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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

September 30, 2010

MEMORANDUM

SUBJECT: Science and Ethics Review of AHE400: A new scenario design and associated protocol from the Agricultural Handler Exposure Task Force (AHETF) describing proposed research to measure dermal and inhalation exposure to applicators who use backpack or hand gun sprayers to apply pesticides in utility rights-of-way

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REF: Bruce, E. (2010) Backpack and Handgun Application of Liquid Sprays in Utilities Rights-of-Way. Unpublished protocol dated June 18, 2010, prepared for the Agricultural Handlers Exposure Task Force under Sponsor ID AHE400, 558 p.

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

Human Studies Review Board. Below is a summary of the conclusions reached in our science and ethics reviews.

Science Review

- The protocol addresses the technical aspects of applicable exposure monitoring guidelines and is likely to produce scientifically valid and useful data.
- No revisions are requested by EPA at this time.

Ethics Review

- The protocol meets the applicable ethical requirements of 40 CFR part 26, subparts K and L.
- Before the research is conducted, the protocol should be revised as follows and resubmitted for review by the approving IRB:
    - The Local Site Coordinator, the Principal Field Investigator, the Analytical Facility, and the Principal Analytical Investigator must be identified in the protocol.
- In future AHETF protocols, please incorporate into the protocol or an SOP the following information (this information was provided separately to EPA – see Supplements 2 and 3):
    - information about how subjects are presented with individual exposure information; and
    - an explanation of the process that the AHETF follows to improve and verify the accuracy of the Spanish translations.

A. Completeness and Contents of Protocol Submission

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

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

- Backpack and Handgun Application of Liquid Sprays in Utilities Rights-of-Way Scenario Submission (June 18, 2010) (558 pages);
- Supplement 1: SOPs Cited in Backpack and Handgun Application of Liquid Sprays in Utilities Rights-of-Way Scenario Submission (142 pages);
- Supplement 2: Details about method for informing subjects about their individual exposure results (8 pages); and
- Supplement 3: Details about work undertaken by AHETF to improve Spanish translations (1 page).

The monitoring unit selection and scenario construction plan appear on pages 11-58 of 558[1]. The rationale for the proposed sample size and cluster configuration is presented on pages 19-27 of 558. The IRB-approved protocol and supporting documents (consent forms and recruitment flyers) appear on pages 266-345 of 558. Documentation of all interactions between the investigators and the Independent Investigational Review Board, Inc., of Plantation FL appears on pages 259-558 of 558.

B. Summary Assessment of the Scenario Designs[2]

1. **Scenario Designs:** This protocol addresses two distinct handler scenarios to address the use of hand-held equipment for treating utility rights-of-way (ROW); backpack sprayers and hand gun sprayers. Although the two scenarios are distinct, the AHETF intends to collect monitoring units (MUs) for each scenario in the same geographic locations. This may result in the AHETF monitoring participants using either equipment types on any given day. However, the recruitment will be structured so that any participant will be monitored using either one of the equipment types but not both. Separate individuals will be recruited for each equipment type. The AHETF will conduct both studies at electric utility ROWs to develop data for these two scenarios. This is largely based Kline & Co. survey data information suggesting that approximately 80 percent of utility ROWs are treated with herbicides compared to pipeline rights of way.

   The backpack sprayer, as the name implies, is a small 3 to 5 gallon tank carried on the back of a handler. The sprayer has a hand pump to provide pressure for the spray and small lengths of hose connected to a hand wand. Backpack sprayers are best suited for ROW treatments in areas where vehicle access is difficult or impossible. Unlike other backpack scenarios, there will be no mixing activities performed for this scenario. However, some participants may load their backpacks with dilute spray from a nurse tank if that is part of their normal work practice.

[1] Unless otherwise noted, referenced pages may be found in the main scenario submission document (containing 558 pages).

[2] Supporting details are in Attachment 1.

Backpack sprayer

There are a wide variety of backpack sprayers available

By contrast, the handgun sprayer consists of a trigger nozzle (handgun) connected to a length of hose which is attached to a vehicle mounted tank. The application of pesticides with this system requires the handler to either treat vegetation from

the truck or drag the hose from the spray vehicle to the treatment area. The length of the hose can range from 500 to 2000 feet and the handgun has an effective spraying distance of 15 to 30 feet.

The ROW scenarios are not covered by EPA's Worker Protection Standard (WPS) at 40 CFR 170. The WPS only addresses agricultural uses on farms, forests, nurseries and greenhouses. Regardless, the study designed for the two scenarios, is based on participants wearing a long-sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves. Other clothing items that may be worn by participants include vests, hats and goggles. ROW applicators that normally wear chemical-resistant headgear will not participate. There is no specific mixing component for either of these two ROW scenarios (common for hand-held equipment scenarios). Therefore, these data will be used specifically to address occupational handler exposure for ROW treatments.

The AHE400 protocol calls for applying one of four surrogate pesticides for the two ROW scenarios. The surrogate pesticides selected by the AHETF are the widely used herbicides fosamine, gyphosate, imazapyr and 2,4-D. Although fosamine and imazapyr are new surrogates for the AHETF, these pesticides have been successfully used in other occupational and non-occupational exposure monitoring studies, including those in the Pesticide Handlers Exposure Database (PHED). The Agency asserts that confirmation of method analysis, as outlined in the governing document, is required prior to study initiation.

A total of 21 Monitoring Units (MUs) are proposed for both the backpack scenario and the handgun scenario. Three MUs for each site will be collected in

7 geographically distinctive EPA growing regions. Once the studies are reviewed and the AHETF primary and secondary objectives (i.e., relative accuracy and proportionality respectively) are substantiated, the two scenarios will be added to the AHED database. EPA intends to use these data to estimate daily dermal and inhalation exposures of pesticide handlers using backpack and handgun equipment for pesticides registered or to be registered for ROW treatments.

2. **Sampling Designs:** Normally the AHETF (task force) select clusters purposively to reflect a diverse range of crops, agronomic practices, geographic regions and likelihood of finding participants that use the AHETF's surrogate pesticides. For the two ROW scenarios addressed in this protocol, the task force needed to identify regions having high ROW pesticide use commensurate with areas having high electric transmission line densities. Furthermore, considerations such as number of utility companies in a given region and its impact on recruitment and the establishment of distinct study sites needed to be addressed. To accomplish this, the AHTEF designed both scenario cluster configurations as having more study sites and fewer MUs per site (7 x 3 design instead of the 5 x 5 design seen in previous protocols presented to the HSRB). That is, seven clusters (i.e., sites) with each site having three handlers (i.e., MUs) per ROW scenario. These diversified clusters were identified through a two stage diversity selection process:

   - Identifying diverse geographic areas based on climate and areas of high pesticide use for ROW treatments (predominantly the north central and south regions of the United States)
   - Configuring three diverse MUs per geographic area within those regions

   The result of executing these steps was the purposive choice of the following seven monitoring sites which may be states or portions of states purposively selected from six EPA growing regions:

   - West Virginia (EPA Region I with some overlap into EPA Region II)
   - North Carolina (EPA Region II)
   - Florida (EPA Region III)
   - Arkansas (EPA Region IV)
   - Indiana (EPA Region V)
   - Minnesota (EPA Region V)
   - Eastern Texas (EPA Region VI)

   There were a number of site selection considerations acknowledged by the AHETF with respect to utility line density, number of utility companies and EPA growing regions. EPA agrees that the site choices made by the task force are well reasoned and appear to strike a balance between maintaining site diversity and likely success of finding a sufficient pool of participants for the two proposed ROW scenarios.

In the next stage of the diversity selection process, the AHETF identified the practical range of amount of active ingredient handled (AaiH) for the two ROW scenarios. For the backpack ROW scenario the range of amount active ingredient handled (AaiH) per day is 0.5 to 50 pounds per day. For the Handgun ROW scenario, the AaiH is 1 to 125 pounds per day. The strata are designed to ensure that the range of AaiH per scenario is at least an order of magnitude. This will help the task force achieve is secondary objective, proportionality. The scenario specific ai strata are as follows:

Backpack ROW strata

- From 0.5 to less than 1.5 pounds active ingredient
- From 1.5 to less than 15 pounds active ingredient
- From 15 to 50 pounds active ingredient

Handgun ROW strata

- From 1 to less than 3.5 pounds active ingredient
- From 3.5 to less than 35 pounds active ingredient
- From 35 to 125 pounds active ingredient

Generally, the AHETF ensure that no 2 participants be in the same AaiH stratum per monitoring site in the same scenario. However, do to recruitment concerns, the AHETF are concerned that this may not always be possible and have modified the protocol to state that "it is preferable that no 2 MUs be in the same stratum in a monitoring area." It is likely that the range of AiaH at a given site would be at least an order of magnitude if this situation presents itself.

The next stage of sample selection results in identifying the employers of handlers who make ROW treatments. This process requires securing the permission of the utility companies as well as employers of contract ROW application companies. The AHETF established a process for identifying handler subjects that could be recruited directly from utility companies that make their own applications or from utility companies that rely on contract application companies. In either case, the AHETF will need to gain the permission of the utility company to participate in the study. The first step in this process in to list and screen all application companies (which may include the utility company). The procedure is as follows:

- Assemble a comprehensive list of all possible application companies. Eliminate all duplicates where possible.
- On a scenario basis, contact all employers on the list to determine if they are qualified and willing to participate. Those willing and qualified will be put on a potentially eligible list.

- In order to establish an efficient configuration for the eventual field studies, the number of available employees from each application company that is eligible as well as the timing of their ROW applications will be identified.

The second step involves identifying participants for the three MUs per scenario. The second step will be conducted independently for each scenario. This second step includes:

- Establishing a set of eligible employers willing to cooperate with the AHETF
- Conducting recruiting activities
- Selecting volunteers meeting the scenario conditions.

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

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

- No handler may be used more than once
- On a site basis, each handler must come from a different employer

The employers 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 employers 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 other eligible application companies.

3. Choice of Surrogate Materials: The surrogate chemicals proposed for these scenarios are fosamine, gyphosate, imazapyr and 2,4-D, formulated as liquids. There are a few wettable powder formulations of 2,4-D, however it is important to note that these two scenarios involve applying sprays without a mixing component. Although two of these surrogates are new to the AHETF, they have been successfully used in other monitoring studies including those in the Pesticide Handlers Exposure Database (PHED). The Agency asserts that confirmation of method analysis is required prior to study initiation. Given this final verification the Agency agrees that these surrogates are generally appropriate choices for this research. Preliminary risk estimates for the surrogates having toxicity endpoints of concern (2,4-D and imazapyr), indicate the estimated exposures of participants in the proposed studies are not of concern.

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

1. **Statistical design:** This protocol describes collecting 21 Monitoring Units (MUs) for the BP/ROW and HG/ROW reflecting the exposure of subjects applying sprays containing fosamine, gyphosate, imazapyr and 2,4-D. These MUs will be collected in seven separate clusters diverse in geographic location and climate. Each cluster or study site will include three MUs. The AHETF recently designed handler scenarios based on a 5 site x 5 MU configuration, largely for agricultural scenarios. The general rationale for the 7 x 3 cluster configuration is primarily based on concerns of being able to identify more than 3 participants per scenario at any given site. Thus, the AHETF selected a configuration weighted towards having more sites and fewer MUs per site. The overall rational for efficient study designs is presented in Appendix C of the revised AHETF Governing Document.

2. **Proposed pattern of exposure:** The proposed minimum exposure duration for each MU will be at least 4 hours. The activities performed by the participants will be primarily spraying however some loading of dilute spray from tanks situated on trucks may be possible for the backpack scenario. Each participant will spray at least 3 tank-loads. The mixing will be done by others not participating in the study. At each site, during the monitoring period, each subject will apply the surrogate active ingredient in one of the following three strata of amount of active ingredient handled (AaiH):

   Backpack ROW strata

   - From 0.5 to less than 1.5 pounds active ingredient
   - From 1.5 to less than 15 pounds active ingredient
   - From 15 to 50 pounds active ingredient

   Handgun ROW strata

   - From 1 to less than 3.5 pounds active ingredient
   - From 3.5 to less than 35 pounds active ingredient
   - From 35 to 125 pounds active ingredient

   The AHETF acknowledges that some scripting may be needed for subjects assigned to the lower AI strata. This is to ensure that at least 3 mixing/loading events are measured for each worker and that a minimum 4 hour work monitoring period is achieved.

3. **Endpoints and Measures:** The study is designed to measure dermal and inhalation exposure for each MU. These data will contribute to development of

[3] Supporting details are in Attachment 2.

Unit Exposures (exposure per unit of pesticide active ingredient applied) or other exposure metrics that will be used to estimate dermal and inhalation exposure to other pesticides for handlers making ROW applications using backpack or handgun sprayers. EPA believes that the proposed measures are appropriate and sound for the study design.

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

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

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

Airborne concentrations of the surrogate will be monitored in the subject's breathing zone using an OSHA Versatile Sampler (OVS) tube sample collector connected to a personal sampling pump. The unit will be calibrated prior to the monitoring event using a rotameter. The OVS tube will be clipped to the subject's shirt collar with the intake facing downward. The air sampling pump will be connected to the OVS tube and will be operated for the total monitoring period including any breaks. Inhalation measures will need to be based on moderate breathing levels due to the higher activity level of applying pesticides in heavy terrain rather than lower activity levels expected of individuals making groundboom applications.

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

4. **QA/QC Plan:** The study will be monitored by three different quality assurance units: one from the exposure monitoring contractor that conducts the study in the

field, one from the analytical laboratory that determines the level of pesticide residues in field samples, and one contracted directly by AHETF.

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

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

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

D. Compliance with Applicable Scientific Standards

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

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

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

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

1. **Societal Value of Proposed Research:** The objective of this study is to develop data to determine the potential exposure for workers who use backpack and handgun sprayers to apply liquid sprays in utilities ROW. This application method is widely used in utilities ROW to maintain vegetation control, and "is critical to the deliverance of electricity, natural gas, and petroleum across the country. Access to utility lines must be available for maintenance and repair purposes, and is accomplished by controlling line-threatening vegetation." (p. 15 of 558) The existing exposure data for this exposure scenario are inadequate. EPA will use the results of this study to estimate the dermal and inhalation exposure likely for a wide range of agricultural pesticides applied under this exposure scenario.

2. **Subject Selection:** Subjects will be recruited among the employees of application companies that apply pesticide sprays for vegetation control to utilities ROW using backpack or handgun sprayers, who are willing to use at least one of the surrogate active ingredients for this study (glyphosate, fosamine, imazapyr, and 2,4-D), and who meet AHETF criteria for participation. Application companies (either those utility companies that make their own applications or contract application companies hired by utility companies) will be eligible to participate in the study. AHETF must obtain employer cooperation before it can recruit workers. This includes willingness of the utility company to have its ROW treated as well as willingness of the application company (either the utility company or its contractor applicator) to volunteer their application equipment and allow AHETF to recruit their workers. Eligible employers will be identified from a complete list of ROW application companies (i.e. either those utility companies that make their own applications or contract application companies hired by utility companies) in the target area, processed in random sequence. Subjects will be recruited who are employees of eligible employers, have experience within the past year with applying liquids with BP (BP/ROW scenario) or HG spray equipment (HG/ROW scenario) in utilities ROW (including the type of equipment to be used), , and who meet the eligibility requirements of the study. If more employees are available and interested than are needed, qualified participants will be selected randomly. Although the design is purposive, and thus participants are not representative in a statistical sense, they are expected to be typical of those who apply liquids with BP or HS spray equipment in utilities ROW.

   Subjects will be recruited according to the standard procedures set forth in SOP AHETF-11.B. The Study Director or designated researcher will seek permission from an eligible employer to approach his/her employees to recruit subjects for the study. Depending on the number of employees and size of the application company, the Study Director or researcher may contact employees using an informational recruitment flyer posted in a common work area. Alternatively, or

[4] Supporting details are in Attachment 2.

subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the employees who express interest in participation. Such recruitment meetings will always occur without the employer 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 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:** Four 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 risks
    - The risk of exposure to surfactants

    In this study risks to subjects are classified as 'greater than minimal', primarily since agricultural work is considered a high risk occupation where the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, 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. At the end of the test day, subjects will be reminded that they have a copy of the consent form with phone numbers to call if they think they have any adverse effects resulting from participation.

4. **Benefits:** This research offers no direct benefits to the subjects. But subjects may request a summary of their personal results from the study. The results will include the distribution of chemical exposure among the various body parts and a comparison to the results for other workers performing the same task. Thus, a potential indirect benefit for subjects is knowledge about how their exposure compares to that of others doing similar work.

    The principal benefit of this research is likely to be reliable data about the dermal and inhalation exposure of workers applying liquid sprays to utilities ROW with BP or HG spray equipment, usable by EPA and other regulatory agencies to

support exposure assessments for a wide variety of pesticides with similar use patterns.

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

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

7. **Informed Consent:** Informed consent will be obtained from each prospective subject and appropriately documented. Oral fluency in English or Spanish is a criterion for inclusion, but literacy is not required. The reading level of the English language consent form is appropriate. Adequate provision is made to meet the needs of subjects who do not read either language. EPA assessments of compliance with the requirements of 40 CFR §26.1116 and §26.1117 appear in Attachments 4 and 5 to this review.

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

F. Compliance with Applicable Ethical Standards

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

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

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: AHETF Applications in Utilities Rights-of-Way Scenario (AHE400)
2. EPA Protocol Review: AHETF Applications in Utilities Rights-of-Way Scenario (AHE400)
3. §26.1111 Criteria for IRB approval of research
4. §26.1116 General requirements for informed consent
5. §26.1117 Documentation of informed consent
6. §26.1125 Criteria for Completeness of Proposals for Human Research

EPA Scenario Review: AHETF Applications in Utilities Rights-of-Way Scenario (AHE400)

Title: **MU (Monitoring Unit) Selection Plan: Backpack and Handgun Application of Liquid Sprays in Utilities ROW**

Date: June 4, 2010

Sponsor: Agricultural Handler Exposure Task Force

1. Scope of Scenario Design

"Both rights-of-way application scenarios are defined by the form of diluted product, application equipment and use site (i.e., ROW) as follows:

- **Backpack application of liquids in utilities ROW (BP/ROW)**

  Backpacks provide a low volume, low pressure directed spray method of application for controlling undesirable utility line-threatening species of vegetation such as weeds, brush and vines. Although there are different brands of backpack sprayers, and there is some variation in nozzle/wand configurations and tank capacity, they are all operated in more or less the same way. That is, the backpack is carried on the back of a worker; and spray pressure is accomplished by manual pumping to pressurize the tank and squeezing a trigger to release spray via the nozzle/wand. In contrast the HG/ROW scenario, backpack application can be use when vehicle access is not possible or difficult.

- **Handgun application of liquids in utilities ROW (HG/ROW)**

  Handgun spray equipment provides a high volume targeted spray method of application for controlling undesirable utility line-threatening species of vegetation such as weeds, brush and vines. The application system itself is comprised of a handgun which is attached to a hose, which is in turn attached, through a pump, to the spray tank. The spray tank and pump system are mounted on a vehicle such as a truck, so this application technique requires the target vegetation to be accessible by service roads. The worker is often required to drag hose from the spray vehicle to the treatment area where the application is then made. (pp. 14 of 558)

"…Although it is possible that backpacks and handguns are used in utilities ROW in all of the EPA Growing Regions listed in Table 3, not all are expected to have significant use. In particular, the drier climate associated with the western portions of states in Regions VII and VII is not expected to be conductive to the type of vegetation growth that would present utility line-threatening conditions (Standart, 2010). This would result in a minimal amount of backpack and handgun use, especially when compared to such in less dry climates in the east. Therefore, portions of the two Kline marketing areas that intersect EPA Growing

Regions VII and VII will be excluded from the Scenario Target Area. Table 4 lists those EPA Growing Regions that are still likely to have significant backpack and handgun use in utilities. This table documents the final restricted Scenario Target Area and the geographic/climatic stratification of the Area.

Table 4: Final Geographic and Climatic Stratification of the Scenario Target Area based on EPA Growing Regions

EPA Growing Region	States (or portions of states) in the Scenario Target Area that are in EPA Growing Regions
I	Eastern OH, Northern WV, Northern MD, DE
II	Southern WV, Southern MD, VA, NC, SC, GA, AL, Eastern TN, Eastern KY
III	Florida, boot heel of AL
IV	Western TN, MS, AR, LA
V	MI, Western OH, IN, Western KY, IL, MO, IA, WI, MN, Eastern ND, Eastern SD, Eastern NE, Eastern KS
VI	Eastern OK, Eastern TX

(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 both the BP/ROW and the HG/ROW scenarios 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 these use patterns. These products are important because maintaining vegetation control in utilities ROW is critical to the deliverance of electricity, natural gas and petroleum across the country. Access to utility lines must be available for maintenance and repair purposes, and is accomplished by controlling line-threatening vegetation. For these reasons, it is necessary to have data in AHED for the application method described by both scenarios." (pp. 15 of 558)

BP/ROW Scenario

"AHETF (in conjunction with EPA, PMRA, and CDPR, collectively the Joint Regulatory Committee (JRC)) reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that satisfy current acceptability criteria and qualify for inclusion in a generic database. For this particular scenario, the JRC reviewed four studies (AH309, AH313, and AH605, AH613) involving either application only or mixing/loading/applying of liquid formulations with backpack sprayers. None of these studies were deemed appropriate for a generic database.

"The AHETF purchased a liquid formulation backpack mixer/loader/applicator study (AH605-MLA) that was conducted in a greenhouse using a typical low pressure backpack with a handwand. Applications were made to plants on benches and, in some cases hanging overhead baskets. Thus, low volume equipment and general directions are comparable in greenhouse and ROW. However, this study was not deemed appropriate for extrapolation to this scenario because there are differences in other important exposure conditions. For example, conditions encountered in ROW application include walking in rough, uneven terrain while targeting a mixture of brush/vine/weed heights and densities, and contending with outdoor environmental conditions…" (pp. 16 of 558)

The AHETF also conducted a detailed review of the data in two potential relevant PHED (EPA, 1998a) backpack application scenarios to determine if any of the data were suitable for a modern generic database. These PHED scenarios were:

- Scenario 20 – Backpack Application (APPL). This PHED scenario contains exposure data for monitoring units making only backpack applications
- Scenario 34 – Liquid/Open Pour/Backpack (MLAP). This PHED scenario contains data for MUs involved in mixing, loading, and applying liquid formulations with backpacks.

The AHETF is interested in only those PHED MUs corresponding to a single layer of clothing with chemical-resistant gloves. In the detailed AHETF review of these PHED data, no MUs were found that met the acceptance criteria established by AHETF (Klonne, 2010a; Klonne 2010b). For Scenario 20 the dermal data are graded as "Low Confidence" due to insufficient dosimetry, although the inhalation data are graded as 'High Confidence". For Scenario 34 the dermal and inhalation data are graded as "Low Confidence", primarily due to low numbers of measurements. Thus, there are no data currently in PHED for this scenario that are useful for a modern generic database.

"Finally, EPA examined data from existing water soluble packet mixing/loading exposure studies or exposure assessments that were not available to the AHETF and concluded that none of the exposure data should be included in the AHETF database (meeting, November 3, 2008)." (pp. 17 of 558)

HG/ROW Scenario

"For the HG/ROW scenario the JRC reviewed on study (AH315-A) involving application of liquid sprays with a handgun sprayer from a truck. This study was ultimately determined not to be appropriate for a generic database due to a variety of clothing combinations and the use of two layers of clothing.

The AHETF review of the handgun application data in PHED focused on data for a single layer of clothing (with gloves) in the following seven PHED scenarios:

- 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 24 – Right-of-Way Sprayer Application (APPL). This PHED scenario contains exposure data for monitoring units making actual ROW handgun applications in brush.

- Scenario 32 – Wettable Powder/ 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.

"For scenario 18 the dermal data are graded as "Low Confidence" due to an inadequate number of dermal and hand measurements. Inhalation data are graded as "Low Confidence" due to an inadequate number of measurements. For Scenario 19 the dermal data are graded as "Low Confidence" due to an inadequate number of dermal and hand measurements and to poor grade quality. Inhalation data are graded as "Low Confidence" due to low number of measurements and to poor grade quality. For scenario 21 the dermal and inhalation data are graded as "Low Confidence". For Scenario 24 the dermal data are graded as "Low Confidence" due to lack of dermal and hand measurements, but the inhalation data are graded as "High Confidence". For Scenario 32 the dermal data are graded as "Low Confidence" due to an inadequate number of dermal and hand replicates. Inhalation data are graded as "Medium Confidence". For Scenario 33 the dermal and inhalation data are graded as "Medium Confidence". For Scenario 35 the dermal and inhalation data are graded as "Low Confidence" due to an inadequate number of measurements." (pp. 17 – 18 of 558)

EPA asserts that rejecting data in PHED based on low numbers of samples is not sufficient justification for not considering PHED data for inclusion in the new database. The more important reasons, as is the case for these data, include issues such as study design (patches, AaiH strata) and that the activities measured are not specific to the ROW scenarios the AHETF are addressing in this protocol (e.g., studies conducted in greenhouses, poultry houses and lawn care settings).

"Lastly, EPA examined data from existing handgun applicator 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, May 05, 2009)." (pp. 19 of 558)

2. Rationale for Scenario Sampling Design

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

"… the Target Area for both scenarios is identical and has been restricted to two of the four major marketing regions defined by Kline & Co. covering 28 states (or portions of states) in the mid-west, south and eastern portions of the US. These two regions account for about 90% of chemicals used in vegetation management in utilities ROW. Although other areas of the U.S. not contained in these two regions may utilize backpacks or handgun in utilities, application conditions are not expected to differ significantly from those in the Target Area. This is because regardless of location, each scenario's application equipment (i.e., backpack or handgun) is typically used under certain growth conditions such as height and density of brush, and can involve terrain ranging from flat to mountainous.

Both of these scenarios focus on treating foliage of the target vegetation because it is the most efficient, and therefore most commonly used, method of application. However, some vegetation situations may require a non-foliar treatment such as frilling (hack and squirt) to be used in conjunction with foliar application. If a non-foliar technique is used in conjunction with foliar application, it will be included in the monitoring; however, MUs will not be monitored solely for non-foliar application." (pp 6 – 7 of 558)

"The selection of monitoring sites within each stratum was purposive and considered several factors including size of the monitoring site (e.g. state or portion of state) and utility transmission line density. The following monitoring sites are proposed for both scenarios to provide the desired diversity in geography and climate within each scenario.

- West Virginia (in EPA Growing Region I, extending slightly into II)
- North Carolina (in EPA Growing Region II)
- Florida (in EPA Growing Region III)
- Arkansas (in EPA Growing Region IV)
- Indiana (in EPA Growing Region V)
- Minnesota (in EPA Growing Region V)
- Eastern Texas (in EPA Growing Region VI)" (pp. 5 or 558)

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

For both scenarios, all choices in the proposed diversity selection process, and stratification by AaiH are purposive choices.

"Both backpack and handgun foliar application to utilities ROW can occur over a wide geographic area and at different times. Locating a potential worker and handling-day condition from which to construct an MU is a complicated process. No comprehensive list of future applicator locations and dates is available. As a result, potential application conditions have to be selected (and/or constructed in stages).

In essence, this selection process for a particular scenario can be envisioned as occurring in two successive stages. The first stage consists of selecting moderately-sized geographic areas from which the monitoring units will be obtained. Each such area is termed a 'monitoring site' and will typically consist of a convenient political entity, such as a state (or portion of a state). Application companies within each monitoring site are screened to indentify qualified employers willing to participate in the monitoring program. The second stage of this process identifies potential worker volunteers and application conditions from among the identified employers and uses this information to construct a diverse set of monitoring units. When feasible, it is preferable that this final set of MUs be arranged in an efficient configuration. That is, all else being equal, the configuration of locations and monitoring dates of the MUs should be as cost-effective as possible. An efficient configuration is expected to result in a single cluster of MUs that are slightly correlated with respect to exposure. Consequently, for scenario design purposes only, it will be assumed, conservatively, that there is only a single cluster per monitoring site. In practice, less cost-effective configuration of MUs consisting of multiple clusters might arise." (pp 11-12 of 558)

"…the basic conditions necessary to construct MUs for either the BP/ROW scenario or the HG/ROW scenario are obtained by a two-stage diversity selection process. These two stages are:

1. Selection of seven monitoring sites that are diverse with respect to geography and climate. (Section 5.2)

2. Selection and construction of a configuration of three diverse monitoring units within each monitoring site. (Section 5.3)

At both stages, diversity among selection units (monitoring sites of MUs) is formally induced by first grouping the available units to be selected into combinations called strata (Section 5.1). Then, similarity restrictions and preferences are imposed on the selection units making use of these strata and other characteristics. For practical reasons, selection of units will usually be purposive. However, whenever feasible, random selection of monitoring units will be used to reduce selection bias. (pp 19 of 558)

"…diversity among MUs is aided by grouping selectable units into 'strata' defined by one or more key characteristics of the scenario. These strata are then utilized at both the first and second stages of selection. At the first stage, the relevant strata are geographic/climatic partitions of the Scenario Target Area. The Scenario Target Area for both scenarios is the geographic extent considered for MUs and encompasses that portion

of the U.S. where both backpack and handgun application in utilities ROW are most likely to occur.

The second stage of selection makes use of a stratification of the amount of active ingredient handled (AaiH) to diversify MUs. A practical AaiH range is first defined for each scenario. The practical range encompasses AaiH levels that can be readily found in practice and are expected to produce detectable exposure results. The practical range is then stratified so that an MU can be selected from each AaiH stratum. (pp 20 of 558)

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

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

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

"…the workers will be allowed to follow their normal procedures as long as they fit the scenario definition. The duration of the work activity will be partially determined by the amount of AaiH but will involve the application of at least three loads (BP/ROW only) and a minimum duration of four hours (both scenarios).

Work activity characteristics that are scenario specific include the following:

- **BP/ROW Scenario**

A parameter that might impact exposure is returning to the filling station and re-filling the backpack. According to experts, ROW backpack application workers typically fill their own sprayer. The filling process can range from using completely closed systems to using a nozzle to a mixing tank to pump liquid into the backpack tank opening, which could result in direct contact with the liquid in cases of overfilling of splashing. In addition, the worker could increase dermal exposure by contacting contaminated surfaces such as the support vehicle or mixing tank. For this scenario, whether or not a subject loads his own backpack will be determined by the standard practice of the particular application company.

Another parameter that might impact exposure is the number of loads handled, primarily because it involves re-filling the backpack tank. AHETF has a standard practice that each MU will apply a minimum of three tank loads. This ensures the generic database will contain exposure data generated from work periods that represent a full day (i.e., generally four hours or more), and from repeated filling and application cycles that increases the chance for exposure (and therefore will not underestimate exposure potential). Some diversity in the number of loads will naturally occur since AaiH and

equipment tank size will vary, as will MU site conditions such as distance from mix tank to target vegetation, thickness of vegetation and roughness of terrain." (pp 37 of 558)

- **"HG/ROW Scenario**

A parameter that might impact exposure is returning to the vehicle. A worker could return to the vehicle to take breaks, wait for a new load of spray mix, or get into the vehicle to move to the next treatment area. In any of these situations, dermal exposure could be increased by contacting contaminated surfaces of the vehicle or contacting treated foliage that is in the path of the worker walking out of the treatment area to the vehicle.

Duration of monitoring is another parameter that could vary between MUs of either scenario, especially since the AaiH will probably vary by more than an order of magnitude. Experts indicate that ROW backpack and handgun applicators spend several hours per day making applications (including walking to and from the treatment site). All monitoring periods for this scenario must meet the general rule of being at least 4 hours. This is designed to overcome the criticism of early exposure studies where many of the sampling regimes monitored workers for only a few minutes. Avoiding very short monitoring intervals will ensure that daily exposure estimates are not biased by unusual conditions during the short interval. If necessary, some minor scripting of worker activities will be done to ensure the lowest levels of AaiH are handled and/or a minimum of four hours are monitored. For example, in the BP/ROW scenario, a worker may be asked to use a smaller tank, or decrease load size, etc., in order to apply 3 loads in four hours. Or, an HG/ROW scenario worker may be asked to adjust the spray concentration in order to achieve the lowest levels of AaiH." (pp 46 of 558)

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

"Because of the diversity obtained for AaiH and the variability of vegetation conditions which may be encountered in this study, equipment will likely differ among MUs as each applicator utilizes the appropriate spray volume, pressure, nozzle configuration, etc." (p. 39 of 558)

"…some workers might wear non label-required items such as leggings or chaps over their regular clothing. However, such additional attire would interfere with AHETF's preference to collect data using baseline clothing (i.e., long pants and long sleeved shirt). Therefore only workers who do not wear items such as leggings or chaps will be used in this study.

…chemical-resistant headgear is not required by any product labels reviewed to date; however, since applications can involve spraying into vegetation that can reach about 10 feet (BP/ROW) or 20 feet (HG/ROW) in height, it is possible that a worker might choose

to wear some type of chemical-resistant headgear. Nonetheless, only workers who do not wear chemical-resistant headgear will be used in this study.

…not all products that might be used in these two scenarios require the use of chemical-resistant gloves. However, AHETF has learned that some companies interviewed require their use as company policy, and that other products frequently used in tank mixes do require the use of gloves. For this reason, and to ensure consistency of data collection for hand residues, it will be the practice of AHETF to only monitor workers wearing chemical-resistant gloves." (pp 48 of 558)

3. Are the proposed test materials appropriate surrogates?

"The following active ingredients will be considered for use in both the BP/ROW and HG/ROW application scenarios.

- Glyphosate
- Fosamine
- Imazapyr
- 2,4-D

These AHETF survey confirmed that one or more of these AIs are commonly used in all seven of the monitoring sites. They provide a range of use rates, including one with a relatively high rate which will enable measurements at the high end of the AaiH per day. Prior to study conduct analytical methods for each surrogate AI will be developed and validated for each matrix used in this study. Matrices include: inner dosimeter, hand rinse, face/neck wipe, socks and OVS tubes. Finally, these active ingredients will be or have been either tested for stability or have been used as surrogates in other studies and are known to have the required stability under field study conditions." (pp. 48-49 of 558)

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

"Appendix C of the Governing Document describes the methodology to calculate sample sizes when the reference model used is cluster sampling from a lognormal distribution. For the purposes of determining sample sizes, the default variation structure for normalized dermal exposure derived in Appendix C from an analysis of multiple studies. This default, a geometric standard deviation (GSD) of 4.0 is also assumed applicable to both the BP/ROW and HG/ROW scenarios. AHETF and the Joint Regulatory Committee agreed there is no evidence to suggest that dermal exposure variation is substantially different from this default value and had no strong opinion to the contrary (meeting with AHETF, May 27, 2010).

The analogous default intra-cluster correlation (ICC) developed in Appendix C of the Governing Document is 0.3. For both of these ROW application scenarios, it is conceivable that the ICC could be less than 0.03. …since there are no data available for estimating a different ICC value to use and since overestimating the ICC results in larger total sample sizes, the use of ICC=0.3 is still considered reasonable, albeit conservative.

As discussed in Appendix C, when this default variation structure is used (and there are no suitable existing MUs) there are several equivalent configurations of number of monitoring sites (N_C) and number of MUs per monitoring site (N_M) that will meet the 3-fold accuracy requirement. These equivalent configurations are listed in Table 2.

Table 2: Equivalent Configurations of Number of Monitoring Sites and Number of MUs per Monitoring Site

Number of Monitoring Sites, N_C	Number of MUs per Monitoring Site, N_M	Fixed/Variable Cost Ratio where Optimal
15	1	0 - 05
9	2	0.5 - 1.5
7	3	1.5 - 2
5	5	2 - 7
4	8	Over 7

Although these five configurations are statistically equivalent, they can differ substantially in cost or in their attainability. When the 5 configurations an Table Two are equal feasible, the choice among them depends upon the expected ration of the overhead (or 'fixed') cost of obtaining and characterizing a monitoring site and the additional (or variable) cost per MU. For most typical scenarios the AHETF estimates that this ratio is between 4.5 and 6. That is, the overhead cost of a new monitoring site is about the same as the cost of adding 5 or 6 new MUs to an existing monitoring site. Given this cost ratio, a sample of 5 monitoring sites (N_C=5) with 5 MUs per site (N_M=5) is usual the most cost effective design configuration that meets the 3-fold accuracy requirement. Configurations with more monitoring sites and fewer MUs per site provide greater statistical information per MU (the reason that fewer total MUs are needed) but they are also more costly due to the large overhead per additional monitoring site.

"Appendix C of the Governing Document also shows that when the benchmark accuracy requirement above is met there may also be sufficient power to permit users of the database to perform a limited examination of the relationship between the normalizing factor (e.g., AaiH) and exposure. This is true provided: (1) the practical range of the normalizing factor is at least an order of magnitude and (2) there is adequate within-cluster variation in the normalizing factor. When these conditions occur, the MU sample will be of sufficient size and diversity to provide at least 80% statistical power to distinguish complete proportionality from complete independence between exposure and the normalizing factor used in the primary benchmark. Since these conditions can be satisfied for the reference sampling design, then the purposive diversity design for both the BP/ROW scenario and the HG/ROW scenario should provide adequate power for the minor (i.e., secondary) objective: the ability to conduct limited examinations of the relationship between AaiH and exposure." (pp. 17-19 of 558)

EPA Protocol Review: AHETF Applications in Utilities Rights-of-Way Scenario (AHE400)

Title: Determination of Dermal and Inhalation Exposure to Workers during Backpack and Handgun Application of Liquid Sprays in Utilities Rights-of-Way

Revision Date: June 4, 2010

Study Director and Principal Investigator:
Eric D. Bruce

Principal Field Director:
Aaron Rotondaro

Local Site Coordinator: TBD

Field Facility: **"**The study…will be conducted in a variety of utilities ROW locations in an outdoor environment. The Principal Field Investigator utilizes a mobile laboratory (a large truck or trailer) that provides the necessary private and clean environment for dressing workers, undressing workers, and collecting exposure samples from workers. Since there is no field facility *per se* where the study is conducted, no address is provided." (p. 303)

Analytical Facility: TBD[5]

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

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

1. Societal Value of Proposed Research

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

"The objective of this study is to develop data to determine the potential exposure for workers making backpack (PB) and handgun (HG) liquid applications in utilities rights-

[5] The analytical laboratory selected will depend on which active ingredients are actually used in the study. This study may involve multiple active ingredients so multiple analytical investigators and analytical facilities may be involved. The final report will document which laboratories and Principal Analytical Investigators are involved with analysis of samples from this study. (p. 304)

of-Way (ROW) at seven monitoring sites spanning six geographical/climatic regions of the United States." (p. 301)

(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 handlers making BP/ROW and HG/ROW applications. This is an important pesticide handling scenario for which existing data are inadequate.

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

EPA will use the results of this study to estimate the dermal and inhalation exposure likely for handlers making BP/ROW and HG/ROW applications.

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

"AHETF (in conjunction with EPA, PMRA, and CDPR, collectively the Joint Regulatory Committee (JRC)) reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that satisfy current acceptability criteria and qualify for inclusion in a generic database. For the BP/ROW scenario, the JRC reviewed four studies (AH309, AH313, AH605 and AH613) involving either application only or mixing/loading/applying of liquid formulations with backpack sprayers. None of these studies except AH605 was found to be appropriate for a generic database. … [This purchased study will, however be considered in another scenario that represents backpack applications in greenhouses and nurseries.]

The AHETF also conducted a detailed review of the data in two potentially relevant PHED (EPA 1998a) backpack application scenarios to determine if any of the data were suitable for a modern generic database . . . Thus there are no data currently in PHED for this scenario that are useful for a modern generic database." (pp. 16-17 of 558)

For the HG/ROW scenario, the JRC reviewed one study (AH315-A) involving application of liquid sprays with a handgun sprayer from a truck. This study was ultimately determined not to be appropriate for a generic database due to a variety of clothing combinations and the use of two layers of clothing.

"AHETF also conducted a detailed review of the data in PHED for this scenario to determine if any of the data were suitable for a modern generic database. . . . Thus there are no data currently in PHED for this scenario that are useful for a modern generic database." (pp. 17 of 558)

(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 apply ROW pesticides for measuring their dermal and inhalation exposure.

2. Study Design

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

"The goal of conducting MUs for the BP/ROW and HG/ROW scenarios 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 these two related scenarios. . . . . the data collected for these two scenarios 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 (pp. 54 of 558)

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

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

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

2.1 Statistical Design

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

"Appendix C of the Governing Document describes the methodology to calculate sample sizes when the reference model used is cluster sampling from a lognormal distribution. For the purposes of determining sample sizes, the default variation structure for normalized dermal exposure derived in Appendix C from an analysis of multiple studies. This default, a geometric standard deviation (GSD) of 4.0 is also assumed applicable to both the BP/ROW and HG/ROW scenarios. AHETF and the Joint Regulatory Committee agreed there is no evidence to suggest that dermal exposure variation is substantially different from this default value and had no strong opinion to the contrary (meeting with AHETF, May 27, 2010).

The analogous default intra-cluster correlation (ICC) developed in Appendix C of the Governing Document is 0.3. For both of these ROW application scenarios, it is conceivable that the ICC could be less than 0.03. …since there are no data available for estimating a different ICC value to use and since overestimating the ICC results in larger total sample sizes, the use of ICC=0.3 is still considered reasonable, albeit conservative." (pp. 17 of 558)

(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?

"A configuration of three MUs is obtained from among the potential volunteers and their possible monitoring conditions. It is desirable that the set of potential MUs be large enough to permit some random selection of equivalent volunteers and to account for situations in which companies of participants are not available at the last minute for the scheduled monitoring. Generally, this means an attempt to identify conditions that might provide about twice the number of MUs actually needed.

… The three MUs in any monitoring site must also satisfy the following similarity restrictions:

- No two MUs obtained for the same scenario can utilize the same worker
- No two workers in the same monitoring site used for the same scenario can have the same employer

In addition, whenever feasible, it is preferable, but not mandatory, that the configuration of MUs in a monitoring site also satisfy the following two similarity restrictions:

- It is preferable that no two MUs obtained for the same scenario in the same monitoring site be in the same AaiH stratum
- If an employer has previously contributed a worker to an MU in a different monitoring site for the same scenario, then it is preferable that this same employer not contribute another worker. (pp. 43 to 44 of 558)

"The study director will determine the meaning of sufficient set of potential MUs' that should apply to a scenario or to an individual monitoring area. In general, however, it is desirable that the set of potential MUs be large enough to permit some random selection of equivalent volunteers and to account for situations in which companies or participants are not available at the last minute for the scheduled monitoring. Therefore, for each monitoring area every effort should be made to obtain (for each scenario):

- At least 6 workers who may potentially volunteer for the study
- At least 2 of these workers available for each of the AaiH strata" (pp. 406 of 558)

(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.'" (pp. 54 of 588)

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

"… the data collected for these two scenarios 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." (pp. 54 of 558)

"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 95^{th} 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." (pp. 55 of 558)

"This secondary benchmark objective [Adequacy of the Data for Distinguishing a Proportional from an Independent Relationship between Exposure and AaiH] applies to both the BP/ROW and the HG/ROW scenarios because the practical range in the amount of the AaiH exceeds an order of magnitude in both cases. 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. 55 of 558)

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

Yes.

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

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

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

"This secondary benchmark objective applies to both the BP/ROW and HG/ROW scenarios because the practical range in the AaiH exceeds an order of magnitude in both cases. In this case it is reasonable to consider the linear regression of log dermal exposure on log AaiH. Such a regression would use a mixed model formulation in order to incorporate random cluster effects. As described in the Governing Document, in such a model the true slope, β, would be equal to one if dermal exposure were directly proportional to AaiH. If exposure were independent of AaiH, then β=0. This benchmark objective requires that the number of clusters and the allocation of AaiH levels to MUs should be adequate to ensure that the regression analysis has at least 80% power to reject the hypothesis that β=0 when β is actually equal to one. By symmetry, the mixed model linear regression would also have the same power to reject the hypothesis that β=1 when β=0. This is the precise meaning of being able to 'discriminate between proportionality and independence'." (pp. 55 of 558)

2.2 How and to what will human subjects be exposed?

"The following active ingredients will be considered for use in both the BP/ROW and the HG/ROW application scenarios.

- Glyphosate
- Fosamine
- Imazapyr
- 2,4-D" (pp. 48 of 558)

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

"The AHETF survey confirmed that one or more of these AIs are commonly used in all seven of the monitoring sites. They provide a range of use rates, including one

with a relatively high rate which will enable measurements at the high end of the AaiH per day." (pp. 40 of 558)

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

"Since the number of pounds of active ingredient handled is the normalizing factor and indirectly influences many other handling conditions, efforts will be taken to generate data in as wide a range of AaiH as practical within each monitoring site. AaiH is selected as the normalizing factor since AHETF feels it is the most reasonable measure of active ingredient contact potential for both of these scenarios. . . . In addition, EPA currently normalizes both backpack and handgun application exposure by AaiH during pesticide product exposure assessments. No other normalizing factor identified as being more appropriate.

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

AHETF has developed practical ranges in AaiH for both scenarios 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. These practical ranges for amounts of active ingredient handled per day are:

- BP/ROW scenario: 0.5 to 50 lbs per day
- HG/ROW Scenario: 1 to 125 lbs per day

The lower practical limits of 0.5 pounds (BP/ROW) and 1 pound (HG/ROW) of active ingredient per day are selected to avoid an inordinate number of non-quantifiable residues on worker exposure matrices. (pp. 23-33 of 558)

(c) What duration of exposure is proposed?

"Duration of monitoring is another parameter that could vary between MUs, especially since the AaiH will be varied by more than an order of magnitude. Experts indicate that ROW backpack and handgun applicators spend several hours per day making applications (including walking to and from the treatment site). All monitoring periods for this scenario must meet the general rule of being at least 4 hours. This is designed to overcome the criticism of early exposure studies where many of the sampling regimes monitored workers for only a few minutes. Avoiding very short monitoring intervals will ensure that daily exposure estimates are not biased by unusual conditions during that short interval. If necessary, some minor scripting of worker activities will be done to ensure the lowest levels of AaiH are handled and/or a minimum of four hours are monitored. For example, a worker might

be asked to adjust the spray concentration in order to achieve the lowest levels of AaiH." (pp. 46 of 558)

2.3 Endpoints and Measures

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

"Full details of procedures for dermal and inhalation exposure sampling and for sample removal are specified in the most recent versions of SOPs AHETF-8.A, 8.B, 8.C and 8.I. At the completion of the monitoring period, exposure samples will be taken in the following order to minimize cross contamination: inhalation samples…, then inner socks, then hand washes, then face/neck wipes, and finally inner dosimeters as described in SOP AHETF-10.E….For this study, inner dosimeters will be cut into 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 AHETF-8.D and 10.G (pp. 334-335 of 558)."

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

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

"In addition for each fortification event, duplicate samples of the inner dosimeters fortified in the field at the highest level, and duplicate OVS tubes fortified in the laboratory at the next-to-highest fortification level, will be processed in the field for immediate frozen storage and used as travel spikes. These travel spikes will be analyzed on if deemed necessary be the Study Director, for example to help determine the cause of unusually low field fortification recovery results." (pp. 336 of 558).

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.

(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 1.14 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 laboratory conducting QA audits, and from the QAU specified in section 1.14." (pp. 343 of 558)

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

Uncertainty in field measurements will be addressed via fortification samples.

"Sample matrix fortifications designed to assess the stability of the active ingredient during field, storage and transit conditions in or on the sampling materials (inner dosimeters, hand wash solutions, face/neck wipes, and air sampling matrices) will be conducted on a minimum of one day of exposure monitoring at each location, or more days as appropriate for environmental conditions. . . . 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." (pp. 335-336 of 558)

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 filling (if applicable) and applying liquid sprays of pesticide to target foliage under both the BP/ROW and

HG/ROW scenarios. Each instance is termed a monitoring unit (MU). Every MU consists of a set of application conditions (including the particular worker) that are intended to represent the scenario activities for a single workday. In many cases monitoring units will be selected from 'naturally occurring' applicator-days. However, the selected application conditions are sometimes modified or scripted slightly to ensure that the complete sample of MUs reflects the expected diversity in the entire population of future applicator-days. . . .Thus, MUs are technically not 'sampled' from a population. More correctly, they should be viewed as synthetic applicator-days derived from both selected and constructed conditions." (pp. 19 of 558)

(b) From what populations will subjects be recruited?

"Not all application companies (i.e. either those utility companies that make their own applications or contract application companies hired by utility companies) will be eligible or be willing to participate in the study. AHETF must obtain employer cooperation before it can recruit workers. This includes willingness of the utility company to have its ROW treated as well as willingness of the application company (either the utility company or its contractor applicator) to volunteer their application equipment and allow AHETF to recruit their workers.

For this reason, employers that are both qualified for a particular scenario and willing to participate need to be identified within each monitoring site. AHETF has determined that it is practical to list and screen the vast majority of application companies within each entire monitoring site for this information." (pp. 40-41 of 558)

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

"Subject recruiting activities can be conducted for any eligible employer, giving preference to those with more time-critical application schedules, more likely to fill a desired AaiH stratum, or expected to provide needed diversity in other important conditions. Specific recruitment procedures will be detailed in the protocol and appropriate SOPs. Workers desiring to volunteer are evaluated to determine if they, and their expected handling conditions, are consistent with the three MUs needed. The recruitment activities and the evaluation of volunteers continue as long as potential MUs are needed or until no further recruitment is possible." (p. 43 of 558)

"Study participants will always use equipment that is typical for a particular scenario and that they have recently operated (within the last year). Recent experience is required to ensure that the activity performed by each worker is on that they typically perform." (pp. 46 of 558)

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

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

3.2 Equitable Selection of Subjects

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

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

- Have experience within the past year with applying liquids with BP (BP/ROW scenario) or HG spray equipment (HG/ROW scenario) in utilities ROW (including the type of equipment to be used)
- Handle pesticides as part of their job
- Be trained in safe pesticide handling procedures
- Provide proof of being at least 18 years old with a government-issued photo ID
- Confirm they do not work for a pesticide company or a contractor of the AHETF
- Consider their general health status to be good and tell researchers they have no medical conditions that affect their ability to participate in the study [See SOP AHETF-11.C.1 for health status determination]
- Not be pregnant or nursing [See SOP AHETF-11.D.1]
- Confirm they do not normally wear personal protective equipment that is not required by the label and that might impact the objectives of the study, such as chemical-resistant clothing. NOTE: Volunteers may not participate in this study if they indicate they always wear extra clothing such as chaps or leggings to protect against physical hazards. However, if application conditions are such that the volunteer would not normally wear this type of additional clothing, then the volunteer is eligible to participate in the study if all other inclusion criteria are met.
- Confirm they will follow label directions.
- Agree to wear chemical-resistant gloves even if the label does not require them.
- Have a private meeting with a researcher to review and discuss the consent form
- Understand English or Spanish [See SOP AHETF-11.I.2 for a detailed discussion of this topic]
- Understand and sign the consent form [SOP AHETF-11.B.5]" (pp. 304-305 of 558]

(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 employers and by requiring employers 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 company selected, AHETF will follow standard procedures (see SOP AHETF-11.B) 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 employer to approach his/her employees to recruit workers for the study. Depending on the number of employees and size of the company'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 company's employees who express an interest in participation. Such recruitment meetings will always occur without 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." (p. 327 of 558)

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

"In accordance with SOP AHETF-11.B[.5], the individual employers will be asked to sign a noncoercion 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. 326 of 558)

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 consent meeting with a researcher who will obtain the informed consent of the worker (Section 2.7). Workers will be paid $20 for their attendance right after the consent meeting, whether or not they decide to participate in the study. Workers who decide to participate in the study will be paid an additional $80 each time they suit up (i.e., put on the long underwear) to participate in the study. Usually, workers will participate in the study on only one day unless their participation is terminated due to weather or other unexpected occurrences. The additional $80 is provided in cash at the end of the monitoring period or at the time the volunteer withdraws from the study. All workers who participate will receive the payment, even if they withdraw or their participation is terminated by the study team." (pp. 305-306 of 558)

(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.

For both the BP/ROW and HG/ROW scenarios, the study could involve any of four active ingredients: imazapyr, 2,4-D, fosamine, and glyphosate. "The pesticide products containing these active ingredients and potentially used in this study are

currently registered for vegetation control in utilities ROW. AHETF will only monitor workers making applications in accordance with all label requirements." (p. 308 of 558)

For imazapyr and 2,4-D, the calculated MOEs meet or exceed the required MOE for both the individual dermal and inhalation routes of exposure, as well as for the combined exposure, and their use is acceptable for this scenario. For fosamine and glyphosate, MOEs cannot be calculated because no adverse effects were reported at the highest dose tested in any of the acute toxicity studies. Their use is also acceptable.

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

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

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

"In this study risks to subjects are classified as 'greater than minimal', primarily since agricultural work is considered a high risk occupation where the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, 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. 306 of 558)

Each of these four kinds of risk is discussed in the protocol (pp. 306-312 of 558) and the consent form (pp. 429-430 of 558).

(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 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 on site to observe the workers and provide urgent care
- Observing study participants throughout the monitoring period
- Ensuring that all tank mix products are used according to approved label(s) and do not require any additional PPE that could adversely affect the study objectives (for example, chemical-resistant coveralls)." (pp. 311-312 of 558)

Risk reduction actions specific to each of the four identified kinds of risk are discussed in the protocol (pp. 306-312 of 558).

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

For imazapyr and 2,4-D, the calculated MOEs meet or exceed the required MOE for both the individual dermal and inhalation routes of exposure, as well as for the combined exposure, and their use is acceptable for this scenario. For fosamine and glyphosate, MOEs cannot be calculated because no adverse effects were reported at the highest dose tested in any of the acute toxicity studies. Their use is also acceptable.

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

"AHETF will monitor ambient conditions outside the cab to determine the heat index near the mixing/filling station. 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. 307 of 558)

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

"As a safety measure, AHETF will have a medical professional on site during the study. This may be a paramedic, physician's assistant, nurse, or emergency medical technician. This professional will also watch you for signs of illness. They will provide medical attention as needed." (p. 429 of 558)

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

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

"During the consenting process each volunteer will be provided the opportunity to request a summary of their personal results from the study. This will require the worker to provide a name and address (mail or e-mail). The results will include the distribution of chemical exposure among the various body parts and a comparison to the results for other workers performing the same task. Results are typically available 9-12 months after monitoring occurs. The personal information related to this follow-up will be retained as described in SOP AHETF-6.D.

"Just prior to the completion of the worker's participation in the study, a researcher will remind the participant he/she should bathe or shower as soon as practical and that they have received a copy of the signed consent form with phone numbers for reporting any health changes they think might be related to participation in the study. Post-study inquiries will be forwarded to the Study Director who will deal with the situation as appropriate and notify AHETF management (SOP AHETF-11.J)." (p. 316 of 558)

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

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

"AHETF will cover the cost of reasonable and appropriate medical attention for a study-related injury or illness that is not covered by your own insurance or insurance

provided through your employer. This includes deductible costs and any out-of-pocket expenses, including co-payments, you might have. The Study Director, in consultation with the on-site medical professional, will decide if you have an illness or injury that is due to your participation in this study." (p. 430 of 558)

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. 390 of 558)

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

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

"Since there are not sufficient existing data suitable for use in a generic database describing the exposure to workers from BP and HG application in rights-of-way, society will likely benefit from data generated by this study through the improved risk assessments by EPA and other regulatory agencies." (p. 390 of 558)

"Data from the AHETF exposure monitoring program has the potential to improve the ability of EPA and other regulatory agencies to accurately assess occupational risks associated with spraying pesticides to rights-of-ways using backpack sprayers and handgun sprayers. The knowledge likely to be obtained from this study is generalizable and will contribute to assessments of the risks of both new and existing pesticides." (p. 390 of 558)

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

"Utility companies (or their contract applicator) who allow the study to be conducted using their equipment will be reimbursed for the pesticides used for the study. While this is beneficial to the application company, it is considered a minor benefit when compared to the costs of running their businesses. The AHETF member companies will likely realize a benefit by addressing regulatory data requirements generically, at lower cost (and using fewer human subjects), than if they conducted similar studies for individual pesticide ingredients." (p. 390 of 558)

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

Identified societal benefits are likely to be realized.

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

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

"The likely benefit to utility 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. BP and HG applications are often essential components of an overall vegetation management program for maintaining utilities ROW. Therefore, exposure data for these scenarios meeting contemporary standards of reliability and quality will likely provide a significant benefit to society. Because the margins of exposure are acceptable for the products proposed for use in this research study, subjects are very unlikely to experience acute toxic effects, and because extensive procedures will be in place to minimize these and other risks to participants, the likelihood of serious adverse effects is very small. In summary, AHETF believes the risks to study participants from participating in this study are reasonable in light of the likely benefit to society of the knowledge to be gained." (p. 391 of 558)

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Independent Investigational Review Board, Inc., of Plantation FL

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

(c) Is this IRB registered with OHRP? Yes

(d) Is this IRB accredited? No.

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

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

Yes.

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

"This study will be conducted in accordance with EPA's final regulation published at

40 CFR Part 26 that establishes requirements for the protection of subjects in human research (see SOP AHETF-11.A). 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/or contract facilities)." (p. 304 of 558)

8. Informed Consent

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

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

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

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

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

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

See SOP AHETF-11.I.1

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

"In all situations, the SD (or designee) will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential workers that would require a response that indicates understanding of key issues. The form in Attachment 11.J.1 will be used to ascertain general understanding." (SOP AHETF-11.J.2 §3.10)

(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 obtaining consent will inform the worker that he/she will receive $20 (or another amount specified in the protocol) for participation in the consent meeting, or the amount specified in the protocol, even if he/she decides not to participate in the research.

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

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

"In accordance with SOP AHETF-11.B, the individual employers 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. 326 of 558)

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. 313 of 558)

"Your name will only appear on the consent form and an optional form for you to request your personal study results. In all other parts of the study you will be identified by a code. Records with your name will be stored in a secure place with limited access.

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

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

"We cannot promise you total confidentiality. There may be a need to give information to some organizations or to parties in legal actions, as required by law. Records which identify you may be looked at or copied by the AHETF and any consultants working with the AHETF, by EPA or other government agencies, and by the Independent Investigational Review Board, Inc., (IIRB). IIRB is a group of people who review and monitor research to make sure the people who take part are protected.

"You may ask the Study Director for a copy of your personal results from this study. You will need to provide your name and a mail or e-mail address." (pp. 430-431 of 558)

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

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

"Any volunteer expressing a need or desire to withdraw from the research after exposure monitoring begins will be paid $80 and allowed to return to their normal work duties for their employer. If a participant withdraws while being monitored, the long underwear, inner socks 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)." (pp. 313-314 of 558)

"Your employer has agreed to let us do the research and has confirmed that it does not care whether you take part in this study or not. Your decision to be in this study is voluntary. This decision is entirely up to you. If you decide to take part, you may change your mind and drop out of the study at any time and for any reason. A decision not to take part, or to withdraw from the study after it starts, will have no effect on your job or pay or include any penalty or loss of benefits you are owed." (p. 431 of 558)

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

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

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

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

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

"No one can force you to take part in this study. Taking part is totally voluntary. If you choose not to take part in this study you will perform your ordinary activities on the day of the study. Your alternative is to not take part." (pp. 431-432 of 558)

§ 26.1111 Criteria for IRB approval of research
AHETF Backpack and Handgun Applications in Utilities Rights-of-Way (Protocol AHE400)

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 Backpack and Handgun Applications in Utilities Rights-of-Way (Protocol AHE400)

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 Backpack and Handgun Applications in Utilities Rights-of-Way (Protocol AHE400)

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 Backpack and Handgun Applications in Utilities Rights-of-Way (Protocol AHE400)

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	p. 352 pp. 266, 282
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y Y Y N n/a	pp. 555-557 The only required changes were minor typographical changes to the ICF No controverted issues
	(3) Records of continuing review activities.		n/a	
	(4) Copies of all correspondence between the IRB and the investigators.		Y	pp. 261, 262, 264, 265, 281, 296, 347, 349, 352, 453, 454, 463-469, 481, 494, 496, 547, 549-551, 553-554
	(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	p. 558
	(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	p. 306 (approved protocol)
		(2) The measures proposed to minimize risks to the human subjects;	Y	p. 306 (approved protocol)
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 312 (approved protocol)
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	p. 15
		(5) The balance of risks and benefits of the proposed research.	Y	p. 313
	§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. 425-445 Approved pp. 266-276, 282-294
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 40, 305, 218-330, 277-8
	§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. 313-316
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 261, 262, 264, 265, 281, 296, 347, 349, 352, 453, 454, 463-469, 481, 494, 496, 547, 549-551, 553-554
	§1125(f): Official notification to the sponsor or investigator…that research involving human subjects has been reviewed and approved by an IRB.		Y	pp. 264-265