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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

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MEMORANDUM

SUBJECT: Science and Ethics Review of AHETF Scenario Design and Protocol AHE80 for Exposure Monitoring of Workers during Open Pour Mixing and Loading of Wettable Powders in the United States

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REF: Collier, R. (2010) Wettable Powder Mixer/Loader Scenario Submission. Unpublished protocol dated October 18, 2010, prepared for the Agricultural Handler Exposure Task Force under Sponsor ID AHE80, 403 p.

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

Science Review

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

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:
    - SOP AHETF-11-B.5 should be revised to specify that potential study participants will be asked about what they normally wear when handling pesticides in a way that does not direct them to a particular answer or lead them to agree to wear less PPE than they normally would out of a desire to participate in the research
    - The language in the consent form about refusing medical treatment should be revised to read as follows:
        - "You may refuse medical treatment unless the medical professional decides you are too sick to make a rational decision about getting medical treatment."
    - The AHETF should revise its plan for providing exposure information to subjects to address subjects who might not speak English and/or are illiterate, and also to incorporate any future guidance from the HSRB's working group on this issue.
- The AHETF should clarify the discrepancy about whether hand wash samples are to be collected prior to water breaks.
    - Supplement 1 of the AHE80 protocol states the subjects will: Have their hands washed again, (with the assistance of a researcher), in mild surfactant and water, before they smoke o*r* eat anything, any time they would normally wash their hands (such as before using the toilet), and at the end of the day. The water from these hand washes will be saved for analysis.
    - SOP AHETF-11.G-2 states: "Urge workers to drink liquid during the monitoring period….NOTE: Hand washes will not be taken during water breaks unless specifically required by the label or requested by the worker."

  Requiring hand washes before water breaks may result in additional exposures to the surfactants and subjects may be reluctant to consume needed water in order to avoid the additional hand washes. However, not requiring hand washes before water breaks may result in hand-to-mouth exposure from the pesticide during water consumption and may confound results if some subjects request hand washes for water breaks while other subjects do not request hand washes.

- In addition, future AHETF protocols or SOPs should incorporate the following (the information has previously been provided in protocol supplements):
    - information about how subjects are presented with individual exposure information, including how this process will handled for subjects who do not speak English or are illiterate; and
    - an explanation of the process that the AHETF follows to improve and verify the accuracy of the Spanish translations

A. Responsiveness to Previous EPA and HSRB Comments

Previous EPA Comments (from Reviews of the Rights of Way Protocol and Mixer/Loader Water Soluble Package Protocols at the October 2010 HSRB Meeting)	**Is this comment addressed in this Protocol (Mixing/Loading Wettable Powder; submitted for review at the January 2011 HSRB Meeting)?**
1. The Local Site Coordinator, the Principal Field Investigator, the Analytical Facility, and the Principal Analytical Investigator must be identified in the protocol	**Yes.** The Principal Field Investigator, three analytical facilities and three Principal Analytical Investigators are identified in Supplement 1. Local Site Coordinators are not being used in this protocol.
2. Provide more information about how individual level exposure data will be presented to subjects upon request. In particular, please explain how the data will be framed and how the AHETF will work to prevent workers from changing future behavior to their own detriment if their individual risk levels are lower than the average of all workers.	**Yes.** The AHETF provided detailed information about how subjects are to be presented with individual exposure information as Supplement 2 for the AHE120 Protocol (reviewed by the HSRB in October 2010). In addition, the AHETF will incorporate any future guidance from the HSRB's working group on this issue. **The AHETF should incorporate this information into future protocols and/or an SOP.**
3. Verify the appropriateness of, or make necessary improvements to, the Spanish translations of the consent form, product risk statements, and recruitment materials. Spanish translations should be written in common, simple Spanish, appropriate to the reading ability of potential Spanish speaking subjects	**Yes.** Supplement 3 for the AHE120 Protocol (reviewed by the HSRB in October 2010) explained the process that the AHETF has followed to improve and verify the accuracy of the Spanish translations **The AHETF should incorporate this information into future protocols and/or an SOP.**

Previous HSRB Comments (from the Report of the October 2010 Meeting; report dated 12/13/10)	**Is this comment addressed in this Protocol (Mixing/Loading Wettable Powder; submitted for review at the January 2011 HSRB Meeting)?**
1. The AHETF should implement the proposed protocol changes designed to address issues of representativeness.	**Yes**. See Section 4.5 in the revised protocol (p. 139 of 392)
2. The AHETF should release individual exposure data to participants only once the study is complete, except in those instances where data collected from individuals suggest an unusually high level of exposure and thus a clear need to mitigate exposure risks.	**Yes**. Supplement 2 for the AHE120 Protocol (reviewed by the HSRB in October 2010) provides detailed information about how subjects are presented with individual exposure information. **The AHETF should incorporate this information into future protocols and/or an SOP.**

Previous HSRB Comments (from the Report of the October 2010 Meeting; report dated 12/13/10)	Is this comment addressed in this Protocol (Mixing/Loading Wettable Powder; submitted for review at the January 2011 HSRB Meeting)?
3. Exposure to the surrogate chemicals should be listed as a potential risk of study participation in the protocol and the informed consent form	**Yes**. Supplement 1states that the final protocol and consent forms will list exposure to the surrogate chemical as a potential risk of study participation.
4. The protocol excludes participants who normally wear additional personal protective equipment (such as chemical-resistant clothing) that is not required by the chemical label and that might impact the objectives of the study. The Board recommended that this assessment be done in a non-directive way, so as not to encourage participants to wear less PPE than they would normally in order to participate in the study.	**Yes**. The AHETF's practice is to ask potential study participants what they normally wear when handling pesticides so as not to direct potential participants to any particular answer. **The AHETF should incorporate this concept in SOP AHETF-11-B.5.**
5. Hand washes should be required before any smoking break to reduce risk of exposure.	**Yes**. Supplement 1 lists changes to the protocol and consent form to require hand washing before smoking.
6. The protocol and informed consent document should be more explicit as to who will make the determination that a participant is too sick to refuse medical treatment	**Yes**. Supplement 1 indicates that the protocol will be revised to state that the medical professional on site in the field will make the determination. The language proposed by the AHETF is as follows: "The revised statement on the consent form is "You may refuse medical treatment unless you get sick from too much exposure to pesticides or from getting too hot, or if the medical professional decides you are too sick to make a rational decision about getting medical treatment." **The statement proposed in Supplement 1 should be revised to read as follows:** **"You may refuse medical treatment unless ~~you get sick from too much exposure to pesticides or from getting too hot, or if~~ the medical professional decides you are too sick to make a rational decision about getting medical treatment."**
7. The protocol must address how the Task Force plans to release individual exposure data to individual study participants who request this information, but who might not speak English and/or are illiterate.	**No**. The AHETF provided detailed information about how subjects are to be presented with individual exposure information as Supplement 2 for the AHE120 Protocol (reviewed by the HSRB in October 2010). This plan does not, however, address how the exposure information will be provided to subjects who might not speak English and/or are illiterate. **The AHETF should revise its plan for providing exposure information to subjects to address subjects who might not speak English and/or are illiterate, and also to incorporate any future guidance from the HSRB's working group on this issue.** **This information should be incorporated into**

Previous HSRB Comments (from the Report of the October 2010 Meeting; report dated 12/13/10)	Is this comment addressed in this Protocol (Mixing/Loading Wettable Powder; submitted for review at the January 2011 HSRB Meeting)?
	future protocols and/or an SOP.
8. The Board also recommended that the request for individual study results be included as a check box on the informed consent document.	**Yes**. Supplement 1 lists this statement to be added to the consent form: "Did Subject request personal study results (on separate form)? □ Yes □ No" Rather than the statement proposed in Supplement 1, the following should be added to the consent form, under the subject signature line: "Do you want to receive your study results? □ Yes □ No"
9. The consent form should explain that the pregnancy test will be provided by the researchers, and explain when it will take place.	**Yes**. Supplement 1 indicates that the consent form will be revised to state: "…If you are female, you must take an over-the-counter urine pregnancy test less than 24 hours before your participation in the study begins. Researchers will provide the materials for the pregnancy test at no cost to you. More than one pregnancy test may be required. This test will be supervised by a female researcher and a private toilet area will be provided…"
10. Clarify whether individuals must be trained in safe pesticide handling practices in order to be eligible to participate, or whether individuals who are not required to be trained under the Worker Protection Standard are also eligible to become subjects	**Yes**. The eligibility criterion states: "[Study participants must] Be trained in safe pesticide handling practices in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training."

B. Completeness and Contents of Protocol Submission

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

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

- Wettable Powder Mixer/Loader Scenario Submission (October 18, 2010) (403 pages); and
- Supplement 1: AHETF Study AHE80 Changes Based on Comments in the October 27-28, 2010 EPA Human Studies Review Board Meeting Final Report. (5 pages).

The monitoring unit selection and scenario construction plan appear on pages 8-51 of 403. The rationale for the proposed sample size and cluster configuration is presented on pages 23-27 of 403. The IRB-approved protocol and supporting documents

(consent forms and recruitment flyers) appear on pages 93-174 of 403. Documentation of all interactions between the investigators and the Independent Investigational Review Board, Inc., of Plantation FL appears on pages 323-403 of 403.

C. Summary Assessment of the Scenario Design[1]

1. **Scenario Design:** AHETF protocol AHE80 is designed to address exposures of individuals involved in the open mixing/loading of pesticide end use products formulated as wettable powders (WP). Wettable powders are a very simple type of pesticide formulation consisting of the pesticide manufacturer's technical material added to inert diluents such as talc or clay. Wetting agents are also added to facilitate the WP's ability to form suspensions when mixed with water.

   The mixing/loading activities involved in this scenario include the transferring of formulated product into a variety of tanks or buckets containing water which will ultimately be transferred to the tanks of various types of pesticide application equipment (e.g., ground boom or airblast sprayers). The AHETF have identified three mixing/loading activities as "categories or equipment and associated procedures used with WPs." These are:

   - Direct pour: the mixer/loader pours the WP directly into the spray tank used for the application
   - Pre-Mix: the mixer/loader pours the WP into a holding tank. The concentration of the dilution in the holding tank has the same concentration that will be used in the application. The mixer/loader will later transfer this dilution to the tank associated with the equipment used to make the application
   - Slurry: the handler pours the WP into a holding tank or bucket with the resulting slurry having a higher concentration than will be used in the application. This concentrated slurry will be further diluted after it is transferred to the tank associated with the equipment used to make the application

   The open mix/load WP scenario is further defined as one where the mixer/loader wears a long-sleeved shirt, long pants, shoes plus socks and chemical resistant gloves. This scenario is likely to result in higher exposures than the AHETF study presented to the HSRB in October 2010: AHE120 mixing/loading water soluble packets. In scenario AHE120, dermal and inhalation exposure is expected to be mitigated by the WP being enclosed in a water soluble packet.

   Protocol AHE80 will involve the open mixing/loading of one of four surrogate pesticides; copper, DCPA (dacthal), sulfur and thiophanate-methyl. A total of 25 Monitoring Units (MUs) are proposed for this scenario consisting of five distinct

[1] Supporting details are in Attachment 1.

geographic locations (i.e., clusters) with each cluster having five MUs. When the scenario is complete, the 25MUs will be added to the AHED database. EPA intends to use these data to estimate daily dermal and inhalation exposures of pesticide handlers mixing/loading pesticides formulated as WPs for a variety of mixing and loading scenarios associated with various types of application equipment (e.g., airblast and groundboom). One cluster is completed and is based on the results of a preexisting, pre-rule study. This study is identified by the AHETF as AHE39. In AHE39, the pesticide diazinon was used as a surrogate.

2. Sampling Design: The remaining four clusters addressed in this protocol are purposively selected to reflect a diverse range of agronomic practices, geographic regions and likelihood of use of one of four surrogate pesticides. The previously conducted study AHE39 was conducted in Idaho, located in EPA Growing Region XI.

The AHETF diversified the four new clusters for this scenario by surrogate pesticide usage and geographic/climatic regions through a purposive five-step process:

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

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

- New York (EPA Growing Region I)
- Florida (EPA Growing Region III)
- Michigan (EPA Growing Region V)
- California (central/southern portion of EPA Growing Region X)

These growing regions are appropriate choices and are likely to address regional and agronomic variations in addition to being likely areas of use for WP formulations of copper, DCPA, sulfur and thiophanate-methyl. This scenario addresses the exposures of individuals involved with mixing/loading WPs into a variety of tanks including those connected to the application equipment. The scenario does not address the exposures of the operators of the various application equipment types used in the above mentioned EPA Growing Regions. Those exposures will be addressed in other AHETF scenarios.

The four purposively selected clusters are described below:

- New York represents a cool climate. Example crops include apples, grapes and snap beans.

- Florida represents a hot and humid climate where the selected surrogate pesticides are applied to crops such as citrus, tomatoes and strawberries.

- Michigan represents a cool climate in the upper Midwest where a wide variety of orchard, small fruit (e.g., blueberries) and vegetable crops are grown.

- California (central/southern portion) represents a hot and dry climate in the western U.S. where a wide variety of tree fruits/nuts, grapes and field crops are grown. Sulfur is widely used in California.

The next stage of the diversity selection process involves dividing the practical range of amount of active ingredient handled (AaiH) for the open WP mix/load scenario into five bands (strata) ranging from 5 to 2000 pounds AaiH. Past studies have shown that AaiH is associated with exposure and is a meta-factor associated with differences in equipment and mixing/loading and spraying practices. AHETF has set a lower limit of 5 lbs, to minimize non-detects on the dosimeters. The upper range of the strata is also likely to be achieved based on the application rates of AHETF membership product labels as well as EPA standard values typically used to estimate AaiH when conducting agricultural scenario risk assessments. The AaiH strata for the WP, Open Mix/Load scenario are as follows:

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

These AaiH strata are proposed for the four new clusters. However, the AaiH applied in the existing cluster (AHE39) was limited to 59 to 138 (the middle stratum). Perhaps because the range of AaiH is low, the resulting GSD for dermal (2.46) and inhalation (1.70) is smaller than the true within cluster GSD (3.19) described in the governing document. The AHETF asserts this narrow range of AaiH will have little impact on the overall results of this scenario because the 20 new MUs in the remaining four clusters will be based on the above mentioned strata. EPA reminds the AHETF a wide range of AaiH is a particularly important element of the study design with respect to the ability to test for proportionality – the AHETF's secondary study objective. Therefore, the AHETF must ensure that all strata be used in each of the four remaining clusters.

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

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

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

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

- The grower is willing to cooperate with the AHETF
- The grower has the necessary mixing/loading equipment
- The grower has at least one worker with experience in the mixing/loading of WPs
- The grower has sufficient acreage that the minimum AaiH can be mixed/loaded
- The grower is willing to use a least one of the surrogates (copper, DCPA, sulfur and thiophanate-methyl)

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

When selecting MUs, these additional restrictions will be enforced to increase diversity within the cluster:

- No handler may be used more than once
- No piece of equipment may be utilized more than once
- No more than one MU may be obtained from one grower or commercial pesticide applicator company
- When mixing/loading procedures in a given area involve participants either pouring directly into the application tank, using pre-mix tanks (holding dilute sprays), or slurry tanks or buckets (holding concentrate sprays), then the MUs may not all be associated with the same equipment

and procedure category (*Note: in AHE39, all participants used slurry buckets*).

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

3. **Choice of Surrogate Materials:** The surrogate chemicals proposed for this scenario are copper, DCPA (Dacthal), thiophanate-methyl and sulfur formulated as WPs. The AHETF are relying on analytical methods developed by the outdoor residential exposure task force (ORETF) for the surrogate DCPA. EPA has reviewed the ORETF data and found them to be acceptable and believes DCPA is a reliable surrogate. Acceptable criteria for surrogate compounds include, low volatility, environmental stability, good field recovery, low limits of quantification (LOQ), etc. For sulfur and thiophanate-methyl, the AHETF have also developed acceptable methods for all matrices. For copper, the hand rinses, face/neck wipes and OVS tubes are developed and acceptable. However, for the Whole Body Dosimeters (WBD), the AHETF are currently attempting to lower LOQs which are currently at 30 µg per section. Generally the AHETF prefer an LOQ of 1µg per dermal matrix. However, due to the high application rates of copper (up to 8 lbs ai/acre) and because the open pour mix/load scenario is considered a high exposure potential, this level may be adequate to minimize the potential for non-detect measurements for inner dosimeter sections.

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

1. **Statistical design:** This protocol describes collecting 20 Monitoring Units (MUs) in addition to the five existing MUs reflecting the exposure of subjects mixing/loading WP formulations to support a variety of applications to field, orchard or trellis crops. These MUs will be collected in four additional separate clusters diverse in geographic location and climate. Each cluster or study site will include five MUs. The general rationale for the 5 x 5 cluster configuration is presented in Appendix C of the revised AHETF Governing Document; details specific to the mixing/loading of WPs are in the scenario design. No characteristics of this scenario have been identified which would justify a departure from the 5 x 5 configuration. However, of concern to EPA is the lack

[2] Supporting details are in Attachment 2.

of diversity with respect to AaiH strata and mix/load category (slurry bucket only) for the existing study AHE39. The study design of the existing study also includes having more than 1 MU per farm/grower. EPA will require additional MUs if the AHETF does not have the ability to test for proportionality.

2. **Proposed pattern of exposure:** The proposed minimum exposure duration for each MU was described as being at least 4 hours in duration involving the mixing/loading of at least 3 tank-loads. The HSRB has noted that imposing a minimum duration may adversely impact the results by potentially "introducing unintended and undesired variability." This protocol was submitted prior to the October 2010 meeting and does not incorporate this recommendation. In subsequent discussions with AHETF study personnel, this recommendation is viewed as acceptable.

   It should be noted that the subjects will only mix and load the surrogate pesticide. Applying the finished spray solution/suspension will be done by others not participating in the study. Over the course of a day each subject will mix/load the surrogate active ingredient in one of the following five strata of AaiH:

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

   There are four designated surrogate pesticide active ingredients formulated as WPs. A cooperating grower may choose to use any of them for a specific MU. The WPs will be mixed with water and/or loaded into the various sprays tanks in one of three possible ways:

   - Pouring WPs directly into the tank associated with the application equipment (e.g., groundboom or airblast sprayers)
   - Loading WPs into holding or nurse tanks before the finished spray solution/suspension is transferred to the application equipment tank (e.g., fixed wing aircraft). The concentration in the holding or nurse tank has the same concentration that will be used by the spray equipment
   - Loading individual WPs into slurry tanks or other tanks resulting concentrated solutions/suspensions that must be further diluted with water before spraying/applying

   The AHETF will attempt to ensure that at least one MU in each cluster will reflect each of the mixing/loading situations described above if it is determined that all three categories are possible in a given study area (i.e., cluster).

   For this scenario, the duration of the monitoring period is expected to vary considerably because of the wide range of AI to be handled by the different

subjects. Furthermore, some subjects may perform other tasks between episodes of mixing and loading, and others may simply wait at the mixing site between episodes. The AHETF acknowledges that some scripting may be needed for subjects assigned to the lower AI strata to ensure at least 3 mixing/loading events are measured for each worker.

3. **Endpoints and Measures:** The study will measure dermal and inhalation exposure for each MU. These data will contribute to development of Unit Exposures (exposure per unit of pesticide active ingredient applied) or other exposure metrics, and to estimates of dermal and inhalation exposure to other pesticides for workers mixing and loading pesticides formulated as WPs. EPA believes that the proposed measures are appropriate and sound for the study design.

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

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

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

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

   Additional measures will record environmental conditions at the time of monitoring. Observers will make field notes of subject activity throughout the

monitoring event, and photographs or videos may be taken selectively to illustrate events.

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

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

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

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

EPA notes the following requirements for approval of the protocol:

- Remove the minimum duration requirement for each MU
- AHETF is to ensure all AaiH strata are applied at each cluster
- AHETF is to strive to include all three mix/load categories at each cluster
- Additional MUs will be required if AHETF are unable to test for proportionality due to the limitations of the existing study AHE39
- Test for within same field correlations for existing study AHE39

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

1. **Societal Value of Proposed Research:** The objective of this study is to develop data to determine the potential exposure for workers who mix and load wettable powder formulations using open pouring techniques in four regions of the United States. This mixing/loading method is widely used and applicable to a large variety of commercially important crops, and the existing exposure data are inadequate. EPA will use the results of this study to estimate the dermal and inhalation exposure likely for a wide range of agricultural pesticides applied under this exposure scenario.

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

   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 the eligible grower to approach his/her employees to recruit volunteers for the study. Depending on the number of employees and size of the grower's facility, the Study Director or researcher may contact employees using an

[3] Supporting details are in Attachment 2.

informational recruitment flyer posted in a common work area. Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the grower's employees who express interest in participation. Such recruitment meetings will always occur without the grower or supervisors being present. The Study Director or researcher will describe the AHETF Exposure Monitoring Program, the goals of this specific study, the procedures to be used in exposure monitoring, and the risks and benefits to participants. The subject eligibility factors listed in the consent form and SOP AHETF-11.B are appropriate.

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

3. **Risks to Subjects:** Five kinds of risks to subjects are discussed in the protocol and Supplement 1, along with specific steps proposed to minimize them:

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

    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.

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 mixing/loading pesticides formulated as wettable powders, 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 record of correspondence between the investigators and IIRB, Inc.

7. **Informed Consent:** Informed consent will be obtained from each prospective subject and appropriately documented. If participating in the study in California, subjects will also receive the California Research Participant Bill of Rights. The reading level of the English language consent form is appropriate. Adequate provision is made to meet the needs of subjects who do not read either English or Spanish. EPA assessments of compliance with the requirements of 40 CFR §26.1116 and §26.1117 appear in Attachments 4 and 5 to this review.

8. **Respect for Subjects:** Subject identifying information will be kept strictly confidential. Provision is made for discrete handling of pregnancy testing, required of all female subjects on the day of testing. Candidates and subjects will be repeatedly reminded that they are free to decline to participate or to withdraw at any time for any reason, without penalty.

F. Compliance with Applicable Ethical Standards

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

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

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

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

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

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

Attachments:

1. EPA Scenario Review: AHETF Mixing/Loading of Wettable Powder (AHE80)
2. EPA Protocol Review: AHETF Mixing/Loading of Wettable Powder (AHE 80)
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 Mixing/Loading of Open Pour Wettable Powder Products (AHE80)

Title: **Monitoring Unit Selection and Construction Plan for Scenario: Open Pour Mixing/Loading of Wettable Powders**

Date: September 30, 2010

Sponsor: Agricultural Handler Exposure Task Force

1. Scope of Scenario Design

"This is a mixing/loading scenario defined by the formulation type and the lack of engineering controls, i.e., WPs that are open-poured into various types of farm equipment and are diluted with water for future application as liquid sprays. This is accomplished by mixing/loading the WP directly into the tank to be used for the application or into a pre-mix tank where the contents will later be transferred to the tank used for the actual application. (pp. 113 and 114 of 403)

"it is felt that the following states proposed for this scenario will ultimately provide monitoring areas with the desired diversity in geography and likely use of one or more surrogates: the following states are proposed for this scenario to provide the desired diversity in geography and likely use of one or more surrogates:

- California (Region X)
- Florida (Region III)
- Michigan (Region V)
- New York (Region I)"

The existing study (AHE39) was conducted in Idaho (EPA Region XI) using Diazinon 50W® Insecticide. Thus, the exposure data obtained for the WP mixing/loading scenario for all five monitoring areas will span five different EPA Growing Regions. (pp. 14 of 403)

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

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

"AHETF also conducted a detailed review of the data in PHED (EPA, 1998a) for this scenario to determine if any of the data were suitable for a modern generic database. Data for mixing/loading of WPs comprise PHED Scenario 4 – Wettable Powder, Open Mixing and Loading (MLOD). …The "Single Layer, Gloves clothing scenario data were graded as Medium Confidence". The inhalation data were also graded as "Medium Confidence"…

"Finally, EPA examined data from existing WP 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 (verbal communication from EPA and JRC meeting, September, 2008)." (pp. 15-16 of 403)

AHETF generated data for this scenario in a 2006 study (AHE39; Klonne, 2007) conducted in Idaho (EPA Growing Region XI) in which five MUs were collected. The surrogate product used in that study was Diazinon 50W® Insecticide. Table 2 summarizes several important characteristics of the MUs obtained from this study.

Table 2. Design Characteristics of the Five Mixing/loading Monitoring Units Obtained from Study AHE39

Date	Worker	Field Site(s)	Pre-Mix Bucket Size (gal)	Appl. Tank Size (gal)	Number of Loads Mixed	Total Amt. a.i. Handled (lbs)
6/1/2006	M3	1	5	55	3	59
6/2/2006	M2	2,3	5	150	3	59
6/2/2006	M4	4	30	150	5	98
6/3/2006	M1	5,2	5	150	7	138
6/4/2006	M5	4	30	150	5	98

"Although this study was conducted prior to adoption of the current MU selection methods (see Section 4.2 below), Table 2 shows that the five MUs are reasonably diverse. The MUs used different workers and their mixing/loading activities spanned multiple dates and field sites. The current practice of capturing the entire practical range of AaiH within each monitoring area was not followed in this study. As a result, the AaiH range in AHE39 is rather narrow compared to what is being proposed for new monitoring areas in this scenario. AHE39 provides a reasonably diverse set of MUs that can be considered an independent cluster of five MUs and can be combined with the new clusters of MUs…" (pp 16-17 of 403)

2. Rationale for Scenario Sampling Design

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

> "Exposure experts within the AHETF have identified equipment type as a parameter that might impact exposure. Factors such as the design of the equipment affect the spatial relationship of the worker to the opening where loading occurs (e.g., a short tank at chest height versus a taller tank where loading may be slightly overhead). Equipment design can also affect the amount of contact the worker has with contaminated surfaces and other factors such as how the WP is loaded (e.g., open poured directly into water in a tank which is then used for application, or added to a tank to make a concentrated solution that must be further diluted and transferred to another tank for application.) whether or not diluted product is transferred to another tank." (p 38 of 403)

"Experts identified three general categories of equipment and associated procedures used with WPs (Honeycutt, 2008):

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

> Consequently, additional diversity will be added by imposing the restriction that the MUs in the same efficient configuration in a monitoring area cannot all use the same equipment and procedure category. This similarity restriction will only apply if the Study Director determines that more than one category is applicable in an efficient configuration in the monitoring area." (p 39 of 403)

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

"EPA has established 13 U.S. Growing Regions. The 12 regions of the continental U.S. … Growing Region XIII consists of Hawaii and Puerto Rico and is not being considered

for this scenario. These Growing Regions provide a convenient basis for geographic stratification. These Regions have been used when planning and conducting pesticide residue trials for various crop types. The regions were based on natural geography and climatic boundaries (ACPA, 1992) and are therefore useful for indicating when locations selected for exposure monitoring are geographically diverse. . . ." (pp. 28 of 403)

"Predominant Surrogate Use: Although WPs may be used in all 12 EPA Growing Regions, not all regions are expected to have wide use of all four AHETF surrogate active ingredients (sulfur, copper, thiophanate-methyl, and DCPA). Thus, for practical reasons, the distribution of surrogate use will be considered when selecting the four monitoring areas… (pp. 29 of 403)

Table 3 summarizes this surrogate distribution with chemical usage data for all four surrogates combined (NASS 2000 through 2007). Since NASS data is only compiled for certain chemicals and crops, but not on a yearly schedule, the data span a number of years. The table shows the highest usage of the four WP surrogates for the top ten states of the 48 contiguous United States. (pp. 30 of 403)

"**Selection of a Geographically Diverse Set of Monitoring Areas:** Four new monitoring areas need to be selected so that all five areas (i.e., including AHE39) are geographically diverse. Such a diverse configuration can be obtained by simply locating each site in a different EPA Growing Region. Because of an existing cluster of MUs (i.e., AHE39) was already obtained from Growing Region XI (Idaho), only 11 growing regions remain in placement of the four new monitoring areas. In theory, four growing regions could be selected at random from among the 11 regions that stratify the continental U.S. A state (or, perhaps adjacent states) could be randomly or purposively chosen from within the selected Region. . . . However, such undirected selection of states would be quite inefficient…Locating monitoring areas in crop areas where the surrogates are currently in use over a wide variety of crops increases the likelihood that surrogates will be in use at the particular monitoring site ultimately chosen….the following states were purposively selected to contain the following five monitoring areas." (pp. 32 of 403)

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

New York is a state with high combined usage of the four surrogates. The primary crops where the surrogates are used include apples (an orchard crop), grapes (a trellis crop), and snap beans (a field crop). This state reflects a cool climate in the northeastern U.S.

2. **Florida (Region III)**

Florida is a state with high combined usage of the four surrogates. The primary crops where the surrogates are used include citrus (an orchard crop), tomatoes and strawberries (field crops). Thiophanate-methyl is also used in Florida on a variety of crops including snap beans, melons, strawberries, and tomatoes. This state reflects a hot and humid climate in the southeastern U.S.

3. Michigan (Region V)

Michigan is as state with high combined usage of the four surrogates. The primary crops where the surrogates are used include sweet and tart cherries, apples, and peaches (orchard crops). Although the primary crops for the surrogates are orchard crops, a significant variety of crops (i.e., cucumbers, blueberries, squash, and potatoes) where the surrogates may be used are also grown nearby. This state reflects a cool climate in the Midwestern U.S.

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

This state involves by far the highest usage of sulfur, usage of all four surrogate chemicals, and a wide variety of crops. The crops include rice, vegetables, grapes, and orchards, which should provide the opportunity for a range of application equipment when constructing MUs. The central and southern portions of California generally reflect a hot and dry climate in the western U.S." (pp. 32-33 of 403)

"**Reduction of Monitoring Areas:** The final step for selecting monitoring areas is to choose a specific area within each selected state identified above where growers and workers can be recruited to conduct the exposure monitoring in a reasonable amount of time. This involves further limiting each monitoring area geographically so that MU identification and selection operations can be conducted efficiently. This will facilitate the logistics of the field research team and keep the costs of study conduct reasonable so a sufficient number of MUs can be obtained in the AHETF monitoring program. (As described in Section 5.2.4, a monitoring area can also be increased in size under some conditions).

"Choosing a cost-effective configuration of MUs is necessary since costs escalate rapidly when a research team makes multiple visits to a location in order to monitor the desired five MUs. Cost-effectiveness is obviously maximized when all MUs are collected during the same visit so researcher salary, travel, food, lodging, and field fortification expenses are minimized.

"Therefore, a smaller portion of each initial monitoring area, a particular area (e.g., a state or a large portion of a state) will be selected and identified in the study protocol and the monitoring area reduced accordingly. The final monitoring area will be determined based on the locations of crops predominantly associated with surrogate use and will likely involve identifying several counties where mixer/loaders are most likely to utilize the surrogate WP product and that have sufficient growers, and equipment, and workers to allow an efficient design." (pp. 34-35 of 403)

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

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

"AHETF has determined that a method of randomly choosing a working pool of growers is practical for this scenario. This pool of growers will provide the workers and mixing/loading conditions needed to construct MUs for the monitoring area. Random selection of growers is preferable, when feasible, to reduce the possibility of selection bias that might arise from researchers purposively choosing specific growers to contact. Therefore, a procedure for generating a list of available growers for each monitoring area, and selecting a pool of growers from that list, will be established in the protocol. The general procedure to be followed is described in the following steps:

1. Contact local resources from each of the following groups and ask for a list of growers that might utilize open pour WP mixing/loading at the identified monitoring area (generally several counties):
    - Farm Market ID
    - Commercial list providers
    - State and local government entities
    - Grower associations
    - Grower Publication subscription lists

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

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

    - The grower is willing to cooperate with AHETF, including the ethical aspects of the research
    - The grower has the necessary mixing/loading equipment
    - The grower has at least one worker with experience in the mixing/loading of WPs
    - The grower is willing to allow AHETF to recruit his/her worker(s)
    - The grower has sufficient acreage that the minimum AaiH can reasonably be handled by a worker in one day
    - The grower is willing to use at least on of the surrogate active ingredients listed in this protocol

Growers who indicate they use commercial pesticide application companies to mix/load their product will also be considered. Those growers will be asked to identify their preferred commercial companies and AHETF will contact them to screen them for willingness to cooperate by providing suitable mixing/loading equipment and workers. The actual workers involved could be the grower himself, a grower's employee, or an owner or employee of a commercial pesticide application company.

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

- Specific location of mixing/loading area
- Description of equipment available (e.g., number, type, and size)
- Surrogate chemical(s) that might be utilized
- Approximate timing of surrogate applications
- Number of workers available
- AaiH those workers might be able to handle in a day." (pp. 39-41 of 403)

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

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

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

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

"A parameter that might impact exposure is the number of loads prepared since each mixing/loading event might require transferring diluted product from tank to tank and potential contact with contaminated surfaces (e.g., water soluble packets, tanks, hoses, etc.)…If other functions are also associated with the mixing/loading event (e.g., transferring from a slurry tank to an application tank) then these events are also included as part of the monitoring." (pp. 43 of 403)

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

"Many other possible MU characteristics might potentially affect exposure potential. For example, measuring WP from a container, i.e., when less than a whole container is required, may influence exposure potential. Other factors such as the crop being treated are not expected to directly affect exposure, but might lead to selection of various equipment set-ups that could impact exposure potential. All such characteristics are expected to vary naturally or indirectly as a result of other differences between MUs." (pp. 44 of 403)

3. Are the proposed test materials appropriate surrogates?

"The following active ingredients are available as wettable powders and will be considered for use in this wettable powder open mixing/loading scenario.

- Sulfur

- Copper
- Thiophanate-methyl
- DCPA (dacthal)

These surrogate active ingredients, except thiophanate-methyl, typically have high use rates for the potential crops of interest that enables measurements at the high end of AaiH per day. Additionally, cooperating growers who will use these products are likely to be available." (pp. 45 of 403)

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. These simulations determine either accuracy or power given the number and configuration of MUs. When there are no existing data, the simulations only consider new MU configurations. However, for this scenario, the simulations require that the structure of the existing MUs be held constant and only the number of new MUs is varied. Regardless, it is still the combination of existing and new MUs that must satisfy the benchmark objectives:

1. **Primary Objective**: Estimates of the geometric mean, the arithmetic mean, and the 95th percentile of normalized dermal exposure generally need to be accurate to within 3-fold of their actual population value assuming the reference random sampling model applies.
2. **Secondary Objective**: There should be at least 80% statistical power to distinguish complete proportionality from complete independence between dermal exposure and AaiH (the normalizing factor for this scenario).

4.5.1. GSD and ICC

Reasonable values of the geometric standard deviation (GSD) and the intra-cluster correlation (ICC) are needed. Based on analysis of exposure from a number of available monitoring studies, Appendix C of the AHETF Governing Document derived a default relative variation structure consisting of GSD=4 and ICC=03. Unless there is other evidence or expert opinion to the contrary, sample sizes are determined for all scenarios using these default values. It is reasonable to as however, whether the existing MU data provide evidence that this scenario will be inconsistent with the default assumptions for the GSD and ICC.

As noted above, the existing data consist only of five MUs from study AHE39. Because this study represents only a single cluster just within-cluster variation can be examined. Based on these five MUs, the observed within-study GSD for normalized dermal exposure is 2.46. The analogous value obtained for normalized inhalation exposure is 1.70. If the true GSD and ICC were 4 and 0.3, respectively, then the true within-cluster GSD is:

$$GSD^{\sqrt{1-ICC}} = 3.19$$

If the normalized exposures of the five MUs are lognormally distributed then the 4· quantity

$$4 \cdot \left[\frac{\log_e \text{ Observed Within – Cluster GSD}}{\log_e \text{ True Within – Cluster GSD}} \right]^2$$

has a chi-square distribution with 4 degrees of freedom. Therefore, if the true GSD=3.19 then, 95% of the time, an observed GSD should vary between the values of 1.50 and 6.93. Since both 2.46 (dermal) and 1.70 (inhalation) lie between these two bounds, they are consistent with a within-cluster GSD of 3.19. Consequently, the single cluster of MUs from study AHE39 is also consistent with a true total GSD of 4 and a true ICC of 0.3. Because the AHETF default values will be used for determining sample size for the WP mixer/loader scenario.

4.5.2. Required Number and Configuration of New MUs

As noted above, Appendix C of the AHETF Governing Document describes several simulation methods that can be used to determine reasonable sample sizes for new clusters of MUs. In principle, these methods are easily extended to accommodate existing MUs as well. In brief, the simulation procedure consists of the following steps:

1. Using the structure of the existing data (e.g., number of clusters, number of MUs per cluster, AaiH levels for each MU, etc.) simulate normalized exposures, and exposures derived from AaiH levels assuming proportionality, from the multistage lognormal reference model.
2. Given candidate values for numbers of new clusters, numbers of MUs per cluster, and AaiH levels, simulate normalized exposure, and exposures derived from AaiH levels assuming proportionality, from the two-stage lognormal reference model
3. Combine the existing and new simulated data together and estimate the geometric mean, arithmetic mean, and 95th percentile of normalized exposure. Calculate the fold relative accuracy of these estimates compared to their true values.
4. In addition, from the combined new and existing exposure data, determine if the slope from a mixed model regression of log exposure of AaiH is significantly different from zero.
5. Repeat steps 1 through 4 10,000 times and calculate the 95th percentile of fold relative accuracy for each normalized exposure statistic and determine if it satisfies the primary benchmark objective. Also compute the percentage of simulations yielding a statistically significant slope. The percentage is the power needed to evaluate the secondary benchmark objective.

For this particular scenario, new simulations to examine the fold-accuracy of the geometric mean, arithmetic mean, and 95th percentiles (i.e., the primary objective) are unnecessary. Appendix C of the AHETF Governing contains the results of such simulations when GSD=4 and ICC=03 are assumed. In

this case, the configuration that satisfies the primary objective is a set of N=4 clusters and M_c=5 MUs per cluster. Since the existing study AHE39 already contributes one cluster of five MUs, only four additional 5-MU clusters need to be obtained.

However, assessing the secondary objective is more complicated since the power to detect proportionality between exposure and AaiH also depends on the particular set of AaiH used. The AaiH levels are known for existing MUs (Table 2), but must be generated for the hypothesized new clusters of MUs in the simulations described in step 4 above. Appendix C of the AHETF Governing Document shows that under the default GSD and ICC, the configuration of MUs satisfying the primary objective will also satisfy the secondary objective if (1) the AaiH levels for the scenario range over an order of magnitude or more and (2) there is adequate within-cluster variation in AaiH levels.

As described in Section 5.2.1 below, diversity selection for new clusters will require that the AaiH levels for MUs extend over the complete practical range expected for the WP mixer/loader scenario. This practical range is 5 to 2000 lbs ai handler per workday and extends over several orders of magnitude (i.e., 400x). For each new cluster, diversity in AaiH levels is achieved by first partitioning this practical range into M_c strata and then obtaining a single MU from within each AaiH stratum. The within-cluster strata are logarithmically spaced within the practical range.

An analogous procedure is followed when obtaining AaiH levels for new MUs in the simulations: within each simulated new cluster, an AaiH level is simulated log-uniformly from within each of the M_c strata. The exposure data are simulated for both existing and new clusters assuming proportionality with the AaiH levels and using the default variation structure. For each simulated set of data, a regression analysis is performed and the significance of the log-log slope determined (2-sided test). The power is the proportion of the time that the slope was significant at $p<0.05$.

When this simulation method is used with the single existing cluster (i.e., AHE39) and four new 5-MU clusters the power was essentially 100%. That is the AaiH diversity in four new clusters is more than sufficient to compensate for the narrow AaiH range in AHE39. Consequently, by obtaining four new clusters of five MUs each, both the primary accuracy objective and the secondary power objective should be satisfied.

Although four new clusters with five MU/cluster is the scenario target, Appendix C of the AHETF Governing Document also shows that some variation in this configuration can be tolerated in the event that five MUs cannot be obtained in every cluster. In particular, the primary benchmark will still be satisfied providing:

- The total number of new MUs is at least 20, and
- No new cluster has more than five MUs

Obviously, this rule implies that if a new cluster has fewer than 5 MUs then more than 4 new clusters will be necessary. (pp. 23- 26 of 403)

EPA Protocol Review: Wettable Powder Open Pour Mixer/Loader Scenario (AHE80)

Title: Determination of Dermal and Inhalation Exposure to Workers during Mixing/Loading Wettable Powders in the United States

Revision Date: October 5, 2010

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1. Societal Value of Proposed Research

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

"The objective of this study is to develop data to determine the potential exposure for workers who mix and load wettable powder formulations using open pouring techniques in four regions of the United States." (pp. 102 of 403)

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

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

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

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

EPA will use the results of this study to estimate the dermal and inhalation exposure likely for mixing and loading agricultural pesticides formulated as wettable powders (WP).

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

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

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

AHETF generated data for this scenario in a 2006 study (AHE39; Klonne, 2007) conducted in Idaho (EPA Growing Region XI) in which five MUs were collected. The surrogate product used in that study was Diazinon 50W® Insecticide. Table 2 summarizes several important characteristics of the MUs obtained from this study (pp. 15-16 of 403)

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

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

2. Study Design

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

"The goal of conducting a WP mixing/loading study is to develop a set of generic dermal and inhalation exposure data which regulators and other potential users of the generic database can utilize to characterize a predicted distribution of future exposures and perform exposure assessments for this scenario." (pp. 48 of 403)

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

2. **Secondary Objective**: There should be at least 80% statistical power to distinguish complete proportionality from complete independence between dermal exposure and AaiH (the normalizing factor for this scenario)." (pp. 23 of 403)

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. These simulations determine either accuracy or power given the number and configuration of MUs. When there are no existing data, the simulations only consider new MU configurations. However, for this scenario, the simulations require that the structure of the existing MUs be held constant and only the number of new MUs is varied.

Reasonable values of the geometric standard deviation (GSD) and the intra-cluster correlation (ICC) are needed. Based on analysis of exposure from a number of available monitoring studies, Appendix C of the AHETF Governing Document derived a default relative variation structure consisting of GSD=4 and ICC=03. Unless there is other evidence or expert opinion to the contrary, sample sizes are determined for all scenarios using these default values. It is reasonable to as however, whether the existing MU data provide evidence that this scenario will be inconsistent with the default assumptions for the GSD and ICC.

As noted above, the existing data consist only of five MUs from study AHE39. Because this study represents only a single cluster just within-cluster variation can be examined. Based on these five MUs, the observed within-study GSD for normalized dermal exposure is 2.46. The analogous value obtained for normalized inhalation exposure is 1.70. If the true GSD and ICC were 4 and 0.3, respectively, then the true within-cluster GSD is:

$$GSD^{\sqrt{1-ICC}} = 3.19$$

If the normalized exposures of the five MUs are lognormally distributed then the 4· quantity

$$4 \cdot \left[\frac{\log_e \text{Observed Within – Cluster GSD}}{\log_e \text{True Within – Cluster GSD}} \right]^2$$

has a chi-square distribution with 4 degrees of freedom. Therefore, if the true GSD=3.19 then, 95% of the time, an observed GSD should vary between the values of 1.50 and 6.93. Since both 2.46 (dermal) and 1.70 (inhalation) lie between these two bounds, they are consistent with a within-cluster GSD of 3.19. Consequently, the single cluster of MUs from study AHE39 is also consistent with a true total GSD of 4 and a true ICC of 0.3. Because the AHETF default values will be used for determining sample size for the WP mixer/loader scenario.

4.5.2. Required Number and Configuration of New MUs

As noted above, Appendix C of the AHETF Governing Document describes several simulation methods that can be used to determine reasonable sample sizes for new clusters of MUs. In principle, these methods are easily extended to accommodate existing MUs as well. In brief, the simulation procedure consists of the following steps:

6. Using the structure of the existing data (e.g., number of clusters, number of MUs per cluster, AaiH levels for each MU, etc.) simulate normalized exposures, and exposures derived from AaiH levels assuming proportionality, from the multistage lognormal reference model.
7. Given candidate values for numbers of new clusters, numbers of MUs per cluster, and AaiH levels, simulate normalized exposure, and exposures derived from AaiH levels assuming proportionality, from the two-stage lognormal reference model
8. Combine the existing and new simulated data together and estimate the geometric mean, arithmetic mean, and 95th percentile of normalized exposure. Calculate the fold relative accuracy of these estimates compared to their true values.
9. In addition, from the combined new and existing exposure data, determine if the slope from a mixed model regression of log exposure of AaiH is significantly different from zero.
10. Repeat steps 1 through 4 10,000 times and calculate the 95th percentile of fold relative accuracy for each normalized exposure statistic and determine if it satisfies the primary benchmark objective. Also compute the percentage of simulations yielding a statistically significant slope. The percentage is the power needed to evaluate the secondary benchmark objective.

For this particular scenario, new simulations to examine the fold-accuracy of the geometric mean, arithmetic mean, and 95th percentiles (i.e., the primary objective) are unnecessary. Appendix C of the AHETF Governing contains the results of such simulations when GSD=4 and ICC=03 are assumed. In this case, the configuration that satisfies the primary objective is a set of N=4 clusters and M_c=5 MUs per cluster. Since the existing study AHE39 already contributes one cluster of five MUs, only four additional 5-MU clusters need to be obtained.

However, assessing the secondary objective is more complicated since the power to detect proportionality between exposure and AaiH also depends on the particular set of AaiH used. The AaiH levels are known for existing MUs (Table 2), but must be generated for the hypothesized new clusters of MUs in the simulations described in step 4 above. Appendix C of the AHETF Governing Document shows that under the default GSD and ICC, the configuration of MUs satisfying the primary objective will also satisfy the secondary objective if (1) the AaiH levels for the scenario range over an order of magnitude or more and (2) there is adequate within-cluster variation in AaiH levels.

As described in Section 5.2.1 below, diversity selection for new clusters will require that the AaiH levels for MUs extend over the complete practical range expected for the WP mixer/loader scenario. This practical range is 5 to 2000 lbs ai handler per workday and extends over several orders of magnitude (i.e., 400x). For each new cluster, diversity in AaiH levels is achieved by first partitioning this practical range into M_c strata and then obtaining a single MU from within each AaiH stratum. The within-cluster strata are logarithmically spaced within the practical range.

An analogous procedure is followed when obtaining AaiH levels for new MUs in the simulations: within each simulated new cluster, an AaiH level is simulated log-uniformly from within each of the M_c strata. The exposure data are simulated for both existing and new clusters assuming proportionality with the AaiH levels and using the default variation structure. For each simulated set of data, a regression analysis is performed and the significance of the log-log slope determined (2-sided test). The power is the proportion of the time that the slope was significant at $p<0.05$.

When this simulation method is used with the single existing cluster (i.e., AHE39) and four new 5-MU clusters the power was essentially 100%. That is the AaiH diversity in four new clusters is more than sufficient to compensate for the narrow AaiH range in AHE39. Consequently, by obtaining four new clusters of five MUs each, both the primary accuracy objective and the secondary power objective should be satisfied.

Although four new clusters with five MU/cluster is the scenario target, Appendix C of the AHETF Governing Document also shows that some variation in this configuration can be tolerated in the event that five MUs cannot be obtained in every cluster. In particular, the primary benchmark will still be satisfied providing:

- The total number of new MUs is at least 20, and
- No new cluster has more than five MUs

Obviously, this rule implies that if a new cluster has fewer than 5 MUs then more than 4 new clusters will be necessary. (pp. 23- 26 of 403)

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

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

(c) How is the study blinded?

The study is not blinded, nor could it be.

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

"After the randomly-selected pool of eligible growers is assembled, researchers (e.g., the Study Director) will examine the details of potential MUs and identify a configuration of MUs (i.e., growers, chemicals, workers, AaiH, timing) that will result in an efficient cluster." (pp. 41of 403)

"When constructing MUs within each monitoring area, the following similarity restrictions and preferences will be used to ensure diversity:

- No worker may be used for more than one MU.
- No more than one MU may be obtained from any grower or commercial pesticide application company (so a grower with several workers and several pieces of equipment can contribute one MU).
- Whenever possible, each MU should use an AaiH level from a different stratum (see Section 5.2.1)
- When more than one piece of equipment and procedure category is applicable in the efficient configuration, the MUs cannot all be associated with the same category (see Section 5.2.2).
- No single piece of equipment may be used for more than one MU. (pp. 42 of 403)

(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. 48 of 403)

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

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

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

2. How well the data can be expected to describe a relationship between exposure and AaiH, if one existed." (pp. 48 of 403)

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

"To evaluate how well the collected data conform to this benchmark, the 95 percent bound on relative accuracy will be calculated from the confidence interval for each of the three parameters given above." (pp. 48 of 403)

"This secondary benchmark objective [Adequacy of the Data for Distinguishing a Proportional from an Independent Relationship between Exposure and AaiH] applies to the WP mixing/loading scenario because the practical range in the amount of active ingredient handled (AaiH) exceeds an order of magnitude. In this case it is reasonable to consider the linear regression of log dermal exposure on log AaiH. Such a regression would use a mixed model formulation in order to incorporate random cluster effects." (pp. 49 of 403)

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

Yes.

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

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

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

"This secondary benchmark objective applies to the wettable powder mixing/loading scenario because the practical range in the amount of active ingredient handled (AaiH) exceeds an order of magnitude. In this case it is reasonable to consider the linear regression of log dermal exposure on log AaiH. Such a regression would use a mixed model formulation in order to incorporate random cluster effects. 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. 49 of 403)

2.2 How and to what will human subjects be exposed?

"Collectively, the complete WP mixing/loading scenario will include instances of worker exposure resulting from the open pouring mixing/loading of wettable powder pesticide formulations." (pp. 17 of 403)

"The test substance active ingredients approved for use in this study are listed in Section 2.3.5 above. The most appropriate end-use pesticide product, based largely on the preference of the grower, will be used at each of the individual MU sites. A different test substance may be used at each site and by each worker within a monitoring area if appropriate." (pp. 127 of 403)

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

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

"The following active ingredients are available as wettable powders and will be considered for use in this mixing/loading scenario.

- Sulfur
- Copper
- Thiophanate-methyl
- DCPA (dacthal)

"These surrogate active ingredients, except thiophanate-methyl, typically have high use rates for the potential crops of interest that enables measurements at the high end of AaiH per day. Additionally, cooperating growers who use these products are likely to be available." (pp. 44-45 of 403)

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

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

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

"AHETF has calculated a practical range in AaiH for this scenario taking into account such factors as typical use rates of products, types of products available on the market, types of crops on which the products are used, number of acres that can be treated in a day, etc. AHETF has selected a range of 5to 2000 lbs active ingredient to be handled per day for this scenario." (pp. 36 of 403)

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

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

"…AaiH diversity between MUs in the same monitoring area will be obtained by attempting to restrict each of the five MUs in each monitoring area to a different AaiH stratum." (p. 37-38 of 403)

(c) What duration of exposure is proposed?

"Duration of monitoring is another parameter that could vary between MUs, especially since the AaiH will be varied by more than two orders of magnitude. Mixer/loaders might spend several hours per day at the mixing area but can also

spend long intervals performing other tasks (or just sitting around) between actual mix/load events (i.e., while the applicator is making the application). So MUs will be monitored during their entire work day since many other unknown factors might contribute to exposure. All monitoring periods for this scenario must meet the general rule of being at least 4 hours. This is designed to overcome the criticism of early exposure studies where many of the sampling regimes monitored workers for only a few minutes. Avoiding very short monitoring intervals will ensure that daily exposure estimates are not biased by unusual conditions during that short interval. If necessary, some minor scripting of worker activities will be done to ensure the lowest levels of AaiH are handled and/or a minimum of four hours are monitored. For example, a worker might be asked to use a smaller tank, make smaller loads, or increase the spray volume slightly in order to mix 3 loads in four hours." (pp. 43-44 of 403)

2.3 Endpoints and Measures

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

"At the completion of the monitoring period, exposure samples will be taken in the following order to minimize cross contamination: inhalation samples (discussed in the next section), then hand washes, then face/neck wipes, and finally inner dosimeters as described in SOP AHETF-10.E.2." (pp. 130 - 131 of 403)

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

"Full details for sampling air with OSHA Versatile Sampler (OVS) tubes and personal air-sampling pumps are given in the most recent versions of SOP AHETF-8.D and 10.G." (pp. 131 of 403)

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

"Field fortification samples are exposure matrix samples that are fortified (or spiked), generally in the field, with known amounts of active ingredient and subsequently analyzed to determine the amount of active ingredient recovered. Field fortification samples are subjected to the same environmental, handling, shipping and storage conditions as worker samples. Because these conditions are similar, and because field fortification samples are analyzed along with worker samples, recovery values calculated from analysis of fortification samples are applicable to worker exposure samples. Field fortification recoveries are therefore used to adjust residue levels found in worker samples for residue losses that might have occurred during collection, handling, shipping and storage." (pp. 223 of 403)

(c) What QA methods are proposed?

"AHETF intends that all regulatory studies are conducted in accordance with the FIFRA GLP Standards (40 CFR part 160). Field and analytical aspects of this study will be monitored by the relevant quality assurance units(s) (QAU) while this study is in progress to ensure compliance with the FIFRA GLP regulation and adherence to this protocol and relevant SOPs. The QAU(s) will submit copies of its/their inspection reports to the Study Director and AHETF Sponsor Representative (40 CFR part 160.35(4)). The final report will be audited by the QAU specified in Section 1.15 to ensure that the contents of the report accurately describe the conduct and findings of the study.

The final report will contain a Quality Assurance Statement from the QAU of each contributing laboratory conducting QA audits, and from the QAU specified in section 1.14." (pp. 138-139 of 403)

(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 monitoring area, 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. 131-132 of 403)

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

3. Subject Selection

3.1 Representativeness of Sample

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

"Collectively, the complete WP mixing/loading scenario data set will include instances of worker exposure resulting from the mixing/loading of packets of pesticides. Each instance is termed a monitoring unit (MU). Each MU consists of a set of mixing/loading conditions (including the particular worker) that are intended to represent the scenario activities for a single workday. In many cases monitoring units will be selected from 'naturally occurring' WP mixing/loading-days. However, the selected application conditions are sometimes modified or scripted slightly to ensure that the sample of MUs reflects the expected diversity in the entire population of future WP mixer/loader-days. . . .Thus, MUs are technically not 'sampled' from a population. More correctly, they should be viewed as synthetic WP mixing/loading-days derived from both selected and constructed conditions." (pp. 17 of 403)

(b) From what populations will subjects be recruited?

"The growers and/or commercial pesticide application companies in the chosen configuration provide the pool of workers from which cluster participants will be recruited." (pp. 42 of 403)

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

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

1. "Contact local resources such as those listed below to obtain a list of growers that might utilize open pour WP mixing/loading at the identified site (generally several counties):

    - Farm Market ID
    - Commercial list providers
    - State and local government entities
    - Grower associations
    - Grower Publication subscription lists

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

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

    - The grower is willing to cooperate with AHETF, including the ethical aspects of the research
    - The grower has the necessary mixing/loading equipment
    - The grower has at least one worker with experience in the mixing/loading of WPs
    - The grower is willing to allow AHETF to recruit his/her worker(s)
    - The grower has sufficient acreage that the minimum AaiH can be reasonably be handled by a worker in one day
    - The grower is willing to use at least one of the surrogate active ingredients listed in the study protocol." (pp. 39-40 of 403)

"The growers and/or commercial pesticide application companies in the chosen configuration provide the pool of workers from which cluster participants will be recruited. (pp. 42 of 403)

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

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

3.2 Equitable Selection of Subjects

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

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

- Have experience within the past year with the work activity being monitored in the study (including the particular equipment to be used during mixing/loading or application)
- Handle pesticides as part of their job
- Be trained in safe pesticide handling practices in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training
- Provide proof of being at least 18 years old with a government-issued photo ID
- Confirm they do not work for a pesticide company or a contractor of the AHETF

- Consider their general health status to be good and tell researchers they have no medical conditions that affect their ability to participate in the study (See SOP AHETF-11.C for health status determination)
- Not be pregnant or nursing (See SOP AHETF-11.D)
- Confirm they do not normally wear personal protective equipment that is not required by the label and that might impact the objectives of the study, such as chemical-resistant clothing. Confirm they will follow label directions.
- Have a private meeting with a researcher to review and discuss the consent form
- Understand English or Spanish (See SOP AHETF-11.I for a detailed discussion of this topic)
- Understand and sign the consent form, and if in California, the California Experimental Research Subject's Bill of Rights" (SOP AHETF-11.B.5)

"For this mixing/loading of wettable powders study, the following inclusion criteria also apply:

- Have experience within the past year with mixing/loading wettable powders by open pouring (including the particular equipment to be used) (p. 106 of 403)

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

None

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

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

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

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

"The Study Director or designated researcher will seek permission from the eligible grower to approach his/her employees to recruit volunteers for the study. Depending on the number of employees and size of the grower facility the Study Director or researcher may contact employees using an informational recruitment flyer posted in

a common work area. Such a flyer will briefly describe the research study and provide a toll-free phone number for employees to express an interest in participating in the study. The flyer shall have been previously reviewed and approved by an IRB.

"Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the grower's employees who express an interest in participation. Such recruitment meetings will always occur without the grower or supervisors being present (SOP AHETF-11.B). The Study Director or researcher shall make a presentation describing the AHETF Exposure Monitoring Program, the goals of the research study, the procedures used in exposure monitoring, and the risks and benefits to participants. A toll-free phone number will be provided, and individuals will be encouraged to contact AHETF if they desire additional information about the study or are interested in participating in the study. All presentation materials, such as handouts or visual aids, shall be reviewed and approved by an IRB prior to use in recruiting subjects." (pp. 123 of 403)

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

"In accordance with SOP AHETF-11.B, the individual growers will be asked to sign a non-coercion statement (Employer Cooperation Statement) affirming to their workers and AHETF that they will not coerce or unduly influence their workers to either participate or not participate in the study. Growers must also certify that alternate work will be provided on study days for workers who choose not to volunteer; and that the employee's decision to participate or not will have no impact on their employment." (p. 122 of 403)

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 6.2) 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 subject withdraws from the study. All workers who participate will

receive the payment, even if they withdraw or their participation is terminated by the study team." (p 106 of 403)

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

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

(d) How and when would subjects be paid?

In cash, immediately after their participation.

4. Risks to Subjects

4.1 Risk Characterization

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

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

This study could involve any of four active ingredients: copper, DCPA (dacthal), sulfur and thiophanate-methyl. "The pesticide products containing these active ingredients and potentially used in this study are currently registered for agricultural use. AHETF will only monitor workers making applications in accordance with all label, Worker Protection Standard (WPS), and state (e.g., California) regulatory requirements." (p. 110 of 403)

For sulfur, copper and dacthal, the Margins of Exposure (MOEs) calculated for the highest level of exposure in this protocol meet or exceed the minimum required MOE, or level of concern (generally 100), for the individual dermal and inhalation routes of exposure, as well as for the combined exposure. For thiophanate methyl, however, the protocol does not permit application of more than 100 lbs AaiH in order to keep MOEs below the level of concern. This means that thiophanate methyl may only be used in the lower two strata (5-17 lbs AaiH or 18-55 lbs AaiH).

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

The protocol and consent form currently lists four kinds of risks:

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

"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. 106 of 403)

In response to the comments from the HSRB in its report of the October 2010 meeting, Supplement 1 indicates that the protocol and consent form will be revised to include the risk of potential exposure to the surrogate chemicals as a risk of study participation. Specifically, the AHETF is proposing to add the following statement to the Consent Form:

> "Handling a pesticide as part of the research may cause sickness, eye or skin irritation, allergic skin reactions, or temporarily affect the nervous system. These kinds of risks occur when you handle many types of pesticides, but might be higher if you are asked to handle more pesticide or work longer than usual. A researcher will show you the label for the product you will be using and discuss the risks of that product with you."

(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 mixing/loading equipment to be used in the study and with mixing/loading products in wettable powder products
- Reminding workers of safe chemical handling practices
- Practicing the face wipe and hand wash procedures with each participant before pesticide handling begins
- Identifying nearby medical treatment facilities in case of emergency
- Monitoring the heat index and stopping the study if conditions warrant
- Providing transportation to medical treatment and covering the costs of treatment
- Having a medical professional on site to observe the workers and provide urgent care

- Observing study participants throughout the monitoring period
- Ensuring that all tank mix products are used according to approved label(s) and state regulations, and do not require any additional PPE that could adversely affect the study objectives (for example, chemical-resistant coveralls or aprons)." (pp. 111-112 of 403)

Risk reduction actions specific to the identified kinds of risk are discussed in the protocol (pp. 108-111 of 403).

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

For sulfur, copper and dacthal, the Margins of Exposure (MOEs) calculated for the highest level of exposure in this protocol meet or exceed the minimum required MOE, or level of concern (generally 100), for the individual dermal and inhalation routes of exposure, as well as for the combined exposure. For thiophanate methyl, however, the protocol does not permit application of more than 100 lbs AaiH in order to keep MOEs below the level of concern. This means that thiophanate methyl may only be used in the lower two strata (5-17 pounds ai handled or 18-55 lbs ai handled).

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

"AHETF will monitor ambient conditions outside the cab to determine the heat index near the mixing/loading station and base monitoring decisions on the current heat index. Exposure monitoring will be discontinued if the heat index cutoff of 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. 107 of 403)

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

"As a safety measure, AHETF will have a medical professional on site during the study. This may be a paramedic, physician's assistant, nurse, or emergency medical technician. This professional will also observe you for signs of illness. They will provide medical attention as needed." (p. 147 of 403)

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

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

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

- SOP AHETF-11.E calls for researchers to monitor worker compliance with label and Worker Protection Standard requirements and labeling, and permits

the Study Director to remove from the study a worker who engages in unsafe work practices.

- SOP AHETF-11.G calls for the Study Director, the on-site medical professional, and all researchers and observers to monitor subjects for any indication of heat-related illness.
- SOP AHETF-11.H defines procedures to be followed if a subject in an AHETF study requires emergency medical attention.

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

"During the consenting process each volunteer will be provided the opportunity to request a summary of their personal results from the study. This will require the worker to provide a name and address (mail or e-mail). The results will include the distribution of chemical exposure among the various body areas measured so the worker can be aware of where most dermal exposure occurs and a comparison to the results for other workers performing the same task. This follow-up procedure is described in SOP AHETF-11.J and 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 a toll free phone number 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. 116 of 403)

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

"If you are injured or get sick because of your participation in this study, medical treatment will be available at your workplace and at a nearby health care facility. If necessary, AHETF will arrange to have you taken to receive medical attention." (p 148 of 403) "You may refuse medical treatment unless you get sick from too much exposure to pesticides or from getting too hot, or if the medical professional decides you are too sick to make a rational decision about getting medical treatment." (p 5 of Supplement 1)

"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. 148 of 403)

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. 112 of 403)

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?

"Data from the AHETF exposure monitoring program has the potential to improve the ability of EPA and other regulatory agencies to accurately assess occupational risks associated with mixing/loading wettable powder pesticides. 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. 112 of 403)

"Since there are not sufficient existing data suitable for use in a generic database describing the exposure to workers from mixing/loading wettable powders, society will likely benefit from data generated by this study through the improved risk assessments by EPA and other regulatory agencies." (p. 112 of 403)

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

"Growers who allow the study to be conducted using their equipment, crops and facilities will be reimbursed for the pesticides used for the study. While this is beneficial to the grower, it is considered a minor benefit when compared to the costs of running their businesses. The AHETF member companies will likely realize a benefit by addressing regulatory data requirements generically, at lower cost (and using fewer human subjects), than if they conducted similar studies for individual pesticide ingredients." (p. 112 of 403)

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

Identified societal benefits are likely to be realized.

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

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

"The likely benefit to agricultural workers as a whole and to society in general, in the form of more accurate measurements of potential exposure to pesticides, must be weighed against the risks to participants. Wettable powder products are common for many agricultural uses across the country and a variety of experts consulted by AHETF reported their use occurs widely throughout the country. Exposure data for this scenario meeting contemporary standards of reliability and quality will likely provide a significant benefit to society. Because 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 113 of 403)

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? Yes.

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

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

"This study will be conducted in accordance with EPA's final regulation published at 40 CFR Part 26 that establishes requirements for the protection of subjects in human research (see SOP AHETF-11.A). The protocol, informed consent form(s), California Experimental Research Subject's Bill of Rights, and other required documentation for this study will be approved by an institutional review board (IRB) and the California

Department of Pesticide Regulation, and submitted to the EPA as required by 40 CFR 26.1125. The report of the completed research is subject to 40 CFR 26.1303 requirements to document its ethical conduct.

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

"Researchers that participate in the study and interact with study participants must undergo ethics training (SOP AHETF-1.B). The training shall include successful completion of the course from the National Institutes of Health (Protecting Human Research Participants (PHRP)) and/or the Basic Collaborative IRB Training Initiative Course (CITI; The Protection of Human Research Subjects). Copies of the certificates of completion for the ethics courses will be submitted to the IRB and stored in the respective personnel files (maintained by the AHETF and all contract facilities.)" (p. 105 of 403)

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. According to documents submitted to IRB, appropriate provision is made for informing English or Spanish-speaking candidates who cannot read the consent form. (p 340 of 403)

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

See SOP AHETF-11.I

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

"In all situations, the person obtaining consent will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential workers that would require a response that indicates understanding of key issues. The form in Attachment 11-J-1 will be used to ascertain general understanding. (SOP AHETF-11.J.1 §3.10) (p 299 of 403)

(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 conducting the consent meeting will provide each worker with a full explanation of the study, its requirements, any potential risks, its benefits, alternatives to participation, etc. Workers will be advised of their right to withdraw from the study at any time and for any reason without jeopardizing their normal position with their employers or their daily wages. Workers will be told they will receive an additional $80 (or another amount specified in the protocol) if they decide to participate and put on the dosimeters, whether or not they complete the monitoring period.

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

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

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

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

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

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

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

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

"In accordance with SOP AHETF-11.B the individual growers will be asked to sign a non-coercion statement (Employer Cooperation Statement) affirming to their workers and AHETF that they will not coerce or unduly influence their workers to either participate or not participate in the study. Growers must also certify that alternate work will be provided on study days for workers who choose not to volunteer; and that the employee's decision to participate or not will have no impact on their employment." (p. 122 of 403)

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. 113 of 403)

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

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

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

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

"You may ask the Study Director for a copy of your personal results from this study. You will need to provide your name and a mail or e-mail address." (pp. 148-149 of 403)

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

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

"Any subject expressing a need or desire to withdraw from the research after exposure monitoring begins will be paid $80 and allowed to return to their normal work duties for their employer. If a subject withdraws while being monitored, the long underwear and air sampling pump will be removed, and the hand and face/neck samples will be collected with the worker's consent. The Study Director will decide whether these samples will be analyzed." (SOP AHETF-8.K). (p. 113 of 403)

"Your employer has agreed to let us do the research and has confirmed that he/she does not mind if you do or do not take part in this study. Your decision to be in this study is voluntary. This decision is entirely up to you. If you decide to take part, you may change your mind and drop out of the study at any time and for any reason. A decision not to take part, or to withdraw from the study after it starts, will not affect your job or pay or include any penalty or loss of benefits you are owed." (p. 149 of 403)

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

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

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

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

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

"No one can force you to take part in this study. Taking part is totally voluntary. If you choose not to take part in this study you will perform your ordinary activities on the day of the study. Your alternative is to not take part." (pp. 149-150 of 403)

§ 26.1111 Criteria for IRB approval of research
AHETF Protocol: Mixing/Loading of Wettable Powders (AHE80)

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

§26.1116 General requirements for informed consent
AHETF Protocol: Mixing/Loading of Wettable Powders (AHE80)

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

§26.1117 Documentation of informed consent
AHETF Protocol: Mixing/Loading of Wettable Powders (AHE80)

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

40 CFR 26.1125 Prior submission of proposed human research for EPA review
AHETF Protocol: Mixing/Loading of Wettable Powders (AHE80)

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

		Requirement	Y/N	Comments/Page Refs
All information relevant to the proposed research specified by § 26.1115(a)		(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.	Y n/a Y n/a	Pp 325-390 pp. 143-171
		(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.	n/a n/a	Pp 397-399 Protocol approved without changes. No controverted issues
		(3) Records of continuing review activities.	n/a	
		(4) Copies of all correspondence between the IRB and the investigators.	Y	pp. 91-95 and 324-403,
		(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.	Y	IIRB roster and credentials on file with EPA.
		(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).	Y	Separately submitted to EPA under confidentiality claim
		(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).	n/a	
The following Information, to the extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	Pp 106-112 of 403 and p 2 of Supplement 1
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 106-112 of 403 and p 2 of Supplement 1
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 112-113
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	pp.15-17 and AHETF Governing Document (reviewed at June 2008 HSRB meeting)
		(5) The balance of risks and benefits of the proposed research.	Y	p. 112-113
		§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 submission pp 349-359 and 375-388 Approved pp. 143-171
		§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	pp. 39-41, 106, 118-126, 155, 173
		§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. 113-116
		§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	pp. 95-96, 324-403
		§1125(f): Official notification to the sponsor or investigator…that research involving human subjects has been reviewed and approved by an IRB.	Y	pp. 95-96