UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

June 21, 2016

MEMORANDUM

SUBJECT: Ethics Review of Completed AHETF Study AHE80 on Worker Exposure during Mixing/Loading of Wettable Powders

FROM: Maureen Lydon, Human Research Ethics Review Officer
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TO: Dana Vogel, Director
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REF: Baugher, Douglas and Rosenheck, Leah. (2016) Determination of Dermal And Inhalation Exposure to Workers during Mixing/Loading Wettable Powders in the United States. Study Number AHE80, 796 p. January 27, 2016 (MRID 49841201)

Klonne, Dennis R. and Holden, Larry R. (2016) Scenario Monograph Report. Agricultural Handler Exposure Scenario Monograph: Open Pour Mixing/Loading of Wettable Powders. Report Number AHE1015, 218 p., April 7, 2016 (MRID 49893001)

Baugher, Douglas. (2016) IRB Correspondence Report for Study AHE80. Related Submissions. Study Report AHE80 and Scenario Monograph Report No. AHE1015. 667 p. plus 337A. March 23, 2016. (MRID 49893002)

I have reviewed the available information concerning the ethical conduct of the research reported by the Agricultural Handler Exposure Task Force (AHETF) in the referenced documents. The documents describe the implementation and results of field studies, the objective of which was to develop data to determine the potential dermal and inhalation exposure for workers who mix and load pesticides formulated as wettable powders (WPs). The monograph report for the open pour mixing/loading of wettable powders summarizes the dermal and inhalation exposure data collected through studies AHE80 and AHE39 for the wettable powder mixing/loading agricultural handler scenario.

In its conduct, study AHE80 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. As outlined in this memorandum, the Office of Pesticide Programs (OPP) has identified follow-up actions for AHETF based on the ethics review of AHE80 and AHETF has agreed to implement them. If study AHE80 and scenario monograph report AHE1015 are determined to be scientifically acceptable, I find no barrier in regulation to EPA's reliance on them in actions under FIFRA or §408 of FFDCA.

In addition, as further explained in the next section, under 40 CFR 26.1604, EPA is required to seek input from the Human Studies Review Board (HSRB) for intentional exposure human studies covered by EPA's human studies rule that are initiated after April 7, 2006. EPA will share study AHE80, scenario monograph report AHE1015, the associated support documents, and EPA's science and ethics reviews of the study with the HSRB for their review. This memorandum and its attachments document EPA's ethics review.

Request and Requirement for HSRB Review

The scenario monograph report on agricultural handler exposure from open pour mixing/loading of wettable powders summarizes the results of two studies: AHE39, which was initiated prior to the effective date of the rule on protecting human subjects, and study AHE80, which was initiated after the effective date of the final rule. Under 40 CFR § 26.1604, EPA is required to seek input from the HSRB for human studies covered by EPA's human studies rule that are initiated after April 7, 2006. For human studies initiated prior to April 7, 2006, EPA may, but is not required to, consult with the HSRB unless the study was conducted to identify or measure a toxic effect.

For the July 12 – 13, 2016 HSRB meeting, EPA is seeking HSRB input on whether available information supports a determination that study AHE80 was conducted in substantial compliance with subparts K and L of 40 CFR Part 26; EPA is not seeking any HSRB feedback on the AHE39 study since HSRB review is not required and EPA has concluded that the study is scientifically valid and relevant and not unethical under §26.1704.

Background on Study AHE80

Study AHE80 developed data to determine the potential dermal and inhalation exposure for workers who mix and load pesticides formulated as wettable powders. The monitored activity included opening bags of product and pouring the powder into a variety of mixing or application equipment as well as the addition of water to the tank.

The AHE80 protocol, approved by an Institutional Review Board (IRB), specified five monitoring units (MUs) to be conducted in each of four geographic monitoring areas (MAs) for an expected total of 20 monitoring units. The four specified monitoring areas for AHE80 were New York (MA 81), Florida (MA 82), Michigan (MA 83), and California (MA 84). A monitoring unit or MU is a single subject carrying out scenario-specific tasks

under a particular set of circumstances that represent a single workday. A monitoring unit refers to a worker who is carrying out activities using a particular pesticide formulation under a specific scenario, on a particular day. Every MU provides an estimate of a single handler-day of exposure to that pesticide. A cluster is a group of monitoring units that are performed close together in terms of location and time. Under study AHE80, all sets of samples were collected; however, the AHETF included 19 in the data analysis because MU 15 was terminated after the water source malfunctioned when MU 15 was mixing/loading his first load.

Attachment 1 lists major study events in chronological order and attachment 2 identifies the surrogate active ingredient used in study AHE80. Attachment 3 provides worker information for each MU, organized by each of the four monitoring areas for AHE80.

The next section highlights the chronology for reviews by the Institutional Review Board (IRB), EPA and the Human Studies Review Board, beginning with the last HSRB review of the protocol for AHE80.

Required Reviews of Protocol and Ethics-Related Chronology

The AHE80 scenario design and protocol, approved by the overseeing Institutional Review Board (IRB), and EPA's ethics review, dated December 27, 2010, were discussed by the Human Studies Review Board (HSRB) at its January 26, 2011 meeting. With regard to ethics, the HSRB's March 17, 2011 final report from the meeting concluded that, "the proposed AHETF scenario and field study proposal submitted for review, if revised as suggested and performed as described, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."

Following the HSRB review, the protocol, consent form, California Experimental Research Subject's Bill of Rights (CaBOR), and recruitment materials for AHE80 were revised to address EPA, California Department of Pesticide Regulation (CDPR), and HSRB comments. Following the January 26, 2011 HSRB meeting, AHETF submitted the first set of revised documents to the Independent Investigational Review Board, Inc. (IIRB) of Plantation, Florida on March 24, 2011. The IIRB approved them on March 29, 2011. Attachment 4 summarizes how the study sponsor addressed the HSRB's comments in the revised materials. The IRB approved six subsequent amendments between June 2011 and November 2013 as reflected in AHETF's chronology of major study events in Attachment 1. [On October 1, 2012, Independent IRB, Inc. was absorbed into its parent company, Schulman Associates Institutional Review Board, Inc. (SAIRB), and a formal name change to SAIRB followed.]

Completeness of Submission

EPA used the checklist in attachment 5 to verify that the requirements of §26.1303 were fulfilled regarding the documentation for this research. This ethics review considered the study material, IRB correspondence, and AHETF's responses to EPA questions which were integrated into this memorandum.

Recruitment

With regard to recruitment, the protocol references SOPs 11.B.7, 11.K.O, 11.L.O, and 11.M.O. The recruitment process outlined in the protocol and these SOPs appears to have been followed in study AHE80 as described in the next section (entitled "EPA Comparison of Recruitment Described in Study versus Protocol and SOPs"). An initial employer universe list was generated from published lists/databases which ranged in size from 1,040 to 12,152 depending on each of the four monitoring areas. Duplicate entries and growers with missing phone numbers were removed to produce the master employer lists. Qualifying calls were placed to the names on the master list, and the lists were narrowed based on responses to qualifying questions, being unreachable, or refusal to talk to interviewer. (Attachment 6 identifies the steps taken to compile the qualified employer list specific to each monitoring area.) Consistent with the protocol, at least seven attempts were made to reach every qualified employer on the qualified list to determine those that use appropriate formulations and might be willing to cooperate and allow recruitment of workers. The result was the Potentially Eligible Employer List. Potentially Eligible Employers are those that meet the research requirements and, at least tentatively, agree to cooperate in the research. Contact/visits occurred to confirm eligibility. The result was the Eligible Employer List. Once eligible employers were identified, the next steps included subject recruitment, informed consent, and study monitoring.

The three phases of the recruitment process are explained below, along with the rationale for AHETF combining the Universe and Master Lists from AHE80 and another agricultural handler exposure study, AHE120, consistent with the IRB-approved protocol amendment. In the study itself, there are four sections (3.1 – 3.4) which detail the recruitment process for each of the four monitoring areas in the study. As described in study AHE80:

> "AHETF located employers who used wettable powders or water soluble packages, were willing to participate in the research using their own equipment, and agreed to allow their employees (if not self-employed) to be recruited for the study. The recruiting procedures were designed to minimize bias in the selection of employers and volunteer participants. The goal was to collect five MUs in each monitoring area.
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> Recruiting activities occurred in three phases that are each described in detail in the sections below and can be summarized as follows:
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> • **Phase 1**: Create a list of growers and commercial applicators (i.e., employers) in the monitoring area that might use a wettable powder or water soluble package (Universal Employer List), and then identify those who are qualified for the study by calling them to determine whether they use wettable powders or water soluble packages (Qualified Employer List or QEL). Alternatively, an employer may be identified and qualified by a local agricultural specialist.
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> • **Phase 2**: Call qualified employers to determine those who use wettable powders

and might be willing to cooperate with the study by allowing AHETF to recruit workers to participate in the exposure monitoring study (Potentially Eligible Employer List or PEEL)

• **Phase 3**: Contact and visit potentially eligible employers, confirm eligibility (Eligible Employer List or EEL) and then schedule and conduct informed consent sessions and monitoring of workers mixing and loading wettable powders into a spray tank(s).

The study protocol required recruitment of employers (growers or commercial applicators) that utilize wettable powder formulations. Since three of this study's monitoring regions overlapped with those from study AHE120 which involved the monitoring of workers mixing/loading water soluble packages, recruitment of these two studies was done simultaneously since many employers utilized both wettable powders and water soluble packaged formulations. Therefore the Universe List, Master List, and Qualified List for these two studies were combined. As such, for Phase 1 recruiting it was much more efficient to combine Universe and Master Lists from AHE80 and AHE120 and utilize one questionnaire for both studies than to produce two separate Universe and Master Lists (one for each study) and survey each group (with many growers in both groups) independently from two questionnaires. Similarly for Phase 2 recruiting, it was much more efficient to call all employers on a combined AHE80 and AHE120 Qualified Employer List since many of the employers were qualified to participate in both studies. Screening results from the secondary survey questionnaire or local agricultural specialist notes were used by the Phase 2 recruiter to confirm the type of formulated product used and direct recruitment discussions to the appropriate study.

For Phase 1 and Phase 2 recruiting in 2011, the California, Florida, and New York AHE80 monitoring areas were combined with the AHE120 monitoring areas. For these three AHE80 monitoring areas, interviews were done using a combined AHE80/AHE120 questionnaire. Qualified respondents were placed on a combined AHE80/AHE120 QEL. These procedures were also used in 2012 for Florida and in 2014 for California and Florida. For recruitment in Michigan in 2013, AHE80 specific questionnaires and Universe, Master, and Qualified Lists were developed (for more details, see individual monitoring area recruiting discussions).

From April 2011 to December 2014, AHETF recruited growers and commercial applicators (referred to as 'employers') to participate in study AHE80. The following table summarizes the list sizes and number of MUs collected for each monitoring area in this study." Attachment 7 to this memo includes the charts on "employer lists and recruitment details" for each monitoring area.

Monitoring Area for AHE 80	Employer Universe List	Qualified Employer List	Potentially Eligible Employer List	Eligible Employer List	MUs Collected
81 = NY	1,040	161	44	7	5
82 = FL	12,152	355	91	12	5
83 = MI	955	209	60	7	4*
84 = CA	9,353	413	383	18	5

**Note: One MU was terminated due to equipment and water source problems.*

EPA Comparison of Recruitment Described in Study AHE80 versus Protocol and SOPs

As part of EPA's ethics review, I compared the recruitment process discussed in study AHE80 with the recruitment process identified in the protocol, as well as the specific AHETF standard operating procedures (SOPs) referenced in the protocol impacting recruitment. These SOPs were previously reviewed by the Human Studies Review Board. The protocol references SOPs 11.B.7, 11.K.O, 11.L.O, and 11.M.O when discussing recruitment. When considered together, these SOPs discuss basic steps to be followed during the process of assembling lists and recruitment. I identify the basic steps below, as well as the applicable SOP per step. The SOP on recruitment also indicates that, **"A study-specific recruitment plan will be specified in each study protocol."** For the convenience of the Human Studies Review Board, beneath each of the steps below, I note where this step was incorporated into the AHE80 recruitment process. This is prefaced by the phrase, "Incorporation of step into AHE80 study" and refers back to the recruitment phases identified in the previous section and on pages 22-23 of the study. The information prior to the phrase "Incorporation of step into AHE80 study" is based on the SOPs referenced in the protocol. **The purpose of this section is to identify where the SOPs referenced in the protocol were taken into account in study AHE80.**

1. Assemble universe list; (Noted in SOPs 11.K.O and 11.L.O)

   Incorporation of this step into AHE80 study: Reflected in recruitment phase 1 in AHE80 study.

2. Randomly select subset as master list for screening; (Noted in SOPs 11.K.O and 11.L.O)

   Incorporation of this step into AHE80 study: Reflected in recruitment phase 1 in AHE80 study. As it relates to this topic, EPA asked AHETF, "In each state, did AHETF "randomly select a subset of the universe list as the master list for screening" for study AHE80?

AHETF's detailed response follows:

"AHETF examined the universe of crop growers from USDA NASS Census of Agricultural estimates for the protocol-specified area and crops. AHETF attempted to locate a sufficient supply or sample of grower names from agriculture list agents that approach NASS estimates. The total number of grower names available from list agents became our Employer Universe List (EUL). **AHETF generally does not initially purchase the total supply of names from list agents but rather a random subset.**

The initial subset size purchased was based on what we know about grower and product use patterns and knowledge gained from researching growers and experts when defining the scenario. The grower subset obtained from list agent(s) was the Master Employer List (MEL). If the initial subset used for the MEL did not provide enough qualified growers, additional subsets from our available universe (the list agents' supply) were purchased and added to the MEL. AHETF always purchased random subsets from list agents. **If the total available universe of grower names from list agents was used for a region then the EUL is the same as the MEL**" excluding missing phone numbers or any caveats specific to monitoring areas as identified in the study.

EPA's follow-up questions to AHETF were, "Who chooses the random subset?" and "How is it chosen randomly?" AHETF's detailed responses follow:

Additional Information Submitted by AHETF

"AHETF determined the size of the subset, and the list agent used a random procedure to select the subset from the total number of growers they had on hand. For a given region, the number of growers was known from the census but percent using wettable powders was estimated because there was no census, market study, or list that specifically identified growers or the number of growers using wettable powders. We tried to obtain a starting list size of about 1,000 growers for each region in 2011.

In NY, we purchased the total universe of growers from the list agents for an unduplicated total of 1,040 growers (32 had missing phone numbers). However, this was all the grower names needed to obtain a sufficient MEL in NY so this EUL became our MEL.

In all other regions, the original subset was insufficient for our recruiting needs and additional grower names were obtained. If we didn't find enough growers in a region and we used up the EUL, then we either expanded to additional crops or increased the size of the Monitoring Area. This was required in the CA and FL monitoring areas. We expanded the original protocol counties in MI to include an additional seven counties. In these regions, the remaining EUL of growers was purchased from the list agents to provide a sufficient MEL for further recruiting. In the CA, FL and MI monitoring areas, the EUL became the MEL." For more detail on the quantities in the EUL and MEL for each monitoring area, see the individual

sections in the report.

"If we purchase a subset of the list agent's list (and not their total list for the region as we initially did for NY), we always asked the list agent to provide a random subset. Farm Market ID uses a stratified sampling program developed by their company. It uses SQL driven commands to: 1) group the total population of names within the target region by zip code, 2) determine the percentage of the population in each zip code, and 3) draw a random sample from each zip code (where the number of names selected is proportional to its percentage of the total population) using an Nth name selection technique.

Meister Media Worldwide uses a simpler randomizing process. They select all the grower names from the target region and crops, assign a random number to each grower using Excel's Rand function, and sort on the assigned random number to randomize the list. They develop our set of names from this randomized list. For both list agents, any additional subsets of growers from the same region are drawn similarly but with preceding subsets excluded." – *End of AHETF additional information* -

3. Third-party professional calling center screens master list; (Noted in SOPs 11.K.O and 11.L.O)

   Incorporation of this step into AHE80 study: Reflected in recruitment phase 1 in AHE80 study. This is discussed in detail in the study in the descriptions of recruitment for the five monitoring areas. As discussed in the study, "Employers on the Master Employer List were prescreened by a commercial calling center…to determine if they used wettable powders or water soluble packages."

4. Identify qualified list; (Noted in SOPs 11.K.O and 11.L.O)

   Incorporation of this step into AHE80 study: Reflected in recruitment phase 1 in AHE80 study.

5. AHETF contacts qualified growers/applicators; (Noted in SOP 11.M.0)

   As discussed in SOP 11.M.0, the caller will use a "discussion guide" during the eligibility assessment call. The goal is to identify potentially eligible growers/applicators for the study. Growers/applicators/employers will be asked for permission to recruit workers for the study. Written assurance will be obtained from employer that workers will not suffer consequences whether or not they decide to participate and will not be subject to coercion. Growers/applicators/employers will be informed that Study Director may contact them. At this point in the process, the pool of eligible growers/applicators/employers now exists.

   Incorporation of this step into AHE80 study: Reflected in recruitment phase 2 in AHE80 study.

AHETF confirmed that "a discussion guide was used by the researcher who made the calls to the qualified growers/applicators. As described in SOP AHETF-11.M.0, Section 5.2, the discussion guide was fashioned after the example discussion guide attached to SOP AHETF-11.M.0 (Attachment 11-M-1). For this study, the one researcher who made the calls to the qualified growers/applicators has 36 years *(of)* experience with field worker exposure testing procedures, is trained in conducting interviews, and has ethics training as required by SOP AHETF-1.B."

6. Recruit workers from the pool of eligible growers, applicators, employers; (Section 4.2 from SOP 11.B.7)

The Study Director (SD) or designee initiates contact with the employees, sometimes by distributing an IRB-approved flyer which generally describes what participation in the study entails and provides a toll-free phone number to accommodate both English and Spanish speakers, or by conducting an on-site visit. Appropriate language flyers (English or Spanish) will be distributed at the discretion of the SD (or designee) or at the request of the employer.

Study Director (SD) organizes the recruitment meetings. (Section 4.3 from SOP 11.B.7) The SD (or designee) organizes a recruitment meeting with only the interested workers present and in the preferred language of the attendees. Recruitment meetings may be done one-on-one or with a group of interested workers. The study, protocol, consent form, and eligibility criteria will be discussed. Workers will be encouraged to take the consent form home for review. Potential volunteers will be given written assurance from their employer that the employee will not suffer consequences whether or not they decide to participate.

Incorporation of this step into AHE80 study: Reflected in recruitment phase 3 in AHE80 study. There are several activities encompassed in this section; for purposes of clarity, they are discussed in separate sections of this ethics review which follow.

Workers' Attendance at Recruitment Meetings

AHETF confirmed that recruitment meetings occurred in all monitoring areas included in the study and required information was covered. Consistent with the protocol, all growers signed the Employer Cooperation Statement (also known as the employer non-coercion statement) before any recruitment meetings affirming that they would not coerce or unduly influence their workers to either participate or not participate in the study. For any study, if the participant is the grower, then signing the statement is not required. An informational flyer was used during the recruitment meetings with volunteers. The tables on pages 27-39 of study AHE80 which are entitled in part, "Summary of Employer Lists and Recruitment Details" did not include the numbers of "workers attending a recruitment meeting." At EPA's request, AHETF provided these figures which are reflected in the updated tables in attachment 7. AHETF explained that recruitment meetings usually involved just one available worker but, in New York, there were two workers at one recruitment meeting.

Subject Selection

Section 6.4 (page 26 of 41) of the protocol includes the following information on random selection of equivalent volunteers:

> **"6.4 Subject Selection and Consenting**
>
> For each monitoring area, the Study Director or designated researcher will contact workers (i.e., potential study participants) from growers in the efficient configuration to begin recruitment activities. When the pool of volunteers at a grower or commercial applicator operation exceeds the number of MUs required (i.e., more than one worker is available and willing to participate), a simple random selection of equivalent volunteers will be made. For example, the names of the volunteers could be written on slips of paper of equal size and placed into a container and mixed thoroughly. A slip of paper would then be drawn from the container to fill the MU. All volunteers will be informed of the possibility of not being selected for this reason. Volunteers who are not selected will be released to resume their normal activities. The method of random selection will be documented in the study file."
>
> *-End of excerpt -*

The participating subjects met the eligibility criteria as identified on the informed consent form which the subjects signed and the IRB and EPA approved. In New York and Michigan, there were more workers who signed consent forms than the number of MUs necessary. EPA asked AHETF about the method of random selection used in each applicable state to select the workers who would participate. In New York, one subject chose to participate in study AHE120 rather than study AHE80. In Michigan, AHETF explained that, "The farm manager decided that the crop needed to be sprayed before the research team was scheduled to be on site. The subject was an employee and did what he was told. By the time the research team arrived, the field had already been sprayed and it did not need to be sprayed again so soon." For that reason, the subject was not used in the study.

Informed Consent Process

All participating subjects completed the informed consent process and signed the consent form. The most recent version of the informed consent form is dated May 2012 and included on pages 338-350 of the IRB correspondence package shared with the HSRB. Subjects participating in the study in California also signed the California Experimental Research Subject's Bill of Rights as referenced in the consent form. AHETF confirmed that all consent meetings were done privately with only the potential volunteer and researcher present. Consent occurred after the recruitment meeting and prior to monitoring. AHETF confirmed that, "the study director or designee met privately with the volunteer and went through the informed consent (IC) document section by section. After the volunteer read a section, the volunteer was asked standard questions from a formal checklist to document understanding of the IC. Additional questions were asked and answered, and the volunteer did not move on to the next section until the SD was sure that the material was understood."

The consent form states that the label for the product to be used will be reviewed

with the subject prior to participating in the study. Please see the pertinent excerpt, below, from the consent form:

> **"PRODUCT HANDLED**
>
> You will be asked to mix/load a pesticide product that is registered by the US Environmental Protection Agency (EPA) and if in California, by the state of California. This product is a wettable powder and must contain one of the following active ingredients: sulfur, DCPA, permethrin or thiophanate-methyl. The label for that product will be reviewed with you before you take part in the study. This review will include how much of that product you might handle during the study, the precautionary health statements on the product label, what clothing and personal protective equipment you must wear, the importance of washing your hands before eating or smoking, and other safety precautions that should be followed. The label for this product will be on hand for you to look over and talk about at any time you want.
>
> The farm or operation management will choose the product that you will use. However, you will know which product you will handle before you sign this consent form.
>
> In addition to the pesticide you will mix/load, farm or operation management may want other registered or approved products added to the mix tank or spray tank. You will be told before you start which materials will be in the tank mix." - *End of excerpt*-

AHETF confirmed that all participating subjects were informed of the active ingredient and the end-use product before signing the informed consent form. AHETF reviewed the following label information with the subjects prior to participating in the study consistent with the informed consent form:

- How much of that product you might handle during the study,
- The clothing and personal protective equipment you must wear,
- The importance of washing your hands before eating or smoking, and
- Other safety precautions that should be followed.

AHETF stated that "this is standard practice at the beginning of each monitoring period." AHETF also noted that, "the field data collection forms contained a checklist of the items." This checklist is in attachment 8. Related to this, the protocol indicates that the specific risks associated with end-use products being handled should be reviewed and "discussed directly from the label." AHETF confirmed that this occurred and that the same information was reviewed with each Spanish-speaking subject using a bilingual researcher. Finally, the consent form outlines the "procedures before the start of the study" and the "procedures on the day of the study." AHETF documented that they followed these procedures, taking into account any approved amendments to the protocol.

The protocol allows for the researcher to read the consent form to non-readers and to have someone present during the consent meeting. For study AHE80, there were no interested workers who were non-readers. The protocol also directs that accommodations will be made for bilingual researchers who must be present if the preferred language is Spanish. In Florida, for study AHE80, there was one worker who opted to have a Spanish-

speaking researcher present during the consent meeting. AHETF confirmed that "in these cases a bilingual researcher (English and Spanish speaking) performed the informed consent process" in their preferred language.

AHETF confirmed that subjects received copies of the signed consent forms at the end of the consenting session or with their compensation at the end of the monitoring period.

Personal Protective Equipment and Outer Clothing

AHETF confirmed that the subjects participating in study AHE80 wore the required personal protective equipment (PPE) as specified on product labeling and in the approved protocol, along with the outer clothing prescribed in the protocol. The clothing and PPE worn by workers was consistent with the requirements of the U.S. EPA Worker Protection Standard (WPS).

As discussed on page 13 of study AHE80, "The subjects wore their own long-sleeve shirt and long pants which had been laundered prior to the monitoring period. The outer clothing was inspected for quality and cleanliness by study personnel and for EPA Worker Protection Standard (WPS, 40 CFR Part 156 and 170) compliance by the Study Director or on-site SD-designee. All clothing was deemed acceptable except for one subject (M15) who was wearing a short-sleeve shirt; he was given a clean long-sleeve shirt to wear by a researcher. One subject (M18) had a small tear on the forearm of one sleeve which was closed up with waterproof tape… All subjects wore some type of protective eyewear, usually goggles, and a few workers wore respiratory protection (dust/mist mask or half-face respirator)." AHETF supplied each subject with new chemical-resistant gloves for use when mixing and loading the wettable powder formulation into the application equipment. Table 4 on pages 68-69 of the study identifies the outer clothing worn by each subject, along with its material and condition. Table 5 on pages 70-71 identifies the PPE and additional clothing or items worn by each subject.

Observers and Medical Professionals on Site

Consistent with the protocol, pages 42-43 of study AHE80 states that, "All research personnel, including the assigned observers, were trained to recognize the signs and symptoms of heat-related illness. A medical professional such as a nurse, Emergency Medical Technician, Certified First Responder, or First Aid Responder (Red Cross Certified) was present for the duration of each monitoring event and periodically checked the subjects for signs of heat-related illness." EPA asked what "periodically checked" meant in practice during study AHE80. AHETF responded that, "For most MUs, the subjects were under constant observation by the medical professional since they were also the observer. However, when a medical professional was on site but not the observer, 'periodically checking' usually meant that after each mixing/loading event the subject was asked whether he/she was still feeling okay and was observed for any effects of heat stress as appropriate or the heat conditions." AHETF identified, in attachment 9, the assigned observers for each monitoring unit for study AHE80.

AHETF confirmed that the Study Director did not receive any phone calls from subjects reporting illness after participating in the study.

Compensation

AHETF confirmed that each subject received compensation consistent with the protocol and informed consent document. Compensation was $20 for participating in the consent meeting and $80 for each day of participation in the study, regardless of whether or not the subject withdrew or was removed from the study.

Eligibility Criteria and Worker Descriptions

Attachment 10 includes the eligibility criteria for AHE80 as amended and approved in advance by the IRB. All of the participating subjects signed the IRB-approved informed consent forms which included the eligibility criteria written in plain English. The 19 monitored workers were all adult males, ranging in age from 18 to 71 years old with work experience ranging from 1 to 44 years. The study identifies subjects with numbers thereby protecting their privacy by not revealing their names. As noted previously, there was one Spanish-speaking worker who requested a bilingual researcher who performed the informed consent process and was at the site during monitoring.

WPS Training Criterion

One of the approved eligibility criteria for handlers to participate in agricultural handler exposure studies reads as follows: "d. Be trained in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training." When reviewing the informed consent form used in the agricultural handler exposure studies (and previously reviewed by the IRB, EPA and HSRB), we noticed that this criterion appeared as follows on the consent form: "Confirm that you have been trained in pesticide safety or that you are not required to take this training."

AHETF appropriately explained that the instructions about WPS in the AHETF SOP is aimed at the research team members, all of whom are familiar with the WPS. The informed consent form (ICF) is aimed at the workers. Early on, in the development of the consent form, emphasis was placed on making the ICFs easy to understand. Asking workers if they have received any training on pesticide safety is a simple question which is easy to understand. EPA agrees with this discussion of the history on this topic. However, given how critical it is that the handlers receive Worker Protection Standard training and the fact that handlers are subject to WPS training, EPA wants to ensure that the study participants have actually completed WPS training as opposed to another type.

For that reason, OPP's experts on WPS have recommended that the training criterion be revised to read as follows: "Be trained in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS) or equivalent Canadian

regulations, or be a certified applicator of restricted use pesticides or a certified crop advisor." Because OPP recognizes that the remaining studies will be conducted in the United States, OPP is comfortable with the criterion reading as follows for the remaining AHETF studies: "Be trained in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS), or be a certified applicator of restricted use pesticides or a certified crop advisor."

Follow-up Action: EPA will ask AHETF to begin using this updated criterion beginning in August, 2016, after the HSRB meeting, for monitoring units that have not yet been initiated in other AHETF studies to which this same criterion applies. This would necessitate the IRB approving a revision to the consent forms for the remaining studies as applicable. (One of the last sections of this ethics review memo, prior to the conclusion, includes a compilation of follow-up actions, including this one, which resulted from this ethics review.)

Because the study covers agricultural handlers, the handlers are subject to WPS. **WPS requires handlers to receive pesticide safety training before doing any handling tasks, unless they are a certified applicator of restricted use pesticides (RUPs) or a certified crop advisor.** The training can be done by: (1) a certified applicator of Restricted Use Pesticides (RUPs); (2) someone who is designated as a trainer of certified applicators or pesticide handlers by EPA or the state or Tribal agency responsible for pesticide enforcement (e.g., extension or knowledgeable EPA/state/tribal employees); or (3) someone who has completed a train-the-trainer program for trainers of handlers. These conditions apply under the current WPS and will continue to apply under the revised WPS (which will become effective in January 2, 2017). [There is actually one other minor exception in the current rule that won't continue in the revised rule.] A major change under the revised WPS is that handlers must be trained annually rather than every five years. One of the main reasons EPA decided to retain certified applicators as qualified trainers of workers and handlers is so there would be enough trainers available to fulfill the annual training obligation. There are a number of videos available for handler training. After January 2, 2017, all WPS worker and handler training will need to be conducted using EPA-approved materials. EPA will maintain a list of approved materials on EPA's web site at https://www.epa.gov/pesticide-worker-safety, and the first draft of the list should be posted by August 2016.

Representativeness of Monitoring Units

At the conclusion of the field phase of study AHE80, the AHETF conducted a survey of local agricultural experts to evaluate how the growers/applicators who participated in the study compare to the local populations of growers and commercial applicators in their region of the state. Approximately one-third responded by sharing their opinion and answering the "representativeness questions." Of the 11 who answered the questions, 10 of the 11 agreed that "the study participants were typical of local growers/commercial applicators in the region/area where the study was performed." One (from the New York monitoring area) did not agree that the study participants were typical of local growers and commercial applicators in the region were the study was performed. The others who

received the opinion poll either returned it but declined to comment, did not return the form, or recommended others with more expertise who might respond. Section 3.5 (pages 39-41) in study AHE80 provides the details.

AHE80 Monitoring Units Resulting in Follow-up Actions Recommended by EPA

The next section through page 21 of this ethics review discusses the monitoring units in AHE80 which prompted EPA to recommend follow-up actions.

Actions of Subject M8 in AHE80

Page 54 of study AHE80 highlights the following regarding the actions of subject M8 during study AHE80: "Two significant events noted. The subject placed his bare hands into a bag of sulfur to feel the powder and then wiped his hands on the ground. It was also noted that the sprayer treated the mixing/loading area; however the subject moved away while this took place."

Additional Ethics-Related Information Related to Subject Placing Hands in Sulfur

Regarding the subject placing his bare hands into a bag of sulfur, the assigned AHETF observer for subject M8 indicated that, "The action probably took only about 10 seconds, so there was no chance to actually stop the action." When asked by EPA if the study director intervened, AHETF clarified that, "The incident occurred so quickly there was no opportunity for intervention." Page 54 of AHE80 states that after placing his hands into a bag of sulfur to feel the powder, subject M8 "then wiped his hands on the ground." With regard to the subject "dry-washing" his hands in the sandy soil on the ground, AHETF stated that, "It is likely the subject's normal way of wiping the sulfur off his fingers. The residue level on the subsequent hand wash sample was low." The hand wash sample was taken approximately 3 hours after this occurred. As AHETF noted, "The product label requires protective eyewear and chemical-resistant gloves while mixing/loading. The label does not anticipate this kind of incident."

EPA asked about the subject's practice of wearing PPE throughout this monitoring period. AHETF shared the following details:

> "The loading records indicate that 9 loading events occurred during the monitoring interval. Observations indicate the subject had a clipboard hanging at the M/L area on which he typically clipped his chemical-resistant gloves in between loads. The subject also got goggles from his tractor cab to wear while loading and he typically wore sunglasses between loads. The goggles were typically laid on the product bags in between loads." AHETF confirmed that the subject wore his chemical-resistant gloves during the mixing/loading periods monitored during AHE80.

Related Information from EPA Product Manager for Applicable Sulfur Products

In early June 2016, OPP coordinated with the EPA product manager for sulfur who

shared the following pertinent information, which is publicly available:

Information Shared by EPA Product Manager

"Acute Effects
Short-term studies show that sulfur is of very low acute oral toxicity and does not irritate the skin (it has been placed in Toxicity Category IV, the least toxic category, for these effects). Sulfur also is not a skin sensitizer. However, sulfur can cause some eye irritation, dermal toxicity and inhalation hazards (it has been placed in Toxicity Category III for these effects)."

As stated, "Sulfur has been assigned to Toxicity Category III for the acute dermal route of exposure. The signal word on all four products is CAUTION. The current appropriate language for products that have been assigned to Toxicity Category III for acute dermal is:

'Harmful if absorbed through skin. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse. Wear (specify any appropriate protective clothing, if appropriate).'

There are slight variations of this language on the product labels. But the language is consistent in that it states that you need to avoid contact with skin and you need to wash hands. Also, the FIRST AID statement for products assigned to Toxicity Category III for acute dermal is:

If on skin:
– Take off contaminated clothing.
– Rinse skin immediately with plenty of water for 15-20 minutes.
– Call a poison control center or doctor for treatment advice."

<u>Follow-up Action</u>:

After subject M8 placed his bare hands into the bag of sulfur and dry-washed his hands in the sandy soil on the ground, EPA believes that the designee for the study director and the licensed practicing nurse (LPN) who was assigned to observe M8 should have directed the subject to wash his hands with water consistent with the product label; the label was on site and this should have occurred immediately.

EPA has shared this information with AHETF and requested that AHETF take the following actions in July 2016 or before:

1) Contact the assigned AHETF observer for M8 and the designee for the study director assigned to monitoring events on that day and inform them, for future reference, that AHETF should have asked M8 to wash his hands with water immediately, consistent with the label on site, and ensured that this occurred. EPA

asked AHETF to share this information in July 2016 or before. The purpose of this communication is to influence future actions as appropriate in a positive manner and promote adherence to the label;

2) Contact subject M8 and notify him that: a) he should not place his bare hands into bags of sulfur or other pesticide products consistent with the label; and b) if this occurs again, consistent with the label, he should wash his hands immediately with plenty of water for the timeframe identified on the label. The product label for sulfur indicates "rinse skin immediately with plenty of water for 15-20 minutes." The purpose of this communication is to influence the subject's future behavior in a positive manner and promote adherence to the label information; and

3) While respecting the confidentiality of subject data, share this example of the actions the research team should have taken with the study director, study director designees, observers and assigned medical professionals, for the remaining AHETF studies not yet initiated and/or completed. The intent is to emphasize appropriate follow-up actions in situations like this for the remaining studies under the purview of AHETF.

AHETF has agreed to implement these follow-up actions.

Unreported Deviation

AHETF should have reported to the IRB that M8 placed his hands in the bag of sulfur and the deviation regarding M8 not washing his hands consistent with the first aid statements on the label.

Statement on Page 54 Regarding Sprayer Treating Mixing/Loading Area

As noted earlier, page 54 of study AHE80 highlights the following regarding the actions of subject M8 during study AHE80: "Two significant events noted. The subject placed his bare hands into a bag of sulfur to feel the powder and then wiped his hands on the ground. It was also noted that the sprayer treated the mixing/loading area; however the subject moved away while this took place." In response to the latter part of this statement regarding the sprayer treating the mixing/loading (M/L) area, AHETF clarified that, "The application was actually made to grape vines adjacent to, but not directly over the M/L area." AHETF added that, "The M/L area was not directly treated. It was adjacent to treated areas. The observer was following the worker and writing observations. The very next sentence (at 1045 of the observations) says 'M8 walks to lab truck area & sits in his chair.' This indicates the subject had left the mixing/loading area and was approximately 300 feet from the mixing/loading area (see site diagram above)." AHETF's site diagram and additional details are included in Attachment 11.

Actions of Subject M17 in AHE80 and Protocol Deviation

Page 12 of the study states that: "Subject M17 (5/28/14) did not wear eye protection

when loading the first tank load of sulfur. He did wear his goggles for subsequent loads. Effect: No negative impact or adverse effect to the subject was observed. A noncompliance Issue/Deviation Submission was sent to the SAIRB on 6/2/14."

AHETF explained the following to the IRB in the deviation submission on page 556 of the IRB correspondence:

> **"Describe the Noncompliance issue in detail, including how it has been resolved.**
>
> Sulfur wettable powder can cause eye irritation when being mixed and loaded into sprayers tanks. The product label requires eye protection (e.g., goggles). The subject reported prior experience with eye irritation from sulfur, was issued new goggles by the research team, and reminded by the Study Director to wear them while in transit to the mixing/loading site. During the loading of the first bag of sulfur, the subject forgot to wear his goggles. The research observer did not notice. I (Study Director, SD) was taking pictures of the equipment and loading from a distance and did not notice. After he emptied the bag of sulfur into the sprayer tank I noticed and brought it to his attention. He donned the goggles to resume mixing/loading the sprayer, and wore them through the rest of the study. There was no eye irritation.
>
> NOTE: Overexposure of the eyes results in immediate irritation that is readily and quickly reversible by flushing the eyes with an eyewash kit. There is no long-term eye injury. The research observer/medical professional had an eyewash kit on her person but it was not needed.
>
> **Please describe the corrective measures that have been put in place to prevent similar noncompliance issues from occurring at your site in the future.**
>
> This was a case of subject and researcher oversight.
> The SD will continue to remind the subject (just prior to handling product) to wear all required personal protective equipment (PPE).
> The subject will remind the observer researcher to be diligent in assuring that all required PPE is used.
> The SD will double-check the subject before he handles test substance to assure that all required PPE is used." – *End of excerpt from IRB correspondence-*

AHETF clarified to EPA that the reference to "subject" underlined above was a mistake. AHETF intended to write, "The Study Director will remind the observer researcher to be diligent in assuring that all required PPE is used."

The first-aid label statement advises that, if sulfur gets into the eyes, the following actions should occur:

- "Hold eye open and rinse slowly and gently with water for 15 to 20 minutes.
- Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.

- Call a poison control center or doctor for treatment advice."

In M17's case, AHETF field notes state that, "There was no eye irritation reported by the subject or observed by the researchers." The subject told the researcher that his eye was not irritated. If the subject had told AHETF that sulfur had entered his eye or that his eyes were irritated, then an eye wash would have been necessary. However, the field notes do not indicate that the subject had sulfur in his eyes. Instead, the subject stated that his eye was not irritated.

Follow-up Action: In light of this, EPA believes that the corrective measures that AHETF outlined to the IRB, with the one revision noted above (i.e. changing "subject" to "Study Director"), are all appropriate and should apply to the remaining AHETF studies as follows:

- The Study Director should continue to remind the participating subjects (just prior to handling the pesticide product) to wear all required personal protective equipment (PPE).
- The Study Director (SD) will remind the observer researchers to be diligent in assuring that all required PPE is used.
- The SD will double-check each subject before he handles test substances to assure that all required PPE is used.

Subject M1's Eye Irritation in AHE80

Page 48 of study AHE80 states the following with regard to subject M1:

"After the first load there was visible powder on the subject's face and clothes, and the subject complained of eye irritation. A face wash was performed and the subject rinsed his right eye with his own eyewash kit and went back to work. He indicated that eye irritation and the need to flush his eyes is common when working with sulfur. He did not have any further issues with eye irritation for the rest of the monitoring activity."

In response to the eye irritation, the subject's actions were consistent with the label instruction to rinse the eye. The length of the subject's eye wash was not documented. AHETF confirmed that the subject was wearing goggles prior to reporting the eye irritation and continued to wear goggles after the eyewash while mixing and loading as part of the study.

When reading the study, EPA considered whether or not this eye irritation should have been reported to the IRB as an "unanticipated problem." Here are relevant facts to consider on this topic:

1. The SAIRB website states that "**Unanticipated problems are events that are:** Unexpected; Related or possibly related to research; and Suggests that the research places the subject or others at increased risk for harm." The precautionary statements section of the label states that the sulfur product "causes moderate eye

irritation" so one could argue that it is a known hazard and not unanticipated which is why protective eyewear is required. However, the expectation is that goggles (or other protective eyewear) will help to protect users from this hazard. The eye irritation occurred while the subject was participating in the research.

2. Another factor for consideration is the AHE80 protocol which references AHETF SOP 11.F.2. "Adverse Events Reporting for IRBs." This SOP states, in part, that "The Study Director, and/or their designees, are required to report adverse events that meet both of the following criteria:

    a. Event is **UNANTICIPATED** (An unanticipated event is any adverse experience where the nature, severity or frequency is not identified in the investigator brochure or described in the protocol. Events which are already cited in the protocol are not unanticipated and do not have to be reported to an IRB), and
    b. Event is **POSSIBLY RELATED** to the study design or procedures. If the adverse event is clearly not related to the study test substance or procedures, it would not represent a risk to other subjects in the research and, therefore, does not have to be reported to an IRB.

    2.3 If these criteria are not met then the event does not have to be reported to an IRB." – *End of excerpt*

3. Point "a" above notes that "Events which are already cited in the protocol are not unanticipated and do not have to be reported to an IRB." Section 2.3.5 of the protocol discusses "risk of exposure in surrogate chemicals." Section 2.3.5 states that the specific risks associated with each end-use product being handled and the precautionary statements should be discussed with the subjects along with other information identified in section 2.3.5. As discussed elsewhere in this ethics review, AHETF confirmed that they discussed this information with participating subjects. From that standpoint, one can argue that the nature of the risk was not unanticipated.

4. In light of the aforementioned three points, the obligation to report the eye irritation to the IRB was not necessarily clear cut.

From EPA's perspective, even though the subject "indicated that eye irritation and the need to flush his eyes is common when working with sulfur," in the interest of full disclosure and out of an abundance of caution, AHETF should have reported the eye irritation to the SAIRB and explained the above.

After reviewing what occurred with subject M1, in hindsight, EPA should have suggested that the protocol include an additional exclusion criterion; EPA could have suggested that the study sponsor ask subjects whether or not they had experienced previous adverse reactions or irritations to the surrogate pesticides to be used in the study. If potential subjects responded positively to this question, they could have been excluded

from the study. Such an exclusion criterion was not part of the approved protocol for AHE80.

Page 43 of the study also states that MU M1 "was given the Study Director's phone number to call if he did experience any further irritation; no calls were received. A follow-up phone call was made by the Study Director two days later; however, the subject could not be reached and did not return the call." The Study Director went beyond the protocol in making this phone call to the subject. In hindsight, EPA should have suggested during the protocol review that if a subject experienced an adverse reaction or irritation, the Study Director should call and try to reach the subject to determine his/her health status as it relates to the adverse reaction/irritation. If the Study Director cannot reach the subject the first time, a second attempt should be made. **Follow-up Action**: In future studies, for new protocols, EPA should ensure that this topic is addressed as appropriate.

Exposure Results Provided to AHE80 Subjects

The consent form asks subjects if they want to receive their personal study results. For AHE80, 17 of the 20 subjects requested their personal study results. The workers identified as MUs 1-10, 12, 13, 14, 16, 17, 18 and 20 requested their personal study results. AHETF confirmed that the Study Director sent the results for these 16 subjects by U.S. Postal Service (USPS) first class mail. One subject did not provide an address and AHETF did not have a telephone number for the subject. Two sets of results were returned as undeliverable by the USPS. As a result, it appears that 14 of the 17 subjects who requested their results received them. This is not a deviation because the protocol was followed with regard to provision of personal study results.

AHETF does not intend to submit any more protocols for future studies. **Follow-up Action**: In the future, when reviewing protocols for other types of studies, EPA should suggest to study sponsors that they request the phone numbers of all subjects who complete the consent process in case the study director needs to reach any of the subjects. Related to this, future protocols which discuss personal study results should suggest that when personal results are returned as undeliverable, the study sponsor should call the affected subjects, at least twice, in an effort to reach them and share the personal study results via telephone; if successful in reaching the subject, the study sponsor can also confirm the address previously provided and resend the personal results if the initial address provided was incorrect. EPA will ask AHETF to implement this approach in their remaining studies which have not yet been initiated and/or completed; this would apply to those studies where the protocol includes a provision to provide personal study results to participating subjects. AHETF could submit a protocol amendment addressing this, as appropriate, to the IRB.

AHETF SOP 11.J.4 contains the following applicable language:

> "4.1 Each study participant will be provided an opportunity to request a copy of the exposure data resulting from their activities in the study. A summary of their personal study data (including 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) will be sent to the address provided by the participant(s) desiring it (the SD or designee will complete the form in Attachment 11-J-2). This form (and all forms that contain the worker's name and address) will be maintained in a confidential file with the study records as outlined in SOPs AHETF-6.B and -6.D."

AHETF verified that the 14 subjects who received their exposures results for AHE80 were provided a summary of their personal study data as prescribed in the excerpt from SOP 11.J.4.

Heat Index Records

Page 57 of study AHE80 reports the following information regarding the heat index:

"In addition, the heat index was monitored approximately hourly after the ambient temperature reached 70ºF during an exposure monitoring period. The heat index was calculated by the field researchers based on temperature (F) and % relative humidity measurements taken from handheld devices and cross-referenced to a heat index chart, or reported from a weather station at the staging area, or from observers' handheld heat index measuring devices. The ambient temperature reached 70 ºF or higher during 10 of the 19 MUs; the highest air temperature recorded during monitoring was 84.2ºF which was reached during the monitoring of M6 in Florida. The maximum heat index threshold (105ºF) was reached by this subject (M6) and monitoring was stopped and samples collected. A summary of the environmental conditions during each monitoring unit are contained in Table 7" on pages 76-79 of the study.

Section 2.3.1 of the protocol for study AHE80 states that researchers will follow SOP AHETF-11.G on identifying and controlling heat stress. The SOP states that, once the ambient temperature reaches 70 degrees Fahrenheit, the Heat Index (HI) will be monitored at least every hour. The protocol also states that AHETF will monitor ambient conditions to determine the heat index and base monitoring decisions on the current Heat Index (HI). The protocol also states that exposure monitoring will be discontinued if the heat index cutoff of 105 degrees Fahrenheit (adjusted for direct sun if applicable) is reached or exceeded.

AHETF stated that:
"SOP 11.G.5 was followed, except as follows:

- *"7.3 The Study Director will inform all study observers at the start of the study of the current Heat Index (Apparent Temperature) Category. The observer will be informed if or when the Heat Index Category subsequently changes."*
    - In practice, the observer started weather monitoring at the first opportunity after observing the first mixing/loading or when it felt warm enough to merit it. This practice had no impact on the subject's risk, as starting time temperatures were usually below

HI calculation thresholds and always below any HI of concern. Likewise, the observer notified the Study Director or Designee of the HI per SOP."

This constitutes a protocol deviation. **Follow-up Action**: EPA will ask AHETF to pay close attention to and follow this aspect of SOP 11.G, as well as to continue to adhere to the rest of the SOP, in their studies which have not yet been initiated or completed.

AHETF complied with the protocol when interacting with MU M6 as described previously. When EPA requested additional details regarding monitoring unit M6, AHETF explained that: "The Heat Index reached and slightly exceeded 105F (adjusted for direct sun) during MU M6. The sun-adjusted heat indices calculated using the National Weather Service Heat Index Chart at 0931 and 1030 were 102.6F and 107.0F, respectively. The Study Director immediately terminated the monitoring upon getting the 107F reading and before the subject could load the spray rig that was just coming in to be filled. During the period 0931 – 1030, the subject worked only 7 minutes on one tank load, completed his last mixing/loading at 1001, and was at rest the remaining time. At termination of the monitoring, the health status of the subject was noted by the Study Director as 'fine.'"

EPA requested a copy of the AHE80 heat index records and raw data from the study sponsor and provided those records to the HSRB in a separate file.

The introductions to the heat index records explain that "Heat Index (HI) cannot be estimated from the National Weather Service HI chart until the threshold temperature is =>80F and relative humidity is =>40%. Monitoring of temperature and humidity started when the temperatures reached =>70F, which helped to ensure that monitoring was underway if the threshold levels for calculating HI were reached." AHETF added that, "When the temperature and humidity levels were below the threshold, the HI entry was usually recorded as 'NA' or 'Below Scale' or 'Not Required' since HI could not be calculated and was not a concern. Some of the weather instruments used later in the study internally calculated HI regardless of temperature or relative humidity levels."

The pages extracted from the field notebooks which were forwarded to the HSRB show the temperature and relative humidity entries recorded in the field. As AHETF explained, "The heat index was either calculated and recorded, or not recorded, based on the National Weather Service chart or the weather instrument algorithms." Protocol amendment 6 allowed the study sponsor the option to use the Wet-bulb Globe Temperature (WBGT) heat index monitoring system, but that option was not exercised during study AHE80.

Protocol Amendments with Ethical Considerations

The protocol for study AHE80 was amended 6 times after it was signed, as summarized in attachment 12. AHETF confirmed that all of the protocol amendments were submitted to, reviewed, and approved by an Institutional Review Board (IRB) prior to implementation. This ethics review discusses specific components of amendments 2, 3 and

4, given their potential impact on ethical considerations. Amendment 6 gave the study sponsor the option to use the Wet-bulb Globe Temperature (WBGT) heat index monitoring system; this option was not exercised and, as a result, did not impact the subjects.

Amendments 2 and 3

The IRB approved amendments 2 and 3, components of which revised the inclusion criteria as underlined below. These amendments are discussed on pages 168 and 224 of the AHE80 IRB correspondence.

> **2.1 Inclusion Criteria**
> [Unchanged] AHETF inclusion criteria applicable to all AHETF studies are presented in SOP AHETF-11.B. For this mixing/loading of wettable powders study, the following inclusion criterion also applies:
>
> - [Add] Have experience within the past year with mixing/loading by open pouring any formulation into the equipment, or similar equipment, to be used.
> - [Change] Have experience ~~within the past year~~ with mixing/loading wettable powders by open pouring. By discussion with the volunteer, the Study Director will determine if the previous experience is sufficient ~~(including the particular equipment to be used).~~
>
> **Reason for Change/Addition:**
>
> The study sponsor justified the changes to the IRB as follows:
>
> "SOP 11.B.5.0 (December 28, 2010) specifies experience with the work activity (in this case, open mixing/loading) and the particular equipment within the last year and allows for other specifications. Wettable powders are sufficiently unique (dusting) to require previous experience, but not necessarily within the last year. For example, under the original protocol a volunteer who had handled WPs only once, but in the last year, would qualify. However, a volunteer who had handled WPs for many years, but not in the past year, would not qualify."

As the study sponsor explained it, the original reference to the equipment to be used "was a carryover from applicator studies in which experience with the heavy equipment (tractor and sprayer) was considered important. Mixing/loading is usually a simple operation consisting of placing the product into a hatch in a tank or into an open tank. Experience with the particular equipment is not necessary." For that reason, the study sponsor added to the criterion, experience within the past year with mixing/loading by open pouring any formulation into the equipment, or similar equipment, to be used.

The rationale for both changes, as explained above, is reasonable. Part of the criteria references the Study Director's conversation with the subjects to determine if their previous experience was sufficient; the intent is to provide further assurance that the subjects had the necessary background related to these criteria. AHETF confirmed that the study director

had these conversations with the subjects. The revisions did not negatively impact the health and safety of the participating subjects, whose requirement to wear the required personal protective equipment was not impacted by these amendments. The IRB approved the amendments prior to implementation.

Second Component of Amendment 2

Under amendment 2, the second change focused on the following, as discussed on pages 168-169 of the AHE80 IRB correspondence:

> **"II. Change/Addition: 2**
> **6.3 Achievement of Design Targets**
> [Add as first text] As described in Section 5.0, an 'efficient configuration' of growers selected from the Potentially Eligible List in each monitoring area permits five MUs to be conducted in a time-effective and cost-effective manner. However, the configuration possible must ultimately depend on the availability of handling activities in the monitoring areas, on the eligible growers, and on the workers willing to volunteer for the study. As a result, the Study Director may have determined that an efficient configuration as defined previously is not feasible for a monitoring area. In this case, eligible growers can be identified on an individual basis from the Potentially Eligible Lists being generated without first constructing a working pool. Workers can then be recruited and MUs scheduled on an individual grower basis as needed. This will not necessarily result in a cost-effective configuration of MUs. In extreme cases, the resulting configuration might even consist of MUs spread out over the entire monitoring area and conducted over several growing seasons." - *End of Excerpt* –

Based on the information available, identifying eligible growers on an individual basis to ensure a sufficient number of monitoring units, as described above, did not negatively impact the rights and/or the health and safety of participating subjects.

Amendment 4

Amendment 4 is discussed on pages 260-273 of study AHE80 and page 278 of the IRB correspondence for study AHE80. In part, amendment 4 replaced the original section 4 of the protocol. The study sponsor needed to adopt additional processes for recruitment to help ensure that they obtained a sufficient number of monitoring units. AHETF explained in the IRB correspondence that they wanted to: (1) add a new process for getting names of qualified employers from local agricultural specialists, referred to as primary sources; (2) list growers and commercial application companies (instead of just growers), to provide secondary sources of qualified names, if needed; and (3) combine certain lists of employers for this study and a similar study, AHE120, involved with mixing/loading of products in water soluble packets (WSPs).

Based on available information, adding a process related to primary and secondary sources, and combining lists of employers for AHE80 and AHE120 did not negatively

impact the rights, health and/or safety of the subjects.

Regarding section 6.2 of the protocol, amendment 4 also deleted the following text as described on pages 260-271 of study AHE80 and pages 286-287 of the IRB correspondence:

> **"VI. Deletion/Addition in Section 6.2**
> Delete the following text:
>
> For each monitoring area, the Study Director or researcher shall continue conducting grower visits as described above until an adequate number of eligible growers and potential subjects have been identified for an efficient configuration of all MUs for that monitoring area. During this process, the following restrictions will be maintained, whenever feasible, for each monitoring area:
> - At least 10 workers who may potentially volunteer for the study
> - At least 2 workers available for each of the AaiH strata that the Study Director determines is feasible for that area (see Section 7.8 for more details)
> - No more than one MU from any one grower or grower/commercial pesticide application company combination (this effectively requires 5 different employers since 5 MUs are desired)
> - No worker may be used more than once
> - No piece of equipment may be used more than once (e.g., a particular sprayer or mixing equipment used by two different workers from different growers)
>
> As indicated above, the efficient configuration and Eligible Grower List must include enough growers and potential subjects to fill all MUs for each monitoring area, even in cases where growers or subjects are not available at the last minute for the time interval scheduled for the field phase of the study in that area." – *End of excerpt* -

This was replaced with the following revised text:

> "During this process, the following similarity restrictions will be maintained for each monitoring area and study:
> - No more than one MU from any one employer for a study
> - No worker may be used more than once in a study
> - No piece of equipment may be used more than once in a study."

As the study sponsor explained in the IRB correspondence, "Cost effectiveness is now a less important consideration than identification of acceptable MUs in a timely fashion."

The restrictions which were maintained, as listed above, help to protect the rights, health and safety of participating subjects. Furthermore, the phrase "whenever feasible"

was included in, and approved for, the original language; this phrase was removed in the revised language which strengthens the obligation on the part of the study sponsor.

Effective Dates on Protocol Amendments for AHE80

AHETF confirmed in writing that the 6 protocol amendments were not implemented prior to IRB approval. OPP noticed that amendments 1, 2, 3, and 5, which were unsigned and submitted for IRB review and approval already had desired "effective dates" listed on them, although they had not been implemented. For amendments 4 and 6, the effective date was identified as the "IRB approval date." OPP wants to ensure that the study sponsor understands that the effective date or implementation date for a protocol amendment can never be prior to the IRB approval date, with one exception discussed later in this section. For example, if the IRB approves an amendment on October 13, 2011, that amendment cannot be implemented until after the IRB approves it. This is the case even if the study sponsor includes a desired "effective date" on the amendment form which was submitted to the IRB. For example, if the desired effective date on the amendment form was October 6, 2011 and the IRB approved it on October 13, 2011, the earliest implementation date must follow the IRB's approval. If the effective date on the amendment form remains October 6, 2011, then that effective date on the form is inaccurate. The effective date or implementation date must follow the IRB approval. The only exception is when changes to the protocol are implemented in order to eliminate an apparent immediate hazard to a research subject without prior IRB approval; in that case, the study sponsor must report changes to the IRB consistent with the IRB reporting timeframes for such immediate hazards.

Follow-up action: When applying for IRB approval of a protocol amendment, if the study sponsor must include an effective date on the protocol amendment form, EPA recommends and requests that the study sponsor insert "IRB approval date" as the effective date. Unless there is an immediate hazard to a research subject, protocol amendments cannot be implemented prior to approval by the IRB.

Applicable Ethical Standards

The following provisions of 40 CFR 26 Subpart Q define the applicable ethical standards which read in pertinent part:

> **§26.1703**: Except as provided in §26.1706, EPA shall not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> **§26.1705**: Except as provided in §26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with all applicable provisions of subparts A through L of this part.

In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) applies. This passage reads:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

Findings

Responsiveness to EPA and HSRB reviews

EPA's and the HSRB's comments on the protocol for AHE80 were addressed as described in attachment 4.

Prohibition of research involving intentional exposure of pregnant or nursing women or of children

40 CFR §26.1703 prohibits research involving intentional exposure of pregnant or nursing women or of children under 18. All subjects who participated in study AHE80 were male and at least 18 years old. Therefore, 40 CFR §26.1703 does not prohibit reliance on this research.

Substantial compliance with 40 CFR 26 subparts A through L

40 CFR §26.1705 requires that EPA have "adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." Within this range, only subparts K and L are directly applicable to the conduct of third-party research such as this. The AHE80 study was conducted in substantial compliance with subparts K and L.

Compliance with 40 CFR §26 subpart M

As documented in attachment 5 to this review, the central requirements of 40 CFR §26 subpart M, §26.1303 to document the ethical conduct of the research were addressed.

Compliance with FIFRA §12(a)(2)(P)

The requirement of FIFRA §12(a)(2)(P) that human subjects of research be "fully informed of the nature and purposes of the test and of any physical and mental health consequences reasonably foreseeable therefrom," and "freely volunteer to participate in the test," was met for this study.

Summary of Follow-up Actions for AHETF

In this ethics review, EPA recommends that AHETF implement the follow-up actions listed below. AHETF has already agreed to these follow-up actions.

1. AHETF should begin using the following updated inclusion criterion in both the protocol and consent form, beginning in August, 2016, after the HSRB meeting, for monitoring units that have not yet been initiated in other AHETF studies to which this same criterion applies:
   "Be trained in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS), or be a certified applicator of restricted use pesticides or a certified crop advisor." This would necessitate the IRB approving an amendment to the consent form and protocol for the remaining studies as applicable.
2. AHETF should contact the assigned AHETF observer for MU M8 and the designee for the study director assigned to monitoring events on the day in question and inform them that AHETF should have asked M8 to wash his hands with water immediately, consistent with the label on site, and ensured that this occurred. EPA asked AHETF to share this information in July 2016 or before. The purpose of this communication is to influence future actions as appropriate in a positive manner and promote adherence to the label.
3. In July 2016 or before, AHETF should contact subject M8 and notify him that: a) he should not place his bare hands into bags of sulfur or other pesticide products consistent with the label; and b) if this occurs again, consistent with the label, he should wash his hands immediately with plenty of water for the timeframe identified on the label. The product label for sulfur indicates "rinse skin immediately with plenty of water for 15-20 minutes." The purpose of this communication is to influence the subject's future behavior in a positive manner and promote adherence to the label information.
4. While respecting the confidentiality of subject data, AHETF should share this example of the actions the research team should have taken with the study director, study director designees, observers and assigned medical professionals, for the remaining AHETF studies not yet initiated and/or completed. The intent is to emphasize appropriate follow-up actions in situations like this for the remaining studies under the purview of AHETF. This should occur in July 2016 or before.
5. As AHETF highlighted to the IRB on their own, AHETF's study directors should continue to: a) remind the participating subjects (just prior to handling the pesticide product) to wear all required personal protective equipment (PPE); b) remind the observer researchers to be diligent in assuring that all required PPE is used; and c) double check each subject before he/she handles test substances to assure that all required PPE is used.
6. For remaining studies which have not yet been initiated and/or completed, AHETF should request the phone numbers of all subjects who complete the consent process in case the study director needs to reach any of the subjects. This would apply to those studies where the protocol includes a provision to provide personal study results to participating subjects. AHETF could submit a protocol amendment addressing this, as appropriate, to the IRB.
7. For the remaining studies which have not yet been initiated and/or completed, AHETF should pay close attention to and follow the section of SOP 11.G. which states that the Study Director will inform all study observers at the start of the study of the current Heat Index (Apparent Temperature) Category. The observer will be

informed if or when the Heat Index Category subsequently changes. Similarly, AHETF will continue to adhere to the rest of SOP 11.G.

8. When applying for IRB approval of a protocol amendment, if the study sponsor must include an effective date on the protocol amendment form, EPA recommends and requests that the study sponsor insert "IRB approval date" as the effective date. Unless there is an immediate hazard to a research subject, protocol amendments cannot be implemented prior to approval by the IRB.

Summary of Follow-up Actions for EPA

In this ethics review, EPA has also identified follow-up actions, listed below, which the Agency should implement.

1. For future protocols which require that interested subjects receive their personal study results, EPA should request the following provision. When personal study results are mailed to subjects and returned as undeliverable, the study sponsor should call the affected subjects, at least twice, in an effort to reach them and share the personal study results via telephone. If the study sponsor reaches the subject, they should also confirm the address previously provided and resend the personal results if the initial address provided was incorrect.
2. EPA should ensure that future protocols include the following provision. If a subject experiences an adverse reaction or irritation, the Study Director should call and try to reach the subject to determine his/her health status as it relates to the adverse reaction/irritation. If the Study Director cannot reach the subject the first time, a second attempt should be made.
3. EPA should ensure that future protocols include a provision for study sponsors to request the phone numbers of all subjects who complete the consent process in case the study director needs to reach any of the subjects regarding the study and/or follow-up actions related to the study.

Conclusion

This study reports research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L. In its conduct, study AHE80 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. AHETF agreed to implement the follow-up actions identified by EPA in this memorandum. From EPA's perspective, if this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA's reliance on it in actions under FIFRA or §408 of FFDCA. This research will also undergo review by the Human Studies Review Board at the July 12-13, 2016 HSRB meeting.

cc: Rick Keigwin
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Attachment 1: AHETF's Chronology of Major Study Events
Attachment 2: Test substance used in study AHE80
Attachment 3: Summary of worker information from each monitoring unit
Attachment 4: AHETF actions in response to EPA and HSRB comments on protocol
Attachment 5: §26.1303 Completeness check for AHE80 Study
Attachment 6: Steps taken to compile qualified employer list
Attachment 7: Updated summary of employer lists and recruitment details
Attachment 8: AHETF checklist from field data collection form
Attachment 9: Assigned observers for each monitoring unit
Attachment 10: Approved inclusion criteria
Attachment 11: Spraying adjacent to mixing/loading area
Attachment 12: Summary of protocol amendments

Attachment 1 – AHETF's Chronology of Major Study Events

Note: This attachment is based on AHETF's table 1 from page 61 of study AHE80, with the HSRB review inserted below in bold type. EPA underlined the IRB approvals.

Date	Major Study Events
9/30/10	Initial submission of AHE80 protocol and related materials to the Independent Investigational Review Board, Inc. (IIRB) for review
10/5/10	Approval by IIRB of final AHE80 protocol and related materials, reflecting comments from EPA and HSRB, plus Spanish translations
1/26/11	**Human Studies Review Board (HSRB) discusses AHE80 protocol and EPA reviews**
3/17/11	**HSRB Final report of January 26, 2011 HSRB meeting**
4/25/11	Protocol signed by Study Director
4/26/11	Start of phase 1 recruiting, calling employers to determine Qualified Employers from initial list of commercial application and utility companies
5/20/11	Start of phase 2 recruiting, calls to Qualified Employers
6/21/11	Approval of Amendment 1 by IIRB
7/5/11	Approval of Amendment 2 by IIRB
7/8/11	Start of phase 3 recruiting, calls to Potentially Eligible Employers, site visits, and participant selection
10/11/11	Approval of Amendment 3 by IIRB
10/19/11	Collection of M1 with field fortifications
3/20/12	Approval of Amendment 4 by IIRB
5/14/12	Collection of M2 with field fortifications
5/15/12	Collection of M3 with field fortifications
5/16/12	Collection of M4 with field fortifications
5/18/12	Collection of M5 with field fortifications
10/9/12	Approval of Amendment 5 by IIRB
10/10/12	Collection of M6 with field fortifications
10/24/12	Notice of change in IRB name from Independent IRB (IIRB) to Schulman Associates IRB (SAIRB)
11/1/12	Collection of M7 with field fortifications
3/27/13	Collection of M8
3/28/13	Collection of M9
3/29/13	Collection of M10 with field fortifications
4/12/13	Collection of M11 with field fortifications
4/26/13	Collection of M12 with field fortifications
5/24/13	Collection of M13 with field fortifications
6/3/13	Collection of M14 with field fortifications
6/14/13	Collection of M15 (terminated) with field fortifications
6/15/13	Collection of M16
3/1/14	Approval of Amendment 6 by SAIRB
5/28/14	Collection of M17 with field fortifications
6/2/14	Noncompliance Issue/Deviation Submission was electronically sent to SAIRB regarding M17 not wearing his eye protection (goggles) as required by the label for the first mix/load cycle. Acknowledgment by SAIRB on 6/2/14.
11/6/14	Collection of M18 with field fortifications
11/26/14	Collection of M19 with field fortifications
12/18/14	Collection of M20 with field fortifications

Attachment 2 – Test Substance used in Study AHE80

Note: The following information is an excerpt from pages 41-42 of study AHE80.

"Two forms of powder sulfur are marketed, wettable powder and micronized powder, and both forms were used in this study. Micronized sulfur claims to be milled to smaller particle sizes than wettable powder, although there is no official distinction between the two. Two of the four wettable powder products (Yellow Jacket Wettable Sulfur II and Microfine Sulfur) used in the study are actually the same product manufactured by Georgia Gulf Sulfur Corporation, but are marketed and sold by two different companies.

All sulfur used in the study was packaged in either paper or plastic 30 pound bags." The brands of sulfur, along with corresponding EPA registration numbers, that were used in this study are shown below.

Product Name	**EPA Registration Number**	**Form of Sulfur Number**
Yellow Jacket Wettable Sulfur II	6325-13	Wettable Powder
Microfine Sulfur	6325-13-34704	Wettable Powder
Microthiol Disperss	70506-187	Micronized Powder
Micro Sulf	55146-75	Micronized Powder

Attachment 3 – Summary of Worker Information from each Monitoring Unit

The tables in this attachment provide information on participating subjects including, but not limited to, age, gender and years of experience, based on each of the four monitoring areas. These tables are from pages 64-67 of study AHE80.

Table 3. Worker Information for New York

Mixer/ Loader MU	Monitoring area 81 = New York				
	M2	M3	M4	M5	M17
Worker ID	WID-81-1	WID-81-3	WID-81-4	WID-81-5	WID-81-6
Task	M/L	M/L	M/L	M/L	M/L
Age	54	55	31	53	71*
Height (in.)	80	68	69	73	64
Weight (lb.)	242	158	167	234	196
Gender	Male	Male	Male	Male	Male
Employment	Farm Owner/ Operator	Farm Employee	Farm Employee	Farm Owner/ Operator	Farm Employee
Years of Experience	39	15	15	40	20
Date Monitored	05/14/12	05/15/12	05/16/12	05/18/12	5/28/14
Country	USA	USA	USA	USA	USA
State	New York	New York	New York	New York	New York
County	Wayne	Wayne	Ontario	Wayne	Niagara
Nearest Town	William-son	Wolcott	Sodus	William-son	Burt

* Eligibility Form based on ID reports 73, Day of Monitoring self-report of 71 years.

EPA Note: AHETF confirmed that "years of experience" refers to experience mixing/loading wettable powders.

Table 3. Worker Information for Florida

Mixer/Loader MU	Monitoring area 82 = Florida				
	M1	M6	M7	M18	M20
Worker ID	WID-82-1	WID-82-3	WID-82-2	WID-82-5	WID-82-6
Task	M/L	M/L	M/L	M/L	M/L
Age	53	55	41	31	42
Height (in.)	73	71	67	72	71
Weight (lb.)	262	258	315	190	279
Gender	Male	Male	Male	Male	Male
Employment	Commercial Applicator Employee	Farm Employee	Farm Employee	Commercial Applicator	Commercial Applicator Employee
Years of Experience	8	2	Not Recorded	17	20
Date Monitored	10/19/11	10/10/12	11/01/12	11/06/14	12/18/14
Country	USA	USA	USA	USA	USA
State	Florida	Florida	Florida	Florida	Florida
County	Hardee	St. Lucie	Polk	Highlands	Hardee
Nearest Town	Zolfo Springs	Fort Pierce	Haines City	Lake Placid	Wauchula

Table 3. Worker Information for Michigan

Mixer/Loader MU	Monitoring area 83 = Michigan				
	M12	M13	M14	M15*	M16
Worker ID	WID-83-1	WID-83-3	WID-83-6	WID-83-5	WID-83-4
Task	M/L	M/L	M/L	M/L	M/L
Age	37	54	62	55	30
Height (in.)	70	70	71	64	71
Weight (lb.)	189	165	198	135	260
Gender	Male	Male	Male	Male	Male
Employment	Farm Owner	Farm Employee	Farm Owner	Farm Owner/Operator	Farm Owner
Years of Experience	9	33	35	32	10
Date Monitored	04/26/2013	05/24/13	06/03/13	NA*	06/15/13
Country	USA	USA	USA	USA	USA
State	MI	MI	MI	MI	MI
County	Berrien	Leelanau	Antrim	Benzie	Antrim
Nearest Town	St. Joseph	Suttons Bay	Central Lake	Frankfort	Elk Rapids

* Monitoring was terminated due to equipment malfunction; no samples were analyzed.

Table 3. Worker Information for California

Mixer/Loader MU	Monitoring area 84 = California				
	M8	M9	M10	M11	M19
Worker ID	WID-84-1	WID-84-2	WID-84-3	WID-84-4	WID-84-5
Task	M/L	M/L	M/L	M/L	M/L
Age	50	69	53	68	18
Height (in.)	71	68	71	74	74
Weight (lb.)	225	184	241	250	165
Gender	Male	Male	Male	Male	Male
Employment	Farm Owner	Farm Owner	Farm Operator	Farm Owner	Farm Employee
Years of Experience	35	44	35	30	1
Date Monitored	3/27/13	3/28/13	3/29/2013	4/12/13	11/26/14
Country	USA	USA	USA	USA	USA
State	CA	CA	CA	CA	CA
County	Fresno	Fresno	Fresno	Fresno	Fresno
Nearest Town	Selma	Del Rey	Selma	Kingsburg	Fresno

Attachment 4
EPA and HSRB Ethics Comments on AHE80 Protocol & AHETF Actions

Comments on AHE80 Protocol	AHETF Actions to Address Comments
EPA comment: 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 SOP has been revised and was sent to EPA and IIRB at the time it was revised. SOP 11.B.5 currently states, in part, that study participants must: "Confirm they do normally wear personal protective equipment that is required by the label. If the worker indicates that they may wear additional PPE not required by the product label, and that additional PPE might impact the objectives of the study, such as chemical-resistant clothing, then the Study Director should be notified to determine if the worker shall be included in the study. Confirm they intend to follow label directions. The research staff shall not influence nor ask in a manner to influence the worker to wear less PPE than they normally wear."
EPA comment: 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."	AHETF explained their perspective that "researchers are not medical professionals and are not in a position to write SOPs that incorporate medical information or decisions. The AHETF prefers leaving this to the medical professionals, particularly since the actions of medical professionals may vary among locations (e.g., in a hot, humid environment versus a hot, dry environment)." The latest consent form dated May 2012 states that: "You may refuse medical treatment unless the medical professional decides you are too sick to make a decision about getting medical treatment."
EPA comment: 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 HSRB did not finalize the report from the HSRB's working group. AHETF updated their original plan for notifying participants of their results.

EPA comment: 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."	AHETF feels that due to the potential risk of heat stress, the consumption of water by the participant should not be restricted by sample collection procedures. AHE80 protocol, section 2.8 states that subjects will have their hands washed (with the assistance of a researcher) before monitoring begins and before they eat or smoke, any time they would normally wash their hands (such as before using the toilet), and at the end of the day. As part of the worker's personal hygiene, they may wash their hands after using the toilet; this is not anticipated to impact the results of the study since the workers' hands will be washed prior to using the toilet.
EPA comment: 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.	The appropriate SOPs were revised where necessary to clarify that the letters with results sent to the participants are translated into Spanish by the same person who translated the other documents and that letters will be sent to non-readers the same as all other participants, assuming they have someone available to read the letters to them. The AHETF consulted with bilingual pesticide trainers throughout the U.S. about the readability of the Spanish documents to ensure there would be no difficulties due to dialects.
HSRB comment: The Board concurred with the Agency's recommendation	

(Evans et al. 2010, 5) that the protocol standard operating procedure (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 personal protective equipment (PPE) than they normally would out of a desire to participate in the research.	The SOP was revised to clearly state that no leading questions will be asked. The final SOP was sent to EPA and IIRB at the time it was revised. The AHE80 consent form dated May 2012 states, in part, in the eligibility section that, to be eligible, you must "usually wear the personal protective equipment (PPE) listed on the label of the pesticide products you will mix and load, and confirm that you would not normally wear personal protective items not required by the label, such as chemical-resistant clothing or an apron, on the day of the study."
The Board concurred with the Agency's recommendation that the language in the consent form about refusing medical treatment should be revised. However, the Board did not concur with the suggested revisions. The Agency recommends that the language 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 Board recommended that the language be revised as follows: "You may refuse medical treatment unless the medical professional decides (based on established criteria) that you are too sick to make a decision about getting medical treatment." In addition, it recommended that in an appropriate SOP, the criteria for decision-making capacity are provided as guidance for medical professionals who perform this function in AHETF research. The criteria for decision-making capacity can be found in the clinical and clinical ethics literature (e.g., Appelbaum 2007) and generally include all the following: The patient a) can appreciate the situation and its consequences; b) can under-	AHETF explained their perspective that "researchers are not medical professionals and are not in a position to write SOPs that incorporate medical information or decisions. The AHETF prefers leaving this to the medical professionals, particularly since the actions of medical professionals may vary among locations (e.g., in a hot, humid environment versus a hot, dry environment)." The latest consent form dated May 2012 states that: "You may refuse medical treatment unless the medical professional decides you are too sick to make a decision about getting medical treatment."

stand the relevant information; c) can reason about the treatment decision; and d) can communicate a choice.	
The Board partly concurred with the Agency recommendation that 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 Board concurred that the AHETF and the Agency need to develop procedures to protect the needs of study participants who do not speak English or who have low levels of literacy. However the Board recommended that these procedures need to be rooted in the vocabulary and best practices of appropriate fields such as cultural competence and literacy. For example, the term illiterate is no longer used by literacy experts. The Agency should consider seeking guidance on these issues from the report of the US Department of Health and Human Services, National Action Plan to Improve Health Literacy (2010) and reports from the Institute of Medicine, Health Literacy: A Prescription to End Confusion (2004); Toward Health Equity and Patient-Centeredness: Integrating Health Literacy, Disparities Reduction, and Quality Improvement, Workshop Summary (2009). The Board concurred that AHETF should incorporate any future guidance from the HSRB‟s work group on return of results to participants after it submits its reports.	The appropriate SOPs were revised where necessary to clarify that the letters with results sent to the participants are translated into Spanish by the same person who translated the other documents and that letters will be sent to non-readers the same as all other participants, assuming they have someone available to read the letters to them. The HSRB's working group report was not finalized. It was not formally submitted to EPA, who received a draft copy. The AHETF consulted with bilingual pesticide trainers throughout the U.S. about the readability of the Spanish documents to ensure there would be no difficulties due to dialects.

The Board concurs with the Agency that AHETF should clarify the discrepancy about whether hand wash samples are to be collected prior to water breaks (Evans et al. 2010, 2).	AHETF feels that due to the potential risk of heat stress, the consumption of water by the participant should not be restricted by sample collection procedures. AHE80 protocol, section 2.8 states that subjects will have their hands washed (with the assistance of a researcher) before monitoring begins and before they eat or smoke, any time they would normally wash their hands (such as before using the toilet), and at the end of the day. As part of the worker's personal hygiene, they may wash their hands after using the toilet; this is not anticipated to impact the results of the study since the workers' hands will be washed prior to using the toilet.
The Board concurs with the Agency review that future AHETF protocols or SOPs should incorporate information about how subjects are presented with individual exposure information, including how this process will be handled for research participants who do not speak English or have low levels of literacy; and an explanation of the process that the AHETF follows to improve and verify the accuracy of the Spanish translations (Evans et al. 2010, 2). The Board recommends that these future protocols be grounded in best practices in literacy and cultural competence and that the Spanish translations be in the appropriate dialect of the research participants.	The appropriate SOPs were revised where necessary to clarify that the letters with results sent to the participants are translated into Spanish by the same person who translated the other documents and that letters will be sent to non-readers the same as all other participants, assuming they have someone available to read the letters to them. The AHETF consulted with bilingual pesticide trainers throughout the U.S. about the readability of the Spanish documents to ensure there would be no difficulties due to dialects.
HSRB comment: The requirement for additional pregnancy tests should be clarified throughout the documents. The Agency review indicates without explanation that the consent form states that "more than 1 pregnancy test may be required" (Evans et al. 2010, 5). However, on page 268 of the protocol it states that female volunteers "will be notified that an additional pregnancy test may be required if there any delays in	The following sections of the informed consent form have been changed to read as follows: Eligibility *7.* …. If you are female, you must take an over-the-counter urine pregnancy test less than 24 hours before you take part in the study. Researchers will provide the materials for the pregnancy test at no cost to you. This test will be supervised by a female researcher and a private toilet area will be provided. … Procedures before the start of the study *8.* If you are female, within 24 hours prior to

the planned start of the study" (Collier 2011, 268). This explanation for why additional pregnancy tests may be required should be made explicit in the informed consent document.	starting the study you will perform an over- the-counter pregnancy test. If there is a delay in the start of the study of more than 24 hours, another pregnancy test may be needed. The negative results of your pregnancy test will be verified by a female member of the study.
HSRB comment: The Agency review states that the return of individual exposure results may benefit research subjects (Evans et al. 2010, 15). The Board recommended that this language be deleted until the Board Working Group finishes its report and the Board reviews it.	Section 17. 1 of the final AHE80 protocol (dated March 29, 2011) states, in part, that "subjects will have an opportunity to request their personal study results when they are available. Individual results requested by subjects will be communicated in accordance with SOP AHETF 11.J." The HSRB working group did not finalize the workgroup report.
HSRB comment: The Board recommended that AHETF clarify how witnesses will be selected for workers who self-identify as non-readers. According to the protocol they "may choose a witness, or a third-party witness will be identified by the Study Director or designee and provided to the worker during the private consent meeting" (Collier 2010a, 292). It needs to be clarified that these witnesses are not associated with the research project.	The SOP and supporting documents were modified to address this comment. Only the worker will select a witness. Study personnel will ensure the witness meets the criteria. If the worker has not identified a witness or if the Study Director determines the witness does not meet the criteria, then that worker will be excluded from further consideration and will not proceed with the recruitment and consent process.
HSRB comment: The Board recommended that the risk of surrogate chemicals be included as one of the risks associated with participation in this study and be listed in the consent forms and in the protocol. When exposure to surrogate pesticides is re-included as a risk of the study, several documents will need revisions, including SOP AHETF-11.J.2. with IC checklist; DSM Form 386; and the Governing Document. The Board concluded that the discussion of the effects of	The appropriate documents were revised as suggested. AHETF stated that: *"Specific symptoms and short-term health effects of accidental exposure may not be provided on a product label or on an MSDS. Labels and MSDSs may have „Precautionary Health" statements listing potential health issues such as eye and skin irritation but may not list symptoms of short-term overexposure."* The consent form includes the following language in the section on risks and discomforts: **" RISKS AND DISCOMFORTS**

surrogate chemicals is conspicuously absent from the consent form and recommended that they either be listed explicitly or, at a minimum, that the consent document be revised to include a statement like: The label for the [surrogate compound] will be reviewed with you before you take part in the study. This review will include how much of that product you might handle during the study, *the symptoms and short-term health effects of accidental exposure to the product*, what clothing and personal protective equipment you must wear, the importance of washing your hands before eating, and other safety precautions that should be followed" (c.f. Collier 2010a, 146-7).	Because you will wear long underwear underneath your normal work clothes, you have a risk of getting sick from being too hot. This is known as heat stress or heat illness and can be serious or life threatening. Early signs and symptoms include feeling overheated, tired, dizzy, irritable, and having decreased concentration. If you feel any of these signs or symptoms during or after the workday notify a researcher right away. If you don't feel well for any reason, notify a researcher right away. A researcher will be watching you for these signs. AHETF will stop your work if the weather gets too hot. As a safety measure, AHETF will have a medical professional on site during the study. This may be a paramedic, physician's assistant, nurse, certified first responder, or emergency medical technician. This professional will also watch you for signs of illness. They will provide medical attention as needed. You may have other risks or discomforts, including: ▪ Eye or skin irritation from the detergent and water mixture used to wash your hands, face and neck ▪ Getting sick from exposure to the pesticide product ▪ Discomfort from wearing a portable air sampling pump around your waist ▪ Being embarrassed during dressing and undressing ▪ Being concerned about taking an over-the-counter pregnancy test ▪ Working longer than normal because of the extra time it takes to collect samples for analysis. You will be mixing and loading a pesticide as part of this research. Handling this pesticide will have risks, including the possible risk of sickness, eye or skin irritation, and allergic skin reactions. These kinds of risks are present when you handle many pesticide types, but might be slightly different if researchers ask you to mix a different amount of pesticide or work slightly longer than usual. On the day of the study, a researcher will show you the label for the product that you will be using and discuss the risks of that product with you. There may be other risks that are not known at this time. You will be told in a timely manner both verbally and in writing of any new information. This new information might cause you to change your mind about being in the study." – End of excerpt -
HSRB comment: The Board recommended that the discussion of "greater than minimal risk" in the protocol be clarified. On page 44, the EPA review states: In this study risks to subjects are classified as "greater than minimal", primarily since agricultural work is considered a	The AHETF position on the study being greater than minimal risk is provided in the AHE80 protocol, which states on page 8 (of 41) that, "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."

high risk occupation where the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life (Evans et al. 2010, 44). However, on page 106, the AHETF protocol states, In this study, risks to subjects are classified as "greater than minimal", since the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation (Collier 2010a, 106). It is not clear whether "greater than minimal risk" refers to agricultural work or the risk of heat-related illness associated with participation in the study or to both.	

<u>Attachment 5</u>: § 26.1303 Checklist for Completeness of Study AHE80 Submitted for EPA Review

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

Requirement			Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y	Provided with protocol and completed study (in IRB correspondence.).
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	
	§1115(a)(3): Records of continuing review activities.		Y	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	
	§1115(a)(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		Y	EPA received this information previously.
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		Y	EPA received this information previously.
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		N/A	
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	
		(2) The measures proposed to minimize risks to the human subjects;	Y	
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	
		(5) The balance of risks and benefits of the proposed research.	Y	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	
	§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	
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.		Y	
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.			n/a	

Attachment 6 – Steps Taken to Compile Qualified Employer List

Excerpt from Page 25 of Study AHE80

In summary, the Qualified Employer List (QEL) for the New York monitoring area was compiled as follows:

Farm Market ID 436
Meister Media Worldwide 759
Less grower duplicates 155
Employer Universe List 1,040
Less: Growers with missing phone numbers 32
Master Employer List 1,008
Less: Not contacted (no answer, disconnected, etc.) 526
Refusal to talk to interviewer 203
Not qualified (does not use wettable powders or water soluble packages) 123
Qualified Employer List from Secondary Source 156
Qualified Employers from local agricultural specialists (Primary Source) 5
Total Qualified Employers 161

Please note that the steps taken to compile the QEL for the other monitoring areas can be found on the following pages of AHE80:

Florida – Page 29
Michigan – Pages 32-33
California – Pages 36-37

Attachment 7: Updated summary of employer lists and recruitment details

The following summaries, by monitoring area, are from pages 27, 31, 34-35, and 38-39 of study AHE80 with one addition from AHETF. AHETF provided the numbers of workers attending recruitment meetings, which was added to each table in attachment 7.

Summary of Employer Lists and Recruitment Details for Site 81 in the New York Monitoring Area

Category	Monitoring area totals
Employers on the Employer Universe List (EUL)	1,040
Employers on the Master Employer Lists (MELs)	1,008
Employers on the Qualified Employer Lists (QELs)	161
Employers contacted from the QELs (direct discussion or voice message response from employer)	145
Employers on the Potentially Eligible Employer Lists (PEELs, i.e., passed suitability screening, including willingness to cooperate)	44
Total qualified workers linked to all the employers on the PEELs	90
Potentially Eligible Employers contacted by Study Director (direct discussion, voice message exchange, or e-mail exchange with employer)	36
Employers on the Eligible Employer Lists (EELs)	7
Total workers linked to all the employers on the EELs	23
Workers attending recruitment meeting	6
Workers signing a consent form	6
Workers who signed a consent form, but were not selected for monitoring	1
Workers withdrawing at their own request (after monitoring began)	0
Workers removed from participation by AHETF	0
Workers completing participation	5

Summary of Employer Lists and Recruitment Details for Area 82 in the Florida Monitoring Area

Category	Monitoring area totals
Employers on the Employer Universe List (EUL)	12,152
Employers on the Master Employer Lists (MELs)	5,176
Employers on the Qualified Employer Lists (QELs)	355
Employers contacted from the QELs (direct discussion or voice message response from employer)	303
Employers on the Potentially Eligible Employer Lists (PEELs, i.e., passed suitability screening, including willingness to cooperate)	91
Total qualified workers linked to all the employers on the PEELs	301
Potentially Eligible Employers contacted by Study Director (direct discussion, voice message exchange, or e-mail exchange with employer)	43
Employers on the Eligible Employer Lists (EELs)	12
Total workers linked to all the employers on the EELs	66
Workers attending recruitment meeting	5
Workers signing a consent form	5
Workers who signed a consent form, but were not selected for monitoring	0
Workers withdrawing at their own request (after monitoring began)	0
Workers removed from participation by AHETF	0
Workers completing participation	5

Summary of Employer Lists and Recruitment Details for Area 83 in the Michigan M A

Category	Monitoring area totals
Employers on the Employer Universe List (EUL)	955
Employers on the Master Employer Lists (MELs)	945
Employers on the Qualified Employer Lists (QELs)	209
Employers contacted from the QELs (direct discussion or voice message response from employer)	187
Employers on the Potentially Eligible Employer Lists (PEELs, i.e., passed suitability screening, including willingness to cooperate)	60
Total qualified workers linked to all the employers on the PEELs	145
Potentially Eligible Employers contacted by Study Director (direct discussion, voice message exchange, or e-mail exchange with employer)	37
Employers on the Eligible Employer Lists (EELs)	7
Total workers linked to all the employers on the EELs	27
Workers attending recruitment meeting	6
Workers signing a consent form	6
Workers who signed a consent form, but were not selected for monitoring	1
Workers withdrawing at their own request (after monitoring began)	0
Workers removed from participation by AHETF (monitoring terminated)	1
Workers completing participation	4

Summary of Employer Lists and Recruitment Details for Area 84 in the California Monitoring Area

Category	Monitoring area totals
Employers on the Employer Universe List (EUL)	9,353
Employers on the Master Employer Lists (MELs)	5,454
Employers on the Qualified Employer Lists (QELs)	413
Employers contacted from the QELs (direct discussion or voice message response from employer)	321
Employers on the Potentially Eligible Employer Lists (PEELs, i.e., passed suitability screening, including willingness to cooperate)	102
Total qualified workers linked to all the employers on the PEELs	383
Potentially Eligible Employers contacted by Study Director (direct discussion, voice message exchange, or e-mail exchange with employer)	61
Employers on the Eligible Employer Lists (EELs)	18
Total workers linked to all the employers on the EELs	65
Workers attending recruitment meeting	5
Workers signing a consent form	5
Workers who signed a consent form, but were not selected for monitoring	0
Workers withdrawing at their own request (after monitoring began)	0
Workers removed from participation by AHETF	0
Workers completing participation	5

Attachment 8 - AHETF checklist from field data collection form

WORKER CHECKLIST—Day of Monitoring

During the Day

- □ Hands should be washed before eating or smoking, but let a researcher wash your hands whenever you choose to do so
- □ Do not get product in eyes, on skin, or on clothing
- □ Avoid breathing vapors or spray mist
- □ Stay hydrated; we have drinks if you need them
- □ Product _____
- □ You may handle up to:

  AHE80: □ 2000 Lb AI for sulfur. □ 160 Lb AI for permethrin.

  AHE120: □ 1680 Lb AI for TPM. □ 400 Lb AI for all other products.
- □ Remember to wear chemical-resistant gloves and:

  □ Sulfur and imidacloprid: Protective eyewear.
- □ Be alert for signs of acute toxicity to the product, including:

  □ Eye irritation.

After the Work Period:

- □ Bathe or shower as soon as practical
- □ Use toll-free number on consent form to report any problems

Heat Stress Briefing

- □ Tell a researcher immediately if you feel over-heated or sick
- □ Identify medical professional on site.
- □ Heat illness poster on site, subject informed.
- □ Water and sports drinks available, subject informed.
- □ Shady or cooler area available for breaks, identified to subject.
- □ Remind subject of heat illness risks, suggest drinks before and during study.
- □ Heat illness symptoms and treatment chart available to researchers.

Attachment 9 - Assigned observers for each MU for AHE80

AHETF provided the following chart in response to a request from EPA. Page 42 of AHE80 refers to the "assigned observers." For AHE80, EPA asked for information on the assigned observers for each of the monitoring units.

AHE80 Observer and Study Director Roster

MU	Observer	Study Director
1	CRO	SD
2	CRO	SD
3	CRO	SD
4	CRO	SD
5	CRO	SD
6	CRO--First Responder	SD
7	CRO--First Responder	SD
8	CRO--LPN	SDD-1
9	CRO--LPN	SDD-2
10	CRO--First Responder	SDD-1
11	CRO--First Responder	SDD-2
12	CRO--LPN	SD
13	CRO--LPN	SD
14	CRO--LPN	SD
15	CRO--LPN	SD
16	CRO--LPN	SD
17	CRO--LPN	SD
18	CRO--First Responder	SD
19	CRO--First Responder	SDD-1
20	AHETF--SDD-3	SD

CRO = Contract Research Organization Researcher
SD = AHE80 Study Director
SDD-1 = AHETF Study Director on other exposure studies
SDD-2 = Qualified Study Director Designee
AHETF--SDD-3 = AHETF Researcher also qualified as SDD

EPA Note: The protocol consistently refers to the "Study Director or designated researcher" or the "AHETF researchers" or the "Study Director or designated member of the study team." For that reason, the aforementioned information is not in conflict with the approved protocol.

Attachment 10 - APPROVED INCLUSION CRITERIA FOR STUDY PARTICIPATION in AHE80

Note: This is the approved inclusion criteria from SOP 11.B.7 with AHE80 revisions incorporated into criteria "a" and "b". The IRB approved the revisions prior to implementation as part of AHE80 protocol amendments 2 and 3.

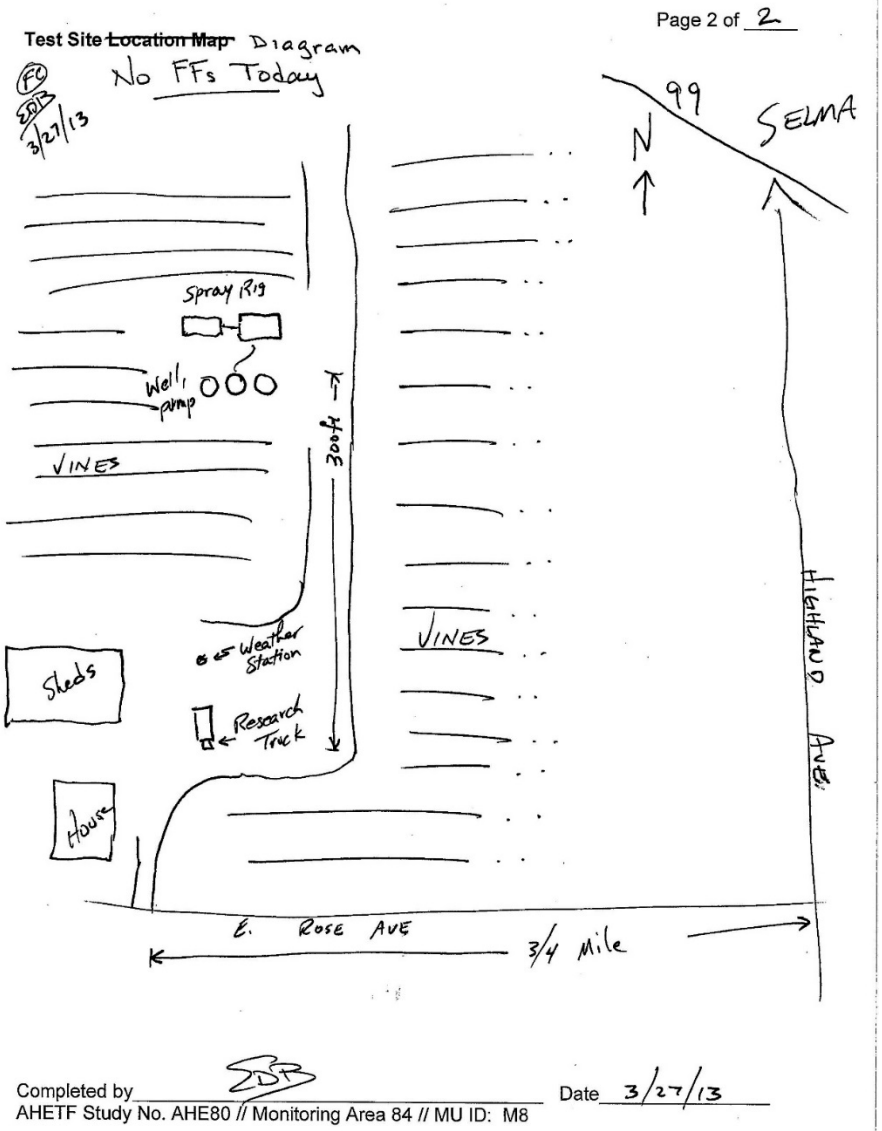
a. Have experience within the past year with mixing/loading by open pouring any formulation into the equipment, or similar equipment, to be used.
b. Have experience with mixing/loading wettable powders by open pouring. By discussion with the volunteer, the Study director will determine if the previous experience is sufficient.
c. Handle pesticides as part of their job.
d. Be trained in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training.
e. Provide proof of being at least 18 years old (or 19 if monitoring occurs in Alabama or Nebraska) with a government-issued photo ID. If other more restrictive age of consent requirements are identified (for example other states or provinces with age of consent above 18 years) they will be enforced by AHETF.
f. Confirm they do not work for a pesticide company (that is, a manufacturer or pesticide registrant or a contractor of the AHETF.
g. 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).
h. Not be pregnant or nursing (See SOP AHETF-11.D).
i. Confirm they do normally wear personal protective equipment that is required by the label. If the worker indicates that they may wear additional PPE not required by the product label, and that additional PPE might impact the objectives of the study, such as chemical-resistant clothing, then the Study Director should be notified to determine if the worker shall be included in the study. Confirm they intend to follow label directions. The research staff shall not influence nor ask in a manner to influence the worker to wear less PPE than they normally wear.
j. Have a private meeting with a researcher to review and discuss the consent form.
k. Understand English or Spanish (see SOP AHETF-11.I for detailed discussion of this topic).
1. Understand and sign the consent form, and if in California, the California Experimental Research Subject's Bill of Rights.

Attachment 11 - Spraying Adjacent to Mixing Loading Area

EPA Question and AHETF Response

EPA Question: Why did the sprayer treat the mixing/loading area?

AHETF Response: "The application was actually made to grape vines adjacent to, but not directly over the M/L area. The following site diagram from the raw data collected during the MU shows that the mixing/loading area was surrounded by grape vines and that there was a well and a pump (including an electrical panel) at the mixing/loading area that would prevent the spray rig from actually spraying the mixing/loading area. There is another note in the observations (at 0943) that the sprayer was about 10 rows from the mixing/loading area which is shortly before the comment (at 1045) about spraying "in M/L area". This indicates the sprayer was near the mixing/loading area, but does not indicate the sprayer actually sprayed over the mixing/loading area." (See site diagram.)



Attachment 12 – Summary of Protocol Amendments Excerpted from Study AHE80

AHE80 Protocol Amendments from pages 11-12 of Study:

Amendment 1:
• Changed the Study Director from Victor M. Cañez, Ph.D. to Douglas Baugher, Ph.D. and included an additional Principal Field Investigator (i.e., Brian Lange).

Amendment 2:
• Expanded the Inclusion Criteria to allow workers with experience mixing/loading *any* formulation within the last year to participate in the study. It also removed the "within one year" restriction of having experience loading wettable powders.
• Revised the Achievement of Design Targets to allow the Study Director to determine whether an efficient configuration as defined by the protocol is feasible for a monitoring area. If the configuration is deemed not feasible, eligible employers can be identified on an individual basis from the Potentially Eligible Lists without first constructing a working pool. Employers can then be recruited and MUs scheduled on an individual basis, as needed.
• Revised the Reference Substances to allow use of the manufacturer's certification of an active ingredient's concentration when a GLP-sourced reference substance is not readily available.

Amendment 3:
• Revised the Inclusion Criteria to allow use of workers who have experience mixing/loading by open pouring into equipment similar to the equipment that will be used in the study.

Amendment 4:
• Included additional researchers to serve as the Principal Field Investigator.
• Added permethrin as another potential surrogate chemical for use in the study.
• Eliminated the requirement for MUs to be conducted in specific counties within each state in order to increase the pool of potential employers.
• Adopted new procedures for identifying qualified employers, and replaced Section 4.0 IDENTIFYING POTENTIALLY ELIGIBLE EMPLOYERS.
• Changed most uses of "grower" or "growers" to "employer" or "employers" since the new recruiting process involves both growers and commercial application companies, which are collectively referred to as employers.
• Changed text to be consistent with the new procedures in protocol Section 4. This included not allowing more than one MU from any one employer to participate in the study; not using a worker more than once in the study; and not using any piece of equipment more than once in the study.
• Allowed the Study Director to implement several options such as obtaining a new grower list based on a different crop or expanding the monitoring area to an adjacent region if it is anticipated the targeted number of MUs might not be attainable for a scenario in a particular monitoring area.

Amendment 5:
• Adjusted field fortification concentrations for sulfur to better bracket the expected residues in worker samples.

Amendment 6:
• Allowed the option to use the WBGT heat index monitoring system (AHETF SOP 11.N.0) instead of following the heat index procedures outlined in Section 2.3.1 of the protocol.