosimeters as described in SOP AHETF-10.E.2. Outer head patches are removed after the worker removes his headgear. Samples will be identified as described in SOP AHETF-8.F. For this study, inner dosimeters will be cut into six sections after collection.

"Full details for sampling air with OSHA Versatile Sampler (OVS) tubes and personal air-sampling pumps are given in the most recent versions of SOP AHETF-8.D and 10.G." (p. 364 of 474)

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

"Field fortification samples are exposure matrix samples that are fortified (or spiked), generally in the field, with known amounts of active ingredient and subsequently analyzed to determine the amount of active ingredient recovered. Field fortification samples are subjected to the same environmental, handling, shipping and storage conditions as worker samples. Because these conditions are similar, and because field fortification samples are analyzed along with worker samples, recovery values calculated from analysis of fortification samples are applicable to worker exposure samples. Field fortification recoveries are therefore used to adjust residue levels found in worker samples for residue losses that might have occurred during collection, handling, shipping and storage." (SOP AHETF-8.E.6; p. 190 of 474)

(c) What QA methods are proposed?

"AHETF intends that all regulatory studies are conducted in accordance with the FIFRA GLP Standards (40 CFR part 160). Field and analytical aspects of this study will be monitored by the relevant quality assurance units(s) (QAU) while this study is in progress to ensure compliance with the FIFRA GLP regulation and adherence to this protocol and relevant SOPs. The QAU(s) will submit copies of its/their inspection reports to the Study Director and AHETF Sponsor Representative (40 CFR part 160.35(4)). Field portions of the Study 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 Study Report will contain a Quality Assurance Statement from the QAU of each contributing facility conducting QA audits, and from the QAU specified in Section 1.14." (p. 374 of 474)

(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, transit and storage 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 monitoring area, or more days as appropriate for environmental conditions." (p. 365 of 474)

"For each fortification event, 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." (p. 366 of 474)

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?

"AHETF will monitor worker exposure resulting from the mixing/loading and application of a pesticide product using powered handgun equipment in nurseries and greenhouses. Each instance of exposure monitoring is termed a monitoring unit (MU). Each MU consists of a set of mixing/loading-application conditions (including the particular worker) that are intended to represent the scenario activities for a single workday. Therefore each MU is an experimental realization of a 'mixer/loader/applicator-day' (or MLA-day) from the scenario population of all possible MLA-days. In many cases monitoring units will be selected from 'naturally occurring' MLA-days. However, the selected mixing/loading-application conditions are sometimes modified or scripted slightly to ensure that the complete sample of MUs reflects the diversity in the entire scenario population. It is important to emphasize that MU conditions are not necessarily associated with the particular active ingredient used. The key assumption underlying the AHETF monitoring program is that exposures are generic: they do not depend upon the chemical identity of any particular active ingredient although they may sometimes depend upon the way in which that active ingredient is handled. As a result, some MUs could be selected for conditions that are less typical for the active ingredient being monitored providing these conditions are expected for other active ingredients. Thus, MUs are technically not 'sampled' from an existing population as would be the case, say, with a statistical survey. More correctly, they should be viewed as synthetic handgun MLA-days derived from both selected and constructed conditions." (p. 23 of 474)

(b) From what populations will subjects be recruited?

"The first step typically involves contacting and selecting growers and/or commercial application companies that can provide the necessary crop/site, equipment and workers, and are willing to use an AHETF surrogate. This will be done by calling from a randomized list of growers in a local area (See SOP AHETF-11.M). Growers

that meet the criteria listed above will be placed in a pool of eligible growers. At this time, growers (employers) will be asked for permission to recruit their workers for the research study. Written assurance will be obtained from the employer that the workers will not suffer any consequence if they decide either to participate or not to participate in the study and that there will be no coercion of the workers (see Attachment 11-B-1)." (SOP AHETF-11.B.6; p. 240 of 474)

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

"A comprehensive list of growers will be created for each monitoring area listed in Section 3 and will be referred to as the Grower Universe List (GUL). Growers on the GUL (or a random subset of the GUL) will undergo various qualifying screenings and interviews (described in later sections) that will identify growers that operate nurseries and/or greenhouses (including ornamental and vegetable greenhouses), that use powered handgun spray equipment, and that are potentially eligible to provide monitoring units (MUs) in the monitoring area. The list of growers for each monitoring area will be obtained from commercial list providers. They include:

- Meister Media Worldwide (publisher of the trade magazine *Greenhouse Grower*)
- Moose River Media (publisher of the trade magazine *American Nurseryman*)
- Dun & Bradstreet

"Names obtained from these list providers will be combined and their order randomized to provide a single list of growers that might operate nurseries and/or greenhouses and use powered handgun spray equipment. Any duplicate names will be removed from this grower list.

"The MGL is that portion of the GUL that will be subjected to the qualifying and eligibility determination process.

"All of the employers on the GUL may be placed on the MGL. However, if the number of growers on the GUL is expected to be larger than needed to provide an adequate set of potentially eligible growers, the Study Director may choose to select a random subset of the GUL to use for the MGL. The size of this subset is at the discretion of the Study Director. The remaining growers on the GUL (or additional random subsets of remaining growers) can be added to the MGL at a later time as needed.

"Missing or duplicate phone numbers on the MGL will be reconciled and/or corrected as needed.

"The MGL will be screened to identify qualifying growers. A professional call center will contact each grower listed on the MGL and conduct screening interviews. Growers that can be screened completely and that meet minimum qualifying

requirements of the study will be identified as 'qualified growers' and added to a qualified grower list (QGL).

"The call center will attempt to contact and administer the screening questionnaire to every grower on the MGL unless notified by the Study Director that additional qualified growers are no longer needed. The call center will make 15-20 attempts to reach each grower; if the grower is not reached after these attempts, then that grower is eliminated.

"The screening questions will be used to identify growers that meet the minimum requirements for the study. As a minimum, a qualifying grower must:

- Make pesticide applications in nurseries or greenhouses within the monitoring area
- Use powered handgun spray equipment
- Have at least one worker within the operation that typically performs mixing/loading and application activities (and equipment cleanup if normally performed) at least 2 hours in a day.

"Additional qualifying questions may be included as appropriate. For qualified growers, the Call Center will also:

- Inform the grower that he will receive an introductory letter from the AHETF and be contacted by an AHETF representative to obtain additional information
- Determine the best time of day to call for follow-up questions (pp. 351-352 of 474)

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

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

3.2 Equitable Selection of Subjects

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

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

- Have experience within the past year with the work activity being monitored in the study (including the particular equipment to be used during mixing/loading or application)
- Handle pesticides as part of their job

- Be trained in safe pesticide handling practices in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training
- Provide proof of being at least 18 years old with a government-issued photo ID
- Confirm they do not work for a pesticide company or a contractor of the AHETF
- Consider their general health status to be good and tell researchers they have no medical conditions that affect their ability to participate in the study (See SOP AHETF-11.C for health status determination)
- Not be pregnant or nursing (See SOP AHETF-11.D)
- Confirm they do normally wear personal protective equipment that is required by the label. If the worker indicates that they may wear additional PPE not required by the product label, and that additional PPE might impact the objectives of the study, such as chemical-resistant clothing, then the Study Director should be notified to determine if the worker shall be included in the study. Confirm they will follow label directions. The research staff shall not influence nor ask in a manner to influence the worker to wear less PPE than they normally wear.
- Have a private meeting with a researcher to review and discuss the consent form
- Understand English or Spanish (See SOP AHETF-11.I for a detailed discussion of this topic)
- Understand and sign the consent form, and if in California, the California Experimental Research Subject's Bill of Rights" (SOP AHETF-11.B.6; pp. 242-3 of 474)

"For this study, the following inclusion criteria also apply:

- Have experience within the past year with open pour mixing and loading of solid or liquid formulations, and with spraying the diluted product using a powered handgun in nurseries or greenhouses, including the type of equipment to be used.
- Agree to wear chemical-resistant gloves even if the label does not require them.
- Agree to wear chemical-resistant headgear during applications involving either 'overhead only' spray situations or a mix of 'overhead' and 'non-overhead' spray situations, even if the label does not require it." (p. 335 of 474)

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

None

(c) If any potential subjects are likely to be especially vulnerable to coercion or undue influence, what is the justification for including them?

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

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

"For each eligible employer identified, AHETF will follow standard procedures (see SOP AHETF-11.B.6; pp. 239-244 of 474) to recruit potential participants for this study. Individual workers will be recruited during an initial interview with (or visit to) a potentially eligible employer once eligibility has been established. Alternatively, recruitment can occur on subsequent interviews with or visit(s) to an eligible employer.

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

"Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the employer's employees who express an interest in participation. Such recruitment meetings will always occur without the grower or supervisors being present (SOP AHETF-11.B). The Study Director or researcher shall make a presentation describing the AHETF Exposure Monitoring Program, the goals of the research study, the procedures used in exposure monitoring, and the risks and benefits to participants. A toll-free phone number will be provided, and individuals will be encouraged to contact AHETF if they desire additional information about the study or are interested in participating in the study. All presentation materials, such as handouts or visual aids, shall be reviewed and approved by an IRB prior to use in recruiting subjects." (pp. 357 of 474)

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

"Written assurance will be obtained from the employer that the workers will not suffer any consequence if they decide either to participate or not to participate in the study and that there will be no coercion of the workers." (p. 240 of 474) A copy of the "Employer Cooperation Statement" is provided on p. 244 of 474.

"In accordance with SOP AHETF-11.B, 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." (pp. 356-7 of 474)

3.3 Remuneration of Subjects

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

"During recruitment, workers will be offered an opportunity to take part in a recruitment meeting with the Study Director or other designated member of the study team (but without the workers' supervisors) to learn about participating in this study. (Section 5.2) No remuneration is offered for this introductory meeting. Workers who are still interested in participating in the study 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 worker 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." (p. 335 of 474)

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

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

(d) How and when would subjects be paid?

In cash, immediately after their participation.

4. Risks to Subjects

4.1 Risk Characterization

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

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

This study could involve any of nine active ingredients: Azoxystrobin, Carbaryl, Chlorothalonil, Fosetyl-al, Imidacloprid, Malathion, Permethrin, Sulfur, Thiophanate-Methyl.

"The pesticide products that contain these active ingredients and potentially used in this study will be products registered for nursery and/or greenhouse use and the specific application planned by the grower. AHETF will only monitor workers mixing/loading and applying products in accordance with all label requirements." (p. 339 of 474)

For all nine of the possible active ingredients for this study, the Margins of Exposure (MOEs) calculated for the highest level of exposure in this protocol meet or exceed the minimum required MOE, or level of concern (generally 100), for the individual dermal and inhalation routes of exposure, as well as for the combined exposure.

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

The protocol and consent form currently list five kinds of risks:

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

"In this study risks to subjects are classified as 'greater than minimal' since the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation. AHETF has adopted an extensive program to minimize these risks." (p. 336 of 474)

(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 (see AHETF SOPS 11.C, 11.E, 11.G and 11.H):

- Selecting only experienced pesticide handlers who consider themselves to be in good health

- Requiring experience with the type of powered handgun mixing/loading and application equipment to be used
- Reminding workers of safe chemical handling practices
- Practicing the face wipe and hand wash procedures with each participant before pesticide handling begins
- Identifying nearby medical treatment facilities in case of emergency
- Monitoring the heat index and stopping the study if conditions warrant
- Providing transportation to medical treatment and covering the costs of treatment, if needed
- Having a medical professional at each MU site to observe the worker, provide urgent care, and decide whether the subject is too sick to make a decision about refusing medical treatment
- Observing study participants throughout the monitoring period
- Ensuring that all tank mix products are used according to approved label(s) and state regulations, and do not require any additional PPE that could adversely affect the study objectives (for example, chemical-resistant coveralls)." (p. 344 of 474)

Risk reduction actions specific to the identified kinds of risk are discussed in the protocol (pp. 336-344 of 474).

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

For all nine of the possible active ingredients for this study, the Margins of Exposure (MOEs) calculated for the highest level of exposure in this protocol meet or exceed the minimum required MOE, or level of concern (generally 100), for the individual dermal and inhalation routes of exposure, as well as for the combined exposure.

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

"AHETF will monitor environmental conditions to determine the heat index near the mixing/loading or application activities. Exposure monitoring will be discontinued if the heat index cutoff of 105^{o} F (adjusted for direct sun, if applicable) is reached or exceeded. The Study Director or other researcher shall stop the monitoring and/or move the worker to a cooler environment until monitoring can be resumed." (p. 336 of 474)

(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 certified first responder, paramedic, physician's assistant, nurse, or emergency medical technician. This professional will also watch you for signs of illness. They will provide medical attention as needed." (p. 416 of 474)

SOP AHETF-11.H.3 (pp. 267-270 of 474) defines procedures to be followed if a subject in an AHETF study requires emergency medical attention.

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

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

- SOP AHETF-11.E.3 (pp. 250-251 of 474) calls for researchers to monitor worker compliance with label and Worker Protection Standard requirements and labeling, and permits the Study Director to remove from the study a worker who engages in unsafe work practices.
- SOP AHETF-11.G.3 (pp. 254-266 of 474) 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.3 (pp. 267-270 of 474) 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 a distribution of chemical exposure among the various body parts and a comparison of results from other workers performing the same task. Results are typically available 9-12 months after all monitoring is completed. 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 volunteer's participation in the study, a researcher will remind the volunteer 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.J)." (pp. 349 of 474)

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

"If you are injured or get sick because of your participation in this study, medical treatment will be available at your workplace and at a nearby health care facility. If necessary, AHETF will arrange to have you taken to receive medical attention. You may refuse medical treatment unless the medical professional decides you are too sick to make a decision about getting medical treatment.

"AHETF will cover the cost of reasonable and appropriate medical attention for a study-related injury or illness that is not covered by your own insurance or insurance provided through your employer. This includes deductible costs and any out-of-pocket expenses, including co-payments, you might have. The Study Director, in consultation with the on-site medical professional, will decide if you have an illness or injury that is due to your participation in this study." (p. 417 of 474)

5. Benefits

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

"There are no personal benefits to the study participants." (p. 344 of 474)

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

"Data from the AHETF exposure monitoring program has the potential to improve the ability of EPA and other regulatory agencies to accurately assess occupational risks associated with mixing/loading and application of pesticides using powered handgun equipment in managed horticultural facilities. 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.

"Since there are insufficient existing data suitable for use in a generic database describing the exposure to workers who mix/load and apply pesticides from powered handgun equipment in managed horticultural facilities, society will likely benefit from data generated by this study through the improved risk assessments by EPA and other regulatory agencies." (p. 345 of 403)

"Growers (employers) who allow the study to be conducted using their equipment, facilities, crops and workers 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 business." (p. 344-5 of 474)

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

Identified societal benefits are likely to be realized.

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

"By monitoring exposure to professional agricultural handlers who follow their normal practices, but wear an additional layer of clothing (as an inner dosimeter which traps chemical that penetrates the work clothing), this study presents a greater than minimal risk to

participants. Participating in this study increases the risk of heat-related illness, but this risk is mitigated by a medical management program which emphasizes prevention measures and guidelines for stopping participation when warranted based on environmental conditions.

"The likely benefit to agricultural workers as a whole and to society in general, in the form of more accurate measurements of potential exposure to pesticides, must be weighed against the risks to participants. Experts consulted by AHETF reported that the use of handgun equipment is a common method of pesticide application in nurseries and greenhouses. Therefore, exposure data for these scenarios meeting contemporary standards of reliability and quality will likely provide a significant benefit to society. Because margins of exposure are acceptable for the products proposed for use in this research study, subjects are very unlikely to experience acute toxic effects, and because extensive procedures will be in place to minimize these and other risks to participants, the likelihood of serious adverse effects is very small. In summary, AHETF believes the risks to study participants from participating in this study are reasonable in light of the likely benefit to society of the knowledge to be gained." (p. 345 of 474)

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?

IIRB, Inc. earned "Full Accreditation" from the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) in December of 2009.

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

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

"This study will be conducted in accordance with EPA's final regulation published at 40 CFR Part 26 that establishes requirements for the protection of subjects in human research (see SOP AHETF-11.A). The protocol, informed consent form(s), 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.)" (p. 334 of 474)

8. Informed Consent

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

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

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

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

The literacy rate of intended subjects is not addressed in the protocol. Procedures for accommodating English- or Spanish-speaking candidates of low or limited literacy are explained in SOP AHETF-11.I.3. (pp. 271-276 of 474)

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

See SOP AHETF-11.I.3 (pp. 271-276 of 474)

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

"In all situations, the person obtaining consent will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential workers that would require a response that indicates understanding of key

issues. The form in Attachment 11-J-1 will be used to ascertain general understanding." (SOP AHETF-11.J.1 §3.10.a; p. 279 of 474)

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

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

"Informed consent will be sought in an individual meeting with each worker. The worker may have a friend, family member, or advisor with them during the meeting. Witnesses may also be present as described in SOP AHETF-11.I.

"The person conducting the consent meeting will inform the worker that he/she will receive $20 (or another amount specified in the protocol) for participation in the meeting, whether or not he/she volunteers to participate in the research.

"During the private consent meeting the person conducting the consent meeting 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 another amount specified in the protocol) if they decide to participate and put on the dosimeters, whether or not they complete the monitoring period.

"The person obtaining consent will provide information about the risk of the surrogate chemical in the study, including signs and symptoms of acute overexposure. This information will be presented in the product label and/or the MSDS. Refer to SOP AHETF-11.E for details.

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

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

"The IRB-approved Consent Form (and all supporting documents, except the product labels and MSDS forms) will be presented in the preferred language (English or Spanish) of the worker. All sections of the Consent Form will be explained in detail. When the person obtaining consent is satisfied that the worker understands the requirements and

risks of the study, and if the worker still wants to participate, he/she will be asked to sign and date the Consent Form and the person obtaining consent will provide a copy of the signed form to the worker.

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

"In all situations, the person obtaining consent will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential workers that would require a response that indicates understanding of key issues. The form in Attachment 11-J-1 will be used to ascertain general understanding.

"The person obtaining consent will not sign the Consent Form unless he/she believes that the process has been free of any element of coercion or undue influence and the witness (when required) has signed the consent form." (SOP AHETF-11.J.1 §3.2-3.11; pp. 278-9 of 474)

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

"In accordance with SOP AHETF-11.B, 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. Employers must also certify that alternate work will be provided on study days for workers who choose not to volunteer; and that the employee's decision to participate or not will have no impact on their employment." (p. 356-7 of 474)

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, 11.D, and 11-J." (p. 346 of 474)

"Your name will only appear on the consent form, 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 we collect while you take 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 guarantee 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." (p. 417-8 of 474)

(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 subject 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 subject 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)." (p. 346 of 474)

"Your employer has agreed to let us do the research and has confirmed that he/she does not mind if you do or do not take part in this study. 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 not affect your job or pay or include any penalty or loss of benefits you are owed." (p. 419 of 474)

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

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

"If you withdraw or if your part in this study is stopped at any time by the researchers or the AHETF, the long underwear, inner socks, chemical-resistant hat with outer patch, inner head patch and air sampling pump will be removed. The handwash and face/neck samples may be collected if you agree.

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

"No one can force you to take part in this study. Taking part is totally voluntary. If you choose not to take part in this study you will perform your ordinary activities on the day of the study. Your alternative is to not take part." (pp. 419 of 474)

§ 26.1111 Criteria for IRB approval of research
AHETF Protocol: M/L/A in Managed Horticultural Facilities w/ Powered Handgun Equipment (AHE600)

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

§26.1116 General requirements for informed consent
AHETF Protocol: M/L/A in Managed Horticultural Facilities w/ Powered Handgun Equipment (AHE600)

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

§26.1117 Documentation of informed consent
AHETF Protocol: M/L/A in Managed Horticultural Facilities w/ Powered Handgun Equipment (AHE600)

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

40 CFR 26.1125 Prior submission of proposed human research for EPA review
AHETF Protocol: M/L/A in Managed Horticultural Facilities w/ Powered Handgun Equipment (AHE600)

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

		Requirement	Y/N	Comments/Page Refs
All information relevant to the proposed research specified by § 26.1115(a)		(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.	Y n/a Y n/a	pp. 335-344 None pp. 411-422, 456-469 None
		(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.	n/a n/a	pp. 472 No controverted issues
		(3) Records of continuing review activities.	n/a	
		(4) Copies of all correspondence between the IRB and the investigators.	Y	pp. 303-474
		(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.	Y	IIRB roster and credentials on file with EPA
		(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).	Y	Separately submitted to EPA under confidentiality claim
		(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).	n/a	
The following Information, to the extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 335-344
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 335-344
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	pp. 344-5
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	pp. 20-22
		(5) The balance of risks and benefits of the proposed research.	Y	p. 345
		§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Original pp. 384, 438 Approved pp. 411, 456
		§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	pp. 39-40, 335, 350-355, 409, 454
		§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.	Y	pp. 346-9
		§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	pp. 308, 400-406, 437, 452-453, 470-471
		§1125(f): Official notification to the sponsor or investigator…that research involving human subjects has been reviewed and approved by an IRB.	Y	pp. 405, 453