UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

June 22, 2016

MEMORANDUM

SUBJECT: Ethics Review of Completed AHETF Study AHE120 on Worker Exposure during Mixing/Loading of Water Soluble Packets

FROM: Maureen Lydon, Human Research Ethics Review Officer
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TO: Dana Vogel, Director
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REF: Canez, Victor and Baugher, Douglas. (2015) Determination of Dermal and Inhalation Exposure to Workers during Mixing/Loading of Pesticide Products in Water Soluble Packets in the United States. Study Number AHE120, 652 p. plus page 313A, July 21, 2015 (MRID 49680501)

Klonne, Dennis R. and Holden, Larry R. (2015) Scenario Monograph Report. Agricultural Handler Exposure Scenario Monograph: Mixing/Loading of Pesticide Products in Water Soluble Packets. Report Number AHE1014, 203 p., August 27, 2015 (MRID 49711901)

Baugher, Douglas. (2015) IRB Correspondence Report for Study AHE120. Related Submissions. Study Report AHE120 and Scenario Monograph Report No. AHE1014. 951 p. July 31, 2015. (MRID 49687701)

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 a field study, the objective of which was to develop data to determine the potential dermal and inhalation exposure for workers who mix and load solid pesticides packaged in water soluble packets (WSPs). The monograph report for the mixing/loading of WSPs summarizes the dermal and inhalation exposure data collected through study AHE120 for the WSP mixing/loading agricultural handler scenario.

In its conduct, study AHE120 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. Therefore, if study AHE120 and scenario monograph report AHE1014 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. I have recommended follow-up actions for EPA and AHETF in this ethics review. EPA's Office of Pesticide Programs (OPP) has shared the recommended follow-up actions with AHETF, who has agreed to implement them.

In addition, 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 AHE120, scenario monograph report AHE1014, 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 constitute EPA's ethics review.

Background

Study AHE120 developed data to determine the potential dermal and inhalation exposure for workers who mix and load water soluble packets into mixing tanks for application as liquid sprays. Water soluble packaging is an engineering control designed to prevent contact between workers and the formulation (e.g., wettable powder) in the packages. WSPs are designed to dissolve in water and release the formulation into the water without forming a dust or liquid aerosol that could contact workers. The formulation (e.g. wettable powders) then either dissolves in the water or becomes suspended in the water (depending on active ingredient solubility) so it can be applied as a liquid spray.

The AHE120 protocol, approved by an Institutional Review Board (IRB), specified five monitoring units (MUs) to be conducted in each of five geographic monitoring areas. 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. Each MU consists of measuring the dermal and inhalation exposure potential for a single subject for a time period that represents a typical workday. 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. Twenty-five sets of MU samples were originally collected in five monitoring areas, but only 16 were included in AHETF's data analysis for this scenario. AHETF invalidated nine MUs because the workers utilized equipment and/or procedures that AHETF determined were not appropriate for this mixing/loading scenario, as discussed later in this ethics review. Monitoring data included in this scenario consists of 16 MUs collected from 2011-2014 in four separate monitoring areas.

The table below identifies the monitoring areas for the 16 MUs, the years during which monitoring occurred, and the number of workers/MUs per monitoring area.

Specified Monitoring Areas for Data Submitted	122 Florida	123 Louisiana	124 North Dakota	125 California
Date of MUs	2011, 2013, 2014	2013, 2014	2012, 2014	2013, 2014
Locations	Florida	Louisiana, Mississippi	North Dakota, Minnesota	California
No. of workers and MUs	4 workers = 4 MUs	3 workers = 3 MUs	4 workers = 4 MUs	5 workers = 5 MUs

Part of protocol amendment 9 expanded the Louisiana monitoring area to Mississippi, as specified in the amendment, and the North Dakota monitoring area was expanded to the states of Michigan and Minnesota. Although AHETF submitted amendment 9, which the IRB approved, AHETF noted that sections 4.3 and 6.3.B of the AHE120 protocol already allow monitoring areas to be expanded as necessary to increase the number of potentially eligible growers.

Attachment 1 lists major study events in chronological order and attachment 2 identifies the surrogate active ingredients used in the study. Attachment 3 summarizes worker information for each MU, organized by each of the four main monitoring areas, identified above, for which data were analyzed.

The ethics-related chronology for reviews by the Institutional Review Board (IRB), EPA and the Human Studies Review Board (HSRB) is summarized in the next section.

Required Reviews of Protocol and Ethics-Related Chronology

EPA and the HSRB originally reviewed the protocol for study AHE120 in 2009. EPA's review was dated April 8, 2009, and the protocol was reviewed favorably at the June 2009 meeting of the HSRB. In November 2009, it became apparent that the surrogates originally selected for this protocol were not optimum choices. In August 2010, the AHETF approved a revised MU Selection Plan using additional surrogates and submitted the revised protocol, informed consent form, recruitment flyer, and California Bill of Rights to the Independent Investigational Review Board, Inc. (IIRB). In August, 2010, IIRB approved the revised documents. AHETF submitted the revised materials to EPA for review and transmittal to the HSRB.

The revised AHE120 protocol, approved by the overseeing IIRB, and EPA's ethics review, dated October 1, 2010, were discussed by the Human Studies Review Board (HSRB) at its October 27-28, 2010 meeting. With regard to ethics, the HSRB's December 13, 2010 final meeting report concluded that, "the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, 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 AHE120 were revised to address EPA, California Department of Pesticide Regulation (CDPR), and HSRB comments. Following the October 27-28, 2010 HSRB meeting and final HSRB meeting report, the AHETF submitted the first set of revised documents to the Independent Investigational Review Board, Inc. (IIRB) of Plantation, Florida on December 16, 2010. The IIRB approved them on December 29, 2010. Attachment 4 summarizes how the study sponsor addressed the HSRB comments in the revised materials. The IRB approved 15 subsequent amendments between June 2011 and June 2015 as reflected in AHETF's chronology of major study events in attachment 1. [In October, 2012, the name of the Independent IRB, Inc. was changed to Schulman Associates Institutional Review Board, Inc. (SAIRB).]

Completeness of Submission

The checklist used by EPA to verify fulfillment of the requirements of §26.1303 as they apply to this research is provided in attachment 5. This ethics review considers the study material, AHETF's responses to EPA questions which were integrated into this memorandum, and IRB correspondence including additional IRB meeting minutes not originally included. The additional IRB meeting minutes were mailed to the HSRB as a separate background file.

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 AHE120 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 64,928 depending on each of the original five 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 16 includes the steps from study AHE120 which describe the compilation of 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 general description of the recruitment process in study AHE120 is quoted below and explains why the Universe and Master Lists from AHE120 and another agricultural handler exposure study, AHE80, were combined, consistent with the IRB-

approved protocol amendment. In the study itself, there are five sections which detail the recruitment process for each of the original five monitoring areas in study AHE120. As described in study AHE120:

> "AHETF located employers that use water soluble packages or wettable powders, were willing to participate in the research using their 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**: List growers and commercial applicators (i.e., employers) in the monitoring area that might use a water soluble package or wettable powder formulation (Universe List), and then identify those that are qualified for the study by calling them to determine whether they use water soluble packages or wettable powders (Qualified Employer List or QEL).
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> • **Phase 2**: Call qualified employers to determine those that use a water soluble package 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 monitoring of workers mixing and loading water soluble packages into a spray tank.
>
> The study protocol required recruitment of employers (growers and commercial applicators) that utilize water soluble package formulations. Since three of this study's regions overlap with AHE80 that involves employers utilizing wettable powder formulations, recruitment of these two studies was concurrent, and many employers utilize both water soluble package and wettable powder formulations, the Universe List, Master List, and Qualified List for these two studies were combined. That is, for Phase 1 recruiting it was much more efficient to combine Universe and Master Lists from AHE120 and AHE80 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 AHE120/AHE80 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 material used and direct recruitment discussions to the appropriate study.

For Phase 1 and Phase 2 recruiting in 2011, the California, Florida, and New York AHE120 monitoring areas were combined with their respective AHE80 monitoring areas. All five AHE120 monitoring areas were interviewed using a combined AHE80/AHE120 questionnaire. Respondents that qualified were placed on a combined AHE80/AHE120 QEL. These procedures were also used in 2012 for Florida and in 2014 for California and Florida. In 2013 Louisiana and 2014 North Dakota AHE120 recruitment and in 2013 Michigan AHE80 recruitment, study specific questionnaires and Universe, Master, and Qualified Lists were used. Phase 3 recruitment received only study specific Potentially Eligible Employers from the Phase 2 recruiter. (For more details, see individual monitoring area recruiting discussions.)" The IRB approved protocol amendment 4, part of which combined certain lists of employers for studies AHE120 and AHE80.

As described in the study, "From April 2011 to December 2014, AHETF recruited growers and commercial applicators (referred to as "employers") to participate in exposure monitoring of study AHE120." The table below summarizes the extent of the lists and numbers of monitoring units (MUs) for each original monitoring area in study AHE120. Attachment 6 to this memo includes the charts on "employer lists and recruitment details" for each monitoring area.

Monitoring Area	Employer Universe List	Qualified Employer List	Potentially Eligible Employer List	Eligible Employer List	MUs Collected
121 = NY	1,040	161	40	7	5
122 = FL	12,152	355	76	12	5
123 = LA	2,284	88	33	8	5
124 = ND	64,928	128	35	5	5
125 = CA	9,353	413	69	16	5

EPA Comparison of Recruitment Described in Study versus Protocol and SOPs

As part of EPA's ethics review, I compared the recruitment process discussed in study AHE120 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 (HSRB). With regard to recruitment, the protocol references SOPs 11.B.7, 11.K.O, 11.L.O, and 11.M.O. When considered together, these SOPs discuss basic steps to be followed during the process of assembling lists and recruitment. I identify the basic steps listed below and note 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 (HSRB), beneath each of the steps below, I note how this step was incorporated into the AHE120 recruitment process. This is prefaced by the phrase, "Incorporation of step into AHE120 study" and refers back to the recruitment phases identified in the previous section of this memo and pages 22-23 of the study. The information prior to the phrase "Incorporation of step into AHE120 study" is

based on the SOPs referenced by number in the protocol. **The intent of this section is to demonstrate how the SOPs referenced in the protocol were taken into account in study AHE120.**

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

   Incorporation of this step into AHE120 study: Reflected in recruitment phase 1 in AHE120 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 AHE120 study: Reflected in recruitment phase 1 in AHE120 study. As it relates to this topic, EPA asked AHETF, "In each state (FL, LA, ND, CA, NY), did AHETF "randomly select a subset of the universe list as the master list for screening" for study AHE120?

   AHETF's detailed response follows:

   "The following is true for each monitoring area in this study: 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**. For this study, this was the case for all monitoring areas except ND. In NY, FL, LA, and CA no subsamples of the available EUL were used since the MEL was the same as the EUL. In ND, except for soybeans, no subsamples of the available universe of crop growers were used and the master list was the same as the universe list. For ND soybeans, the study report specifically states that a random subset of growers was used. (Second to last sentence of section 3.4, Phase 1, Paragraph 1.)"

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 water soluble packages was estimated because there was no census, market study, or list that specifically identified growers or the number of growers using water soluble packages. Given that we like to start with approximately 50 growers on the QEL and our interview response rate for growers using water soluble bags was estimated at about 5%, 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, FL, LA, and ND monitoring areas. In these regions, except ND, the remaining EUL of growers was purchased from the list agents to provide a sufficient MEL for further recruiting. In the CA, FL, and LA monitoring areas, the EUL became the MEL. For ND, our EUL was about 65,000 growers. We only purchased 10% of these growers for our MEL, which was enough to provide a sufficient MEL for our recruiting needs. For more detail on the quantities in the EUL and MEL for each region, see the individual sections in the report or monograph.]

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 AHE120 study: Reflected in recruitment phase 1 in AHE120 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 water soluble packages or wettable powders."

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

   Incorporation of this step into AHE120 study: Reflected in recruitment phase 1 in AHE120 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 AHE120 study: Reflected in recruitment phase 2 in AHE120 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 AHE120 study: Reflected in recruitment phase 3 in AHE120 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. In some cases, the participant was the grower and signing the statement was not required. An informational flyer was used during the recruitment meetings with volunteers. The tables on pages 27-43 of the study which are entitled "Summary of Employer Lists and Recruitment Details" incorrectly left blank the numbers of "workers attending a recruitment meeting." At EPA's request, AHETF provided these figures in the updated tables in attachment 6. AHETF explained that recruitment "meetings usually involved just one available worker, but occasionally there were a few workers at a meeting."

Subject Selection

Section 6.4 (page 29 of 45) 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 outlined on the informed consent form that was reviewed and approved by the IRB and EPA and signed by participating subjects. In every state except California, there were more workers who signed consent forms than the number of MUs necessary. EPA asked AHETF to identify the method of random selection used in each applicable state to select the workers who would participate. AHETF conformed to random selection of volunteers in those cases where more than one eligible volunteer was available during the desired timeframe and in the designated location for testing. AHETF explained that, "For one MU in FL, a random selection was made. Three volunteers at one employer location were consented and considered to be equivalent, so one was selected through a series of coin tosses. In most of the other monitoring areas, consented volunteers were available for more employers than the number of MUs needed, so some of the employers/volunteers were not used; however, a random selection of multiple employers was never made since they were generally not equivalent (for example, because timing or location made some more obtainable than others)."

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 November 6, 2014 and included on pages 796-805 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 packaged in water soluble packets and must contain one of the following active ingredients: acephate, dithiopyr, imidacloprid, or thiophanate-methyl. The label for that product will be reviewed with you prior to participation in the study. This review will include how much of that product you might handle during the study, 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 by the time they completed the informed consent process. 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 7. 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 AHE120, 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, there were three workers at one site and one worker at a second site 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 documented that, "Each subject received a signed copy of their consent form at the conclusion of consenting or a later date (usually the day of monitoring)." Attachment 8 provides AHETF's summary of the dates when subjects received their informed consent (IC) forms. As explained by AHETF, MU 10 "did his work on 16 January (2013) and inadvertently did not receive a copy of the IC. The Spanish-fluent researcher contacted him by telephone the morning of 17 January to leave contact information, obtain his mailing address for the document, and assure that there were no adverse events as a consequence of participation in the study. On January 22, he again contacted the subject and made sure he had received the copy of the document. The subject indicated that he indeed had obtained the document." This does not constitute a deviation because the protocol, the AHETF SOP on informed consent, and the consent form do not

specify when the subject will receive a copy of the consent form. Only the AHETF SOP on informed consent specifies that the subject will receive a copy of the consent form.

Personal Protective Equipment

AHETF confirmed that the subjects participating in study AHE120 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). All subjects wore long sleeved shirts and long pants, provided by the workers, over their whole body dosimeters. In addition, AHETF provided the required chemical-resistant new gloves worn by all participating workers. Subjects wore their own shoes (i.e. leather shoes/boots or rubber boots) and socks. Many workers wore protective eyewear (e.g. goggles or protective glasses) as required by the pesticide label or based on their own preference. As a reference on PPE and additional clothing and eyewear worn by subjects, tables 4 and 5 from pages 71-74 of the AHE120 study are provided in attachment 9, along with table 3 from page 95 of the monograph scenario report AHE1014.

Medical Professional on Site

Consistent with the protocol, page 47 of the study states that, "A medical professional (i.e. nurse or certified first responder) was present for the duration of each monitoring event and periodically checked the subjects for signs of heat-related illness." In response to a question from EPA, AHETF indicated that, "For MUs 1 – 7, local Nurses or fire department EMTs were on site at all times. After MU 7, one of the two field contract research organizations (CROs) used by AHETF employs a Licensed Practical Nurse and the other CRO employs a Certified First Responder. Both of these latter medical professionals also recorded the worker observations during the monitoring, so they were in close contact with the subjects during the entire monitoring period." EPA asked what "periodically checked" meant in practice during study AHE120. 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." AHETF identified, in attachment 10, the assigned observers for each monitoring unit for study AHE120.

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 11 includes the eligibility criteria for AHE120 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 16 monitored workers reflected in AHE120 were all adult males, ranging in age from 18 to 71 years old with work experience ranging from 1 to about 50 years. In Florida, there were three workers at one site and one worker at a second site who opted to have a Spanish-speaking researcher present during the consent meeting. The study identifies subjects with numbers thereby protecting their privacy by not revealing their names. Table 3 for each monitoring area on pages 67-70 of study AHE120 provides more details on the 16 monitored workers; those tables are included in attachment 3 to this memo.

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: AHETF should 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.

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 AHE120, the AHETF conducted a survey of area experts to evaluate the representativeness of the growers/applicators who participated in the study. Less than one-third responded to the opinion poll by answering the "representativeness questions." Of the 10 who answered the questions, 9 of the 10 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 size of the farms in the study was representative. Section 3.6 (pages 43-46) in study report AHE120 provides the details.

Reportable Event and Unacceptable Work Practices

Water soluble packaging is an engineering control designed to prevent contact between workers and the formulation (e.g., wettable powder) in the packages. WSPs are designed to dissolve in water and release the formulation into the water without forming a dust or liquid aerosol that could contact workers. Breaching the packets to facilitate release of the powders is contrary to the intent of packaging the powdered formulation in WSPs and circumvents the engineering control properties of WSPs.

During the early course of the study, AHETF observed workers using procedures which they later realized circumvented the goal of WSPs to reduce potential exposure. As described on page 58 of study AHE120, "During the early monitoring in this study, it was observed that some workers placed the WSPs in removable baskets hanging from the open hatch or directly into the tank; and then used streams of water from hoses to break open the

WSPs. These procedures caused visible amounts of airborne powder that came out of the mix tanks where the mixer/loader was working." On June 7, 2012, AHETF filed a reportable event with the IRB associated with the above, as described on page 489 in the IRB correspondence. This was the only reportable event that AHETF identified to the IRB. The description provided to the IRB states, in part, "Four of these workers used suspended baskets to mix/load air blast sprayers. During this process the workers placed the water soluble packages into a basket suspended within the tank opening and allowed water to flow over and rupture the WSP. This resulted in a plume of formulated product contributing to the handler's exposure."

In a June 6, 2012 letter, AHETF informed EPA of this issue. In a subsequent June 21, 2012 conference call with EPA, California's Department of Pesticide Regulation (CDPR) and the Canadian Pest Management Regulatory Agency (PMRA), it was decided that directing water onto WSPs in baskets in sprayer hatches would not be a supported practice. Protocol amendment 6 (June 23, 2012) requiring removal of baskets before adding the WSPs reflected this decision. When AHETF observed different unexpected mixing methods later in the study and subsequently realized their impact on exposure, they submitted additional amendments to the IRB. Subsequent amendments 8 and 13 were based on observations of different mixing methods that also circumvented the engineering control and caused visible aerosols that exited the mixing tank.

Pages 11-12 of study AHE120 summarized these protocol amendments as follows:

Amendment 6:
• Disallowed the use of suspended baskets inside tank openings that prevent the WSPs from going directly into standing water in the tank. AHETF identified the use of suspended baskets as an unanticipated cause of higher exposure. The AHETF does not want to include the use of baskets as part of the definition for the WSP mixer/loader scenario.

Amendment 8:
• Provided specific mixing instructions for the use of WSP to address the use of overhead addition of water, filling order, and the use of baskets.

Amendment 13:
• Modified the WSP mixing/loading instructions to reflect best practice techniques over a wide range of equipment and loading configurations.

The unacceptable practices identified by AHETF for the nine monitoring units (MU M1, 2, 4, 5, 8, 9, 16, 17 and 19) are listed in attachment 12. After reviewing the description of the "unacceptable monitoring units" in study AHE120, EPA asked AHETF a number of questions and requested that additional information be formally submitted to EPA. AHETF's supplemental information is in Appendix G to the study and was provided to the HSRB in a separate file.

From an ethics standpoint, EPA has highlighted some pertinent information below:

- **EPA asked AHETF about the years of experience of the workers identified as monitoring units M1, 2, 4, 5, 8, and 9 with regard to loading water soluble packets (WSPs). These are the workers who directed water onto the WSPs and four of them used baskets while doing so. Except for MU M2, the workers had between 10 and 35 years of experience loading WSPs prior to participating in the study.** (AHETF's response included the years of experience per MU and is provided in attachment 13). This information is relevant to EPA's proposed follow-up action discussed later in this section.
- Researchers confirmed that they reviewed the following label information with these workers prior to their 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 reiterated that review of this information is standard practice at the beginning of each monitoring period.
- In addition, the protocol also 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 with these workers.
- Their field data collection forms contained a checklist of items provided in attachment 7.
- Page 14 of 45 of the protocol states that AHETF is supposed to "ensure that all tank mix products are used according to the approved label" and AHETF is supposed to remind workers of "safe chemical handling practices."
- Page 30 of the protocol states that "researchers will watch and take notes on their work activities" and "monitor the workers and environmental conditions to ensure safe working conditions."
- **After reviewing the aforementioned information, EPA noted that the consent form and protocol do not require AHETF to review the use directions for the surrogate chemicals with subjects.**
- **The protocol (page 12 of 45) also states that "AHETF will only monitor workers mixing/loading in accordance with all label, Worker Protection Standard (WPS) and state (e.g. California) regulatory requirements".**

As a result of the information learned during study AHE120, AHETF developed a standardized set of loading instructions for WSPs included in attachment 14. The instructions were developed by AHETF in consultation with members of the Joint Regulatory Committee [including representatives from AHETF, EPA, the Health Canada Pest Management Regulatory Agency **(**PMRA), and the California Department of Pesticide Regulation (CDPR)] to provide "best practices" for handling and adding WSPs to spray tanks. The goal of these instructions is to ensure that WSPs are allowed to dissolve in water and prevent them from being ruptured by streams of water or other means. Six monitoring units (MUs M1, M2, M4, M5, M8, and M9) who used baskets, and/or streams of water, and/or overhead recirculation to rupture/agitate the WSPs were monitored before

the new instructions were completely adopted for use in the remainder of study AHE120.

Before AHETF developed the best practice mixing/loading instructions for water soluble packets, the Study Director (SD) talked with handlers MU M5 and M9 in the field on an individual basis at the end of their monitoring periods when the SD recognized an approach that the workers could use to reduce their exposure. The SD advised the sprayer/operator who was carrying boxes of WSPs for MU M19 to avoid rough handling practices which appeared to break the WSPs. The interactions with MUs M5, M9 and M19 are summarized below and excerpted from Appendix G.

> As described on page 8 in Appendix G:
> "MU M5 loaded WSPs into baskets in air blast sprayer hatches on 17 May 2012. The WSPs were broken by water from the overhead drop-pipe used to fill the sprayers. At the end of the monitoring period, after seeing a co-worker mix/load a tank with WSPs by first removing the basket in the hatch, the Study Director orally advised MU M5 to change to that practice (17 May 2012). The practice of removing the basket appeared to generate less aerosol exiting the tank." AHETF clarified that the Study Director observed what the other mixer/loader was doing while subject M5 was having his samples collected. When talking with subject M5 before he left the site, the SD described what he had witnessed and advised the subject that loading WPS into the tank, rather than the basket, would be a better practice and subject M5 agreed. AHETF stated that, "this conversation was not recorded in the field notes as we did not yet appreciate its significance." Not recording this conversation in the field notes was not a deviation from the protocol. In hindsight, it would have been beneficial for all concerned to formally record any work practices observed in the field that reduced exposure and to share this information with other study director designees and/or observers for monitoring units not yet implemented as part of the same study. However, this was not a component or requirement of the approved protocol.
>
> The Study Director also advised MU M9 to change his work practice near the end of his monitoring period. As explained on page 9 of Appendix G, "MU M9's air blast spray rigs did not have baskets. He loaded WSPs directly into the tanks, loaded other products while adding water via an overhead drop-pipe, and then walked away while the tanks filled on 13 July 2012. He was at the hatch adding other products while the water was disrupting WSPs. At that time, AHETF had not identified overhead water as an issue, but near the end of the monitoring period, based on observations of aerosols exiting the tank, the Study Director orally advised him not to add overhead water to the tank until the WSPs had dissolved."
>
> The Study Director (SD) also suggested that workers carry boxes containing WSPs from the truck to the spray rig and not drop them on the ground, prior to the fourth and final load for MU M19, after what the SD observed during the first three loads. The explanation on page 9 of Appendix G includes the following:
> "MU M19 mixed three loads into a large self-propelled ground boom spray rig (no basket) on 20 August 2014. During the first load there were no work practice

issues. For the second and third loads, the sprayer operator assisted by dropping boxes of pouches containing WSPs from the back of a truck ~7 feet to the ground, then carrying them to the spray rig. WP dust was observed while pouring WSPs from pouches into the tank. A total of 10 of 36 pouches contained broken WSPs. For the fourth and last load, the Study Director instructed the workers to carry boxes from the truck to the spray rig and not drop them to the ground: no broken WSPs were observed during the final load. The Study Director orally reminded them to continue that practice and AHETF incorporated handling instructions in its recommended best practices based on this observation."

Study AHE120 indicates that, before the study was initiated, the study sponsor AHETF was knowledgeable about the label directions for using WSPs but they were not familiar with practices that the individual agricultural handlers would use in the field that are not reflected on the label and about which the label is unclear or silent. Because water soluble packaging is an engineering control designed to prevent contact between workers and the wettable powder in the packages, AHETF did not anticipate that workers would use practices not listed on the label which ultimately broke open the packages because a primary purpose of WSPs is to prevent contact between workers and the content of the packages. In hindsight, one could argue that AHETF should have investigated the work practices used in the field with regard to WSPs in advance of conducting the study. However, the approved protocol states that the study sponsor will "only monitor workers mixing/loading in accordance with all label, Worker Protection Standard (WPS) and state (e.g., California) regulatory requirements." So, the stated intention in the protocol is for AHETF to only monitor and be aware of practices which are in accord with the label, WPS and state regulatory requirements. Reviewing this completed study identifies a number of lessons, one of which is the value of determining actual use practices in the field prior to conducting the study. The need to do this was not anticipated by either EPA or AHETF and it was not required in the protocol. The remaining AHETF studies to be conducted should consider these lessons going forward.

Once the "best practice" directions for using WSPs were identified, in subsequent monitoring units, AHETF implemented the following procedures:

"For the two MUs in California, the Study Director designee showed the WSP directions to the workers before monitoring started and asked them to follow those directions. In all other cases, the Study Director did not show the list of instructions to the workers prior to monitoring. Instead, on the day of monitoring, he examined the equipment and asked the subject how the equipment worked and how he normally handled the WSPs. In cases where the equipment set-up and procedures conformed to the amended instructions, the subject was asked to follow those normal procedures.

In cases where the practices did not conform to the instructions, possible procedural changes were discussed with the subject. Typically this involved removing a basket (Amendment 6) and/or shutting off overhead water (Amendment 8). After Amendment 13, the Study Director sometimes had to ask that the WSPs be first

added to still water before agitation was begun; or that the subject should close the hatch during agitation if there was overhead recirculation. The Study Director explained why the changes were requested and none of the subjects objected to the modifications. The actual mixing/loading procedures used were documented, but the discussions with the subjects were informal and not documented."

Although not required by the protocol, it would have been preferable if the discussions with subjects had been documented for purposes of these reviews.

The revised directions for using WSPs were identified, and brought to EPA's attention, as a result of study AHE120 and are included on page 29 of scenario monograph report AHE1014. In order for EPA to rely on these recommended procedures, or a revised version thereof, and any other data resulting from human study AHE120 and associated report AHE1014, EPA must comply with 40 CFR Section 26.1604, and submit study AHE120 and scenario monograph report AHE104 to the HSRB for review, along with EPA's ethics and science reviews and support materials.

From an ethics perspective, in order to help promote the effectiveness of any revised procedures for the proper use of water soluble packages (WSPs), the procedures, or a revised version thereof, must be incorporated into required label language and replace any inconsistent label language, and the procedures must be followed. To increase the likelihood that the appropriate procedures and label language will be followed, agricultural handlers using WSPs must be trained on the appropriate procedures. In summary, in order to achieve the intended benefits from the revised procedures, the appropriate, updated procedures should be incorporated into required label language for water soluble packets, any conflicting language should be removed from the same labels, and agricultural handlers who are, or will be, using water soluble packets must receive effective and timely training on the updated appropriate procedures.

Follow-up Action: EPA will pursue appropriate required label revisions identifying the proper use of water soluble packages (WSPs), as well as associated training for agricultural handlers using WSPs. In the process of doing this, EPA will consult with various stakeholders, such as the State FIFRA Issues Research and Evaluation Group (SFIREG) on the most effective approaches for ensuring that the updated procedures for the proper use of water soluble packages reach the regulated community and influence their behavior when using WSPs.

Review of Use Directions with Subjects

As stated above, neither the protocol nor the consent form requires that the use directions for the surrogate chemicals be reviewed with participating subjects. In response to an EPA question, AHETF accurately pointed out that, "'Directions for Use' cover many topics not relevant to the study and were the farm operators' and subjects' responsibilities (e.g., Resistance Management). The 'Mixing Instructions' and 'Mixing Order' topics under the 'Directions for Use' were covered informally prior to mixing/ loading. The workers were then generally allowed to perform their tasks using in their

normal procedures and application rates. As the AHETF WSP best practices were developed, they were discussed with the participants."

Follow-up Action: For the limited number of remaining agricultural handler exposure studies which are underway in the field and for those monitoring units that have not yet been initiated, the Office of Pesticide Programs has asked AHETF, beginning in August, 2016, to direct the Study Directors and/or the qualified study director designees to review with participating subjects the pertinent sections of the "directions for use" on the label which are applicable to each study. This assumes that this is not already a requirement in the study-specific protocols. The AHETF could submit a short protocol amendment to the IRB only if the associated study protocols do not already include this requirement. The review of this information would be in addition to the other information which the study staff are already required to review with participating subjects as dictated by the consent form and study-specific protocol approved for each of the remaining studies.

Provision of Personal Exposure Results to Subjects in AHE120

Page 7 of the consent form references the form for subjects to request their personal study results. In addition, AHETF SOP 11.J.4 contains the following 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."

Sixteen of the twenty five subjects who were monitored requested their personal results. These sixteen MUs were M 1-9, 11-12, 14, 16-17, 20 and 22.

AHETF confirmed that the personal exposure study data, including the information underlined above "was provided to all of the MUs included in the scenario analysis (conforming to best practices). Personal results were not provided to the non-conforming MUs. Instead, they were given the mean results for the conforming MUs. The AHETF list of best practices was attached to the letters." AHETF verified that 8 of the 9 "non-conforming MUs" requested their personal results. When AHETF refers to the "non-conforming MUs" they are discussing the MUs whose work practices were excluded from Study AHE120. The workers who requested their personal results and fall into this category are MUs M 1, 2, 4, 5, 8, 9, 16 and 17. AHETF explained that these workers "received a letter at the end of the study with the mean results from the conforming MUs and a list of best practices." In addition to these end-of-study letters, workers M1 and M2 received initial notification letters, shortly after the exposure results were available, that essentially told them that their exposures were higher than expected without providing

quantitative results and without pictorially showing the distribution of the residues on their bodies.

In response to EPA's questions as to why the personal results were not provided to these subjects, AHETF explained that, "The samples from three of the MUs were not analyzed so we did not have any results to send them. For the MUs with higher than expected exposure, we did not believe the results reflect what their exposure would be when using best practices and would not be comparable to the mean results from the conforming MUs. For the MUs that had results in the range of the conforming MUs, we wanted to send them our best practices as an encouragement to adopt them. Giving them results that were similar to the mean of the conforming MUs would not necessarily be an incentive for them to change their way of handling WSPs. In all cases, we sent them the mean results across all conforming MUs and a copy of our best practices." The MUs who requested personal results, but whose samples were not analyzed were M16 and 17.

The Study Director sent sample results by USPS first class mail. None were returned as undeliverable.

EPA believes that the personal exposure data in existence should have been sent to each of the subjects who requested their personal data consistent with the protocol, consent form and SOP 11.J.4. The instances where samples were analyzed but the personal results were not provided to the workers who requested them constitute a protocol deviation which should have been reported to the SAIRB. EPA agrees that it was appropriate to share with these workers the updated procedures for proper handling of water soluble packets, however the workers' personal exposure data should have been provided as well, along with a comparison to the results for other workers performing the same task.

Follow-up Action: EPA requested that AHETF provide the personal exposure data to every worker who requested but did not receive it consistent with the signed informed consent forms, protocol and AHETF SOP 11.J.4. The results should be provided in a way that is comprehensible, relevant, contextualized and usable to those who requested this information. EPA requested that AHETF provide confirmation to EPA that the personal results were sent so the Agency can share this confirmation with the Human Studies Review Board (HSRB) at the July HSRB meeting. AHETF agreed to do this and intends to send the personal results to the six remaining workers.

Heat Index Records

During the 25 monitoring events implemented during study AHE120, the heat index did not reach 105 degrees Fahrenheit and, as a result, none of the monitoring events had to be terminated due to the heat index.

Section 2.3.1 of the protocol for study AHE120 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.

EPA requested a copy of the AHE120 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 12 allowed the study sponsor the option to use the WBGT heat index monitoring system, but that option was not exercised during study AHE120.

Protocol Amendments with Ethical Considerations

The protocol for study AHE120 was amended 15 times after it was signed, as

summarized in attachment 15. (Regarding amendment 4, a few pages were missing from the AHE120 IRB correspondence so amendment 4, in its entirety, was emailed to the HSRB as a separate file.) 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, 6 – 9, and 13 given their potential impact on ethical considerations. Amendment 12 allowed the study sponsor the option of using the Wet Bulb Globe Temperature approach; the study sponsor never used this option and, as a result, amendment 12 did not impact participating subjects.

Amendment 2

Page 290 of the IRB correspondence discusses the following component of amendment 2:

Excerpt:

"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 water soluble packets study, the following inclusion criterion also applies:

- [Delete] Have experience within the past year with mixing/loading water soluble packets.
- [Add] Have experience within the past year with mixing/loading by open pouring any formulation into the equipment to be used. By discussion with the volunteer, the Study Director will determine if the previous experience with other formulations or WSPs is sufficient.

Reason for Change/Addition:

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. This has not changed.

Water soluble packets are an engineering control designed to reduce exposure. They are easy to use and label directions for proper use are direct and simple. Previous experience with WSPs is not necessary.

- *End of Excerpt –*

Based on the information known at the time of the amendment, the AHETF's rationale for the amendment was a reasonable one taking into account the safeguard included in the amendment that, "By discussion with the volunteer, the Study Director will determine if the previous experience with other formulations or WSPs is sufficient." The health and safety of the participating subjects was not put at risk as a result of this amendment; the participating subjects who used work practices that were found to be

problematic when handling WSPs had between 10-35 years of experience loading WSPs prior to participating in the study.

Amendment 3

Page 344 of the IRB correspondence provides the following information on amendment 3:

Excerpt

"I. Change/Addition: 1

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 water soluble packets study, the following inclusion criterion also applies:

- Have experience within the past year with mixing/loading by open pouring any formulation into the equipment to be used.
- **[Add]**….equipment**[, or similar equipment]**, to be used….

Reason for Change/Addition:

This 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."

- *End of protocol amendment excerpt* -

The amendment did not negatively affect the participating subjects' health and safety. However, in the future, EPA will advise study sponsors that it's critical to take such information into account during the initial process of developing the inclusion/exclusion criteria. The AHETF does not intend to submit additional protocols for agricultural handler exposure studies to EPA.

Amendment 6

Amendment 6 was discussed with EPA in 2012 prior to approval and implementation. As summarized on page 11 of the study, this amendment "Disallowed the use of suspended baskets inside tank openings that prevent the WSPs from going directly into standing water in the tank. AHETF identified the use of suspended baskets as an unanticipated cause of higher exposure. The AHETF does not want to include the use of baskets as part of the definition for the WSP mixer/loader scenario." As part of this amendment, as stated on page 491 of the IRB correspondence, section 2.3.5 of the protocol was revised to add the following at the end: "Remove any basket or strainer that may be in the tank hatch. Add the WSPs directly to the water in the tank. The basket or strainer may

be returned to the tank hatch after the WSPs have been added. Follow all specific label directions."

The EPA supported this amendment because the AHETF identified the use of suspended baskets as the unanticipated cause of higher exposure. This amendment positively impacted the practices of subjects who had not yet completed their participation in the study.

Amendment 7

As summarized on page 12 of study AHE120, amendment 7 "allowed participants to handle more than 400 lb AI of thiophanate-methyl (TPM), which was previously the highest amount that could be handled in a day for this study. Only the highest strata for TPM was changed."

AHETF consulted with OPP scientists and ethics reviewer in 2012 prior to implementing this amendment and obtained EPA's support for the amendment. After reviewing the Margin of Exposure (MOE) calculations including the adjustments, EPA determined that this amendment was acceptable.

Amendment 8

As summarized on page 12 of the study, amendment 8, "provided specific mixing instructions for the use of WSP to address the use of overhead addition of water, filling order, and the use of baskets." The revised instructions contribute in a positive manner to the practices used by workers who handle water soluble packets.

Amendment 9

As summarized on page 12 of the study, amendment 9, "discontinued reviewing the Material Safety Data Sheets. The brand of product or qualified active ingredient may change between the informed consent process and monitoring. Reviewing the label on the day of monitoring is a standard practice." Below is the pertinent excerpt from page 696 of the IRB correspondence.

Excerpt from page 696 of IRB correspondence

"IV. 2.3.5 Risk of Exposure to Surrogate Chemicals
[Delete this Paragraph] During the informed consent process and prior to participation, a researcher will show the subject a copy of the label and MSDS for the product that will be handled. The label will then be reviewed with the subject to remind him/her of:

- The specific risks associated with the particular end-use product being handled (discussed directly from the label)

[Replace With]

During the informed consent process a researcher will show the subject a copy of the label for the product anticipated to be handled. The label will be reviewed with the subject to remind him/her of:

- The specific risks associated with the end-use product being handled (discussed directly from the label)
- Precautionary statements that should be followed
- The requirement to use label-specified PPE
- The importance of washing hands prior to eating or smoking
- Other safe pesticide handling practices that should be followed

The procedure will be repeated immediately prior to monitoring with the product actually being handled on the day of monitoring.

Rationale for the Change

The brand of product or qualified active ingredient may change between the informed consent process and monitoring. Reviewing the label on the day of monitoring is a standard practice. Review of the Material Safety Data Sheets has been discontinued per AHETF SOP 11.E version 4, which also specifies that copies of the product label and MSDS will be on site during the monitoring period. This change does not require a change to the Informed Consent." – *End of AHETF excerpt* -

EPA understands the challenges with the logistics involved in implementing agricultural handler exposure studies. However, from an ethics standpoint, EPA does not believe that AHETF should have implemented this amendment. Having said that, EPA does not believe that this amendment jeopardized the health and safety of participating subjects. The researchers confirmed that they reviewed with participating the specific risks associated with the end-use product being handled (discussed directly from the label), precautionary statements that should be followed, the requirement to use label-specified PPE, the importance of washing hands prior to eating or smoking, and other safe pesticide handling practices that should be followed. Although the AHETF discontinued the requirement to review safety data sheets (SDS) with subjects, they still required the medical professional on-site to review the SDS before the monitoring event began and to have the SDS on hand during the monitoring interval. EPA believes the same information should have been reviewed with the participating subjects consistent with the original provision in the protocol.

Follow-up Action: There are a limited number of agricultural exposure studies which have not yet been implemented. For any of those studies, if the review of safety data sheets with participating subjects was originally part of the approved protocol, EPA requests that AHETF continue with that practice consistent with the approved protocols for these studies and for any monitoring units not yet implemented as of August 1, 2016.

Amendment 13

As summarized on page 12 of the study, amendment 13 "modified the WSP mixing/loading instructions to reflect best practice techniques over a wide range of equipment and loading configurations." The revised instructions contribute in a positive

manner to the practices of workers handling water soluble packets.

Effective Dates of Protocol Amendments for AHE120

AHETF confirmed in writing that the 15 protocol amendments were not implemented prior to IRB approval. OPP noticed that amendments 4, 7, 8 and 9 had an effective date of "IRB approval date" when they were submitted for review by the IRB. The remaining 11 amendments, which were also unsigned and submitted for IRB review and approval, already had desired "effective dates" listed on them, although they had not been implemented. 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: In the future, if the study sponsor must include an effective date on the protocol amendment form when applying for IRB approval, EPA recommends and requests that the study sponsor insert "IRB approval 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 HSRB's comments on the protocol for AHE120 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 AHE120 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 AHE120 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 Recommended Follow-up Actions

The follow-up actions which EPA recommends in this ethics review include the following:

1) EPA will pursue appropriate required label revisions identifying the proper use of

water soluble packages (WSPs), as well as associated training for agricultural handlers using WSPs. In the process of doing this, EPA will consult with various stakeholders, such as the State FIFRA Issues Research and Evaluation Group (SFIREG) on the most effective approaches for ensuring that the updated procedures for the proper use of water soluble packages reach the regulated community and influence their behavior when using WSPs.

2) For the limited number of remaining agricultural handler exposure studies which are underway and/or have not yet been implemented and for those monitoring units that have not yet been initiated, the Office of Pesticide Programs has asked AHETF, beginning on August 1, 2016, to direct the Study Directors and/or the qualified study director designees to review with participating subjects the pertinent sections of the "directions for use" on the label which are applicable to each study. This assumes that this is not already a requirement in the study-specific protocols. The AHETF could submit a short protocol amendment to the IRB only if the associated study protocols do not already include this requirement. The review of this information would be in addition to the other information which the study staff are already required to review with participating subjects as dictated by the consent form and study-specific protocol approved for each of the remaining studies.
3) EPA requested that AHETF provide the personal exposure data which exists to every worker who requested but did not receive it. EPA requests that AHETF provide confirmation to EPA that the personal results were sent to these workers so the Agency can share this confirmation with the Human Studies Review Board at the July 2016 HSRB meeting.
4) EPA will ask AHETF to pay close attention to and follow the following 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: "*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.*"
5) There are a limited number of agricultural handler exposure studies which are underway and/or have not yet been initiated. For any of those studies, if the review of safety data sheets with participating subjects was originally part of the approved protocol, EPA requests that AHETF continue with that practice consistent with the approved protocols for these studies and for any monitoring units not yet implemented as of August 1, 2016.
6) In the future, if the study sponsor must include an effective date on the protocol amendment form when applying for IRB approval, EPA recommends and requests that the study sponsor insert "IRB approval date." Unless there is an immediate hazard to a research subject, protocol amendments cannot be implemented prior to approval by the IRB.

Conclusion

This study reports research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L. In its conduct, study AHE120 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied.

EPA recommended follow-up actions in this ethics review to which AHETF agreed. 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.

cc: Rick Keigwin
Matt Crowley
Jeff Dawson
David Miller
Jackie Mosby
Rich Dumas
Nancy Fitz

Attachment 1: Major AHE120 study events in chronological order
Attachment 2: Surrogate active ingredients used in study AHE120
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 checklist for AHE120 Study
Attachment 6: Updated summary of employer lists and recruitment details
Attachment 7: AHETF checklist from field data collection form
Attachment 8: Dates when subjects received consent forms
Attachment 9: Workers' outer clothing and PPE worn during AHE120
Attachment 10: Assigned observers for each monitoring unit
Attachment 11: Eligibility criteria
Attachment 12: Summary of excluded MU work practices
Attachment 13: Years of experience of workers/MUs M 1, 2, 4, 5, 8 and 9
Attachment 14: Revised procedures for proper use of water soluble packets ("Best Practices")
Attachment 15: Summary of protocol amendments
Attachment 16: Steps used to compile the qualified employer list

Attachment 1

Chronological Listing of Major Study Events for AHE120

Note: Information from Table 1, Page 63 of AHE120, was included in this attachment. EPA added reference to HSRB review and first submittal of revised materials to IRB after HSRB meeting.

Date	Major Study Events
12/11/08	Initial submission of AHE120 protocol and related materials to the Independent Investigational Review Board, Inc. (IIRB) for review
5/18/09	Submission of study materials to CDPR
12/16/09	Approval of Ongoing Research by IIRB (i.e., annual renewal)
8/18/10	Approval by IIRB of final AHE120 protocol and related materials, reflecting comments from EPA, CDPR, and HSRB, plus Spanish translations
10/27-28/10	HSRB review and meeting
11/03/10	Provisionary approval of revised protocol by CDPR
12/07/10	Approval of Ongoing Research by IIRB (i.e., annual renewal)
12/13/10	Final HSRB Meeting Report
12/16/10	Submittal of revised materials to IRB
3/23/11	Protocol signed by Study Director
4/26/11	Start of phase 1 recruiting, calling employers to determine Qualified Employers from initial list of growers and commercial application companies
5/16/11	Start of phase 2 recruiting, calls to Qualified Employers
6/21/11	Approval of Amendment 1 by IIRB
7/05/11	Approval of Amendment 2 by IIRB.
7/06/11	Start of phase 3 recruiting, calls to Potentially Eligible Employers, site visits, and participant selection
8/02/11	Collection of M1
10/11/11	Approval of Amendment 3 by IIRB.
10/20/11	Collection of M2
11/05/11	Collection of M3 with field fortifications
3/20/12	Approval of Amendment 4 by IIRB.
5/14/12	Collection of M4
5/17/12	Collection of M5
5/31/12	Approval of Amendment 5 by IIRB.
6/12/12	Approval of Amendment 6 by IIRB.
6/12/12	Approval of Informed Consent, version 07-Jun-2012, by IIRB
6/12/12	IIRB accepted Problems in Research Reporting Form dated 07-Jun-2012. Subject: Analysis of samples from M1 and M2 showed higher than expected residues but not at a toxicological level of concern.
6/27/12	Approval of Amendment 7 by IIRB.
7/11/12	Collection of M6 with field fortifications used for MUs M6 and M7
7/12/12	Collection of M7
7/12/12	Collection of M8
7/13/12	Collection of M9
10/09/12	Approval of Amendment 8 by IIRB.
10/10/12	Approval of English Informed Consent, version 10/1/12 by IIRB
10/24/12	Notice of change in IRB name from Independent IRB (IIRB) to Schulman

	Associates IRB (SAIRB)
1/16/13	Collection of M10 with field fortifications
3/26/13	Approval of Amendment 9 by SAIRB
3/28/13	Collection of M11 with field fortifications
8/6/13	Collection of M12 with field fortifications
9/20/13	Approval of Amendment 10 by SAIRB
12/05/13	Approval of Amendment 11 by SAIRB.
4/15/14	Approval of Amendment 12 by SAIRB.
6/18/14	Collection of M13 with field fortifications
7/16/14	Collection of M14 with field fortifications
7/30/14	Collection of M15 with field fortifications
7/30/14	Collection of M16. Monitoring shut down due to equipment failure.
8/04/14	Approval of Amendment 13 by SAIRB.
8/05/14	Collection of M17
8/06/14	Collection of M18 with field fortifications
8/20/14	Collection of M19
9/03/14	Collection of M20
11/05/14	Collection of M21 with field fortifications used for MUs M21 and M22
11/07/14	Collection of M22
11/19/14	Collection of M23
11/20/14	Collection of M24 with field fortifications used for MUs M23, M24, and M25
11/25/14	Collection of M25
6/19/15	Approval of Amendment 14 by SAIRB.
6/19/15	Approval of Amendment 15 by SAIRB.

Attachment 2

Surrogate Active Ingredients Used in AHE120

Three of the four surrogate active ingredients listed in the protocol were used for mixing/loading WSPs during the study. The following list identifies how often each of the protocol-specified surrogates was used. This is an excerpt from page 46 of Study AHE120.

Surrogate	Number of MUs Using Surrogate	Product Name	EPA Reg. No.
Acephate	1	Acephate 90 WSP	34704-862
Imidacloprid	6	Malice 75 WSP	34704-1009
	1	Merit 75 WSP	432-1318
Thiophanate-methyl	3	Nufarm T-Methyl 70 WSB	228-655
	5	Topsin M WSB	73545-16-70506

Total MUs 16

Attachment 3 – Summary of Worker Information by Monitoring Area

Excerpt from Study AHE120 – Pages 67-70

Table 3. Worker Information for MUs

Monitoring Area 122: Florida				
MU	**M3**	**M10**	**M21**	**M22**
Employer ID [1]	20882	22269	22294	23294
Worker ID	122-1	122-6	122-11	122-12
Task	Mixer/Loader	Mixer/Loader	Mixer/Loader	Mixer/Loader
Age	38	26	58	31
Height (in.)	72	66	71	72
Weight (lb.)	298	165	232	190
Gender	Male	Male	Male	Male
Employment	Farm Manager	Farm Employee	Farm Employee	Commercial Applicator
Years of Experience	15	5	24	10
Date Monitored	11/5/2011	1/16/2013	11/15/2014	11/7/2014
Country	USA	USA	USA	USA
State	FL	FL	FL	FL
County	Hillsborough	Palm Beach	Manatee	Manatee
Nearest Town	Thonotosassa	Boca Raton	Bradenton	Sebring

[1] Corresponds to the Respondent Identification number (RespID) used by AHETF recruiters.

Table 3. Worker Information for MUs (Cont.)

Monitoring Area 123: Louisiana			
MU	**M12**	**M15**	**M18**
Employer ID [1]	30512	35941	90008
Worker ID	123-1	123-4	123-5
Task	Mixer/Loader	Mixer/Loader	Mixer/Loader
Age	62	62	22
Height (in.)	69	71	71
Weight (lb.)	184.3	235	198.2
Gender	Male	Male	Male
Employment	Farm Employee	Owner-Operator	Farm Employee
Years of Experience	39	~50	7
Date Monitored	8/6/2013	7/30/2014	8/6/2014
Country	USA	USA	USA
State	LA	MS	LA
County	Morehouse Parish	Tunica	Franklin Parish
Nearest Town	Bastrop	Dundee	Gilbert

[1] Corresponds to the Respondent Identification number (RespID) used by AHETF recruiters.

Table 3. Worker Information for MUs (Cont.)

Monitoring Area 124: North Dakota				
MU	**M6**	**M7**	**M14**	**M20**
Employer ID [1]	51525	51943	50188	76804
Worker ID	124-1	124-2	124-4	124-7
Task	Mixer/Loader	Mixer/Loader	Mixer/Loader	Mixer/Loader
Age	52	71	23	19
Height (in.)	73	70	73	71
Weight (lb.)	222.5	240	210.2	213
Gender	Male	Male	Male	Male
Employment	Owner-Operator	Owner-Operator	Farm Employee	Farm Employee
Years of Experience	2	7	7	3
Date Monitored	7/11/2012	7/12/2012	7/16/2014	9/3/2014
Country	USA	USA	USA	USA
State	ND	ND	ND	MN
County	Ward	Renville	Bottineau	Swift
Nearest Town	Donnybrook	Tolley	Bottineau	Appleton

[1] Corresponds to the Respondent Identification number (RespID) used by AHETF recruiters.

Table 3. Worker Information for MUs (Cont.)

Monitoring Area 125: California					
MU	**M11**	**M13**	**M23**	**M24**	**M25**
Employer ID [1]	10113	10886	90503	90501	90504
Worker ID	125-1	125-2	125-3	125-4	125-5
Task	Mixer/ Loader	Mixer/ Loader	Mixer/ Loader	Mixer/ Loader	Mixer/ Loader
Age	52	68	26	48	18
Height (in.)	71	75	74	74	62
Weight (lb.)	245.6	220.2	170.1	223.0	165.1
Gender	Male	Male	Male	Male	Male
Employment	Owner-Operato	Owner-Operato	Farm Employee	Owner-Operato	Farm employe
Years of Experience	4	40+	~8	30	1
Date Monitored	3/28/2013	6/18/2014	11/19/2014	11/20/2014	11/25/2014
Country	USA	USA	USA	USA	USA
State	CA	CA	CA	CA	CA
County	Fresno	Fresno	Fresno	Fresno	Fresno
Nearest Town	Firebaugh	Kingsburg	Sanger	Reedley	Fresno

1 Corresponds to the Respondent Identification number (Resp ID) used by AHETF recruiters.

Attachment 4:
Ethics Comments from October 2010 HSRB Meeting & AHETF Actions

EPA Comments on AHE120 Protocol	AHETF Actions to Address Comments
Before the research is conducted, the protocol should be revised as follows and resubmitted for review by the approving IRB: • The Local Site Coordinator (LSC), the Principal Field Investigator, the Analytical Facility, and the Principal Analytical Investigator must be identified in the protocol.	As suggested, the protocol reviewed and approved by the IRB identifies the Principal Field Investigator, the Analytical Facility, and the Principal Analytical Investigator(s). Since the implementation of the final rule on protecting human subjects, AHETF has not used an LSC for any study, including AHE120.
In addition, in future AHETF protocols please incorporate the following information into the protocol or an SOP: • Information about how subjects are presented with individual exposure information.	Section 17 of the protocol states that "Individual results requested by subjects will be communicated in accordance with SOP AHETF-11J." Section 4.1 of SOP AHETF-11.J.4 states the following: "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."
In addition, in future AHETF protocols please incorporate the following information into the protocol or an SOP: • An explanation of the process that the AHETF follows to improve and verify the accuracy of the Spanish translations.	In December, 2010, the Task Force made the following request of the overseeing IRB, as documented on page 29 of the IRB correspondence provided to the HSRB: "As with our most recent submission to IIRB, AHETF would like Americo Gomez to certify our Spanish translations. Since AHETF spent significant time contacting Spanish-speaking pesticide handling trainers across the US to get input on the most appropriate terminology, we prefer this approach rather than having Americo do the entire translations. After the English versions are approved by the IIRB, we will submit new Spanish translations for certification."

EPA Comments on AHE120 Protocol	AHETF Actions to Address Comments
	AHETF hired a Spanish-fluent senior scientist, Vicky Standart, who translates into Spanish all consent forms and other written material requiring translation. Vicky Standart has been the AHETF Spanish expert since the AHETF was formed, first as a member representative and later as a consultant. AHETF submits her work to the IRB, who requests that a certified translator review it. One of the independent translators used by the IRB is Americo Gomez, Independent Translator, 435 NE 23rd Street. Suite 204, Miami, FL 33137-4902. He sometimes requests changes which the task force incorporates. The IRB's independent translator attaches, as appropriate, a Letter of Accuracy that indicates the Spanish translation is an accurate representation of the document provided in English. This is submitted along with each of the translator's reviews submitted to the IRB. The Spanish translation always follows the approved English version. AHETF also prepared a Document Translation Review Project report that documents the efforts AHETF took to ensure that Spanish translations were accurate and appropriate.
Several members noted that exposure to the surrogate chemicals is no longer listed as a potential risk to study participants in either the protocol or in the informed consent documents. Study volunteers, it was argued, are likely to handle these chemicals as part of their daily activities and the possibility of exposure is thus a risk of employment and not a risk of study participation. However, because of the nature of the study (including scripted handling of specific amounts of chemical), the Board felt that exposure to the surrogate chemicals was a potential risk of study participation and recommended that the sponsor explicitly list this risk in the protocol and informed consent	Section 2.3.5 of the protocol was revised to address the risk of exposure to surrogate chemicals. The informed consent form was also revised to discuss this risk. The rest of this response refers to the Institutional Review Board (IRB) correspondence shared with EPA and the HSRB, and focusses on the protocol revisions and/or other requests which the AHETF submitted to the Schulman IRB after the HSRB made the comment in the adjacent column. The submitted correspondence between AHETF and the IRB indicates that the following IRB meetings involved a discussion of AHETF requests: December 7, 2010; December 28, 2010; January 4, 2011; March 8, 2011; June 21, 2011; July 5, 2011; July 12, 2011; October 3, 2011; October 11, 2011; November 29, 2011; March 20, 2012; March 27, 2012; May 1, 2012; May 8, 2012; May 31, 2012; June 12, 2012; October 9, 2012; November 20, 2012; March 26, 2013; November 14, 2013; December 19, 2013; April 24, 2014; November 6, 2014; August 14, 2014; and November 20, 2014. The IRB did not include the minutes for the following meetings in its original correspondence package: January 4,

EPA Comments on AHE120 Protocol	AHETF Actions to Address Comments
documents. The Board raised concerns that the revised water-soluble packaging protocol was reviewed by IIRB, Inc. using an expedited procedure. Future protocol revisions that involve major changes like substitution of surrogate compounds and/or change in study site should be reviewed under full-board procedures and reflected properly in the IRB minutes.	2011; July 12, 2011; March 27, 2012; and May 8, 2012. The IRB provided these minutes and EPA forwarded them to the HSRB in a separate file. The IRB correspondence also indicates that protocol amendments #7, and 10 – 15 were approved by the IRB using an expedited process. The SAIRB website (http://www.sairb.com/) states that, "Schulman can provide expedited review services for elements of research involving no greater than minimal risk. The following items may be reviewed by expedited review: recruitment materials, study-related materials, translated materials, qualifying new protocol submissions and some amendments." The SAIRB website also states that: "Every study submitted to Schulman will be evaluated to determine if it qualifies for Minimal Risk Review, including studies that are not submitted using Schulman's Minimal Risk submission forms."
As noted above, the Board recommended that accidental exposure to the surrogate chemicals be listed in the protocol and that the informed consent form also list surrogate exposure as a potential risk of study participation.	Section 2.3.5 of the protocol and the revised consent form both address risk from the surrogate chemicals.
The protocol excludes participants who normally wear additional personal protective equipment (such as chemical-resistant clothing) that is not required by the chemical label and that might impact the objectives of the study. The Board recommended that this assessment be done in a non-directive way, so as not to encourage participants to wear less PPE than they would normally in order to participate in the study.	Regarding this topic, the eligibility criteria in the consent form includes, in part, the following language: "To be eligible to participate in this study 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." In AHETF's December 20, 2010 response to HSRB recommendations, AHETF states "AHETF will continue to ask potential study participants what they normally wear when handling pesticides so as not to direct potential participants to any particular answer."

EPA Comments on AHE120 Protocol	AHETF Actions to Address Comments
Study participants will undergo hand washes prior to eating anything, which will reduce their risk of accidental ingestion of the surrogate compounds. As many of the adults in the U.S. still smoke, however, the Board recommended that hand washes also occur before any smoking break to further reduce their risk of accidental pesticide ingestion.	The section of the consent form entitled "procedures on day of study" states, in part, that "hand washes will occur before you eat anything or smoke...". In the AHETF's December 20, 2010 response to HSRB recommendations, AHETF states, "The protocol was changed to specify that hand wash samples will be collected before smoking."
The informed consent document states that "you may refuse medical treatment unless you get sick from too much exposure to pesticides or from getting too hot, or if we believe you are too sick to make a rational decision about getting medical treatment" (Collier 2010b, emphasis added). It was unclear how this determination of rationality will be made. The protocol and informed consent document should be more explicit as to who will make this determination, and what criteria would be used.	The section of the consent form on "injury to participants" states in part that, "You may refuse medical treatment unless you get sick from too much exposure to pesticides or from getting hot, or if the medical professional decides you are too sick to make a rational decision about getting medical treatment." Sections 2.3.5 and 7.4 of the protocol address this same point, as does AHETF SOP 11.H.4 (entitled "Emergency Procedures for Human Subjects") which includes the following language on this topic: "The study participant (worker) may refuse medical treatment unless the medical professional decides the worker is not competent to make a decision about getting medical treatment. In order to refuse treatment, the participant must be able to do all the following: a) appreciate the situation and its consequences; b) understand the relevant information; c) reason about the treatment decision; and d) communicate a choice (see Appelbaum, P. S. Assessment of Patients' Competence to Consent to Treatment. N Engl J Med 2007; 357:1834-1840. November 1, 2007)."
The Board raised some concerns about how the Task Force plans to release individual exposure data to individual study participants who request this information. For example, the Board encouraged the sponsor to consider how this information might be provided to participants who do not speak	The consent form was revised to address this topic. The confidentiality section of the consent form refers to an optional form for the subject to request their personal study results. The same section of the consent form also states that, "You may ask the Study Director for a copy of your personal results for this study. You will need to provide your name and a mail or email address." Both actions are required. The participant will request their results during the Informed Consent process (i.e., box checked by SD or designee as recommended by HSRB) and will complete the

EPA Comments on AHE120 Protocol	AHETF Actions to Address Comments
English and/or are illiterate. The Board also recommended that the request for individual study results be included as a check box on the informed consent document. The HSRB will be establishing a small working group to develop some guidance for the Agency and sponsors regarding the release of individual exposure data to study participants.	Request for Personal Study Results form. The subject could request a translator and the consent form was provided in English or Spanish depending on the preference of the subject. Only one Spanish speaker participated in AHE120 but did not request results. In previous studies, the result letters were translated before being mailed.

Attachment 5
§ 26.1303 Checklist for Completeness of AHE120 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	
	§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 before submittal of completed study.
	§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 previously.
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		n/a	Subjects received personal exposure results.
(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 – Updated Summary of Employer Lists and Recruitment Information

FLORIDA – Excerpt from Page 44 of Scenario Monograph Report

Category and 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) 76
Total qualified workers linked to all the employers on the PEELs 266
Potentially Eligible Employers contacted by Study Director (direct discussion, voice message exchange, or e-mail exchange with employer) 40
Employers on the Eligible Employer Lists (EELs) 12
Total workers linked to all the employers on the EELs 66
Workers attending a recruitment meeting **AHETF response**: **12**
Workers attending a consent meeting 11
Workers signing a consent form 11
Workers who signed a consent form, but were not selected for monitoring 6
Workers withdrawing at their own request (after monitoring began) 0
Workers removed from participation by AHETF 0
Workers completing participation 5

LOUISIANA – Excerpt from page 48

Summary of Employer Lists and Recruitment Details for Area 123 in the Louisiana Monitoring Area

Category and Monitoring Area totals
Employers on the Employer Universe List (EUL) 2,284
Employers on the Master Employer Lists (MELs) 1,997
Employers on the Qualified Employer Lists (QELs) 88
Employers contacted from the QELs (direct discussion or voice message response from employer) 68
Employers on the Potentially Eligible Employer List (PEEL, i.e., passed suitability screening, including willingness to cooperate) 33
Total qualified workers linked to all the employers on the PEELs 68
Potentially Eligible Employers contacted by Study Director (direct discussion, voice message exchange, or e-mail exchange with employer) 19
Employers on the Eligible Employer Lists (EELs) 8
Total workers linked to all the employers on the EELs 16
Workers attending a recruitment meeting **AHETF response**: **6**

Workers attending a consent 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

Excerpt from page 52

4.2.3 North Dakota Recruiting Summary
Summary of Employer Lists and Recruitment Details for Area 124 in the North Dakota Monitoring Area

Category and Monitoring Area totals
Employers on the Employer Universe List (EUL) 64,928
Employers on the Master Employer Lists (MELs) 6,896
Employers on the Qualified Employer Lists (QELs) 128
Employers contacted from the QELs (direct discussion or voice message response from employer) 105
Employers on the Potentially Eligible Employer Lists (PEELs, i.e., passed suitability screening, including willingness to cooperate) 35
Total qualified workers linked to all the employers on the PEELs 71
Potentially Eligible Employers contacted by Study Director (direct discussion, voice message exchange, or e-mail exchange with employer) 17
Employers on the Eligible Employer Lists (EELs) 5
Total workers linked to all the employers on the EELs 11
Workers attending a recruitment meeting **AHETF response**: **7**
Workers attending a consent meeting 7
Workers signing a consent form 7
Workers who signed a consent form, but were not selected for monitoring 2
Workers withdrawing at their own request (after monitoring began) 0
Workers removed from participation by AHETF 0
Workers completing participation 5

Excerpt from page 56

4.2.4 California Recruiting Summary

Summary of Employer Lists and Recruitment Details for Monitoring Area 125 in the California Monitoring Area

Category and 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) 69
Total qualified workers linked to all the employers on the PEELs ' 208
Potentially Eligible Employers contacted by Study Director (direct discussion, voice message exchange, or e-mail exchange with employer) 34
Employers on the Eligible Employer Lists (EELs) 16
Total workers linked to all the employers on the EELs 31
Workers attending a recruitment meeting **AHETF response**: **5**
Workers attending a consent 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 7 – Note: Please see the end of this document for attachment 7, AHETF checklist.

Attachment 8 - Dates When Subjects Received Copy of Consent Form

MU	State	Date Consented	Date Rec'd Copy	Date of Study
M1	NY	7/29/11	7/29/11	8/2/11
M2	FL	10/10/11	10/10/11	10/20/11
M3	FL	10/11/11	11/5/11	11/5/11
M4	NY	5/14/12	5/14/12	5/14/12
M5	NY	5/11/12	5/17/12	5/17/12
M6	ND	7/10/12	7/11/12	7/11/12
M7	ND	7/9/12	7/12/12	7/12/12
M8	NY	7/11/12	7/12/12	7/12/12
M9	NY	7/12/12	7/12/12	7/13/12
M10 [a]	FL	1/15/13	1/22/13	1/16/13
M11	CA	3/20/13	3/25/13	3/28/13
M12	LA	8/5/13	8/6/13	8/6/13
M13	CA	6/17/14	6/18/14	6/18/14
M14	ND	7/9/14	7/10/14	7/16/14
M15	MS	7/24/14	7/24/14	7/30/14
M16	MS	7/30/14	7/30/14	7/30/14
M17	LA	7/23/14	7/23/14	8/5/14
M18	LA	7/28/14	7/28/14	8/6/14
M19	ND	8/6/14	8/15/14	8/20/14
M20	MN	8/28/14	8/28/14	9/3/14
M21	FL	10/29/14	10/29/14	11/5/14
M22	FL	11/7/14	11/7/14	11/7/14
M23	CA	11/17/14	11/18/14	11/19/14
M24	CA	11/18/14	11/18/14	11/20/14
M25	CA	11/24/14	11/24/14	11/25/14

[a] Note from AHETF: The MU did his work on 16 January and inadvertently did not receive a copy of the IC. The Spanish-fluent researcher contacted him by telephone the morning of 17 January to leave contact information, obtain his mailing address for the document, and assure that there were no adverse events as a consequence of participation in the study. On January 22, he again contacted the subject and made sure he had received the copy of the document. The subject indicated that he indeed had obtained the document.

Attachment 9

Workers' Outer Clothing and PPE Worn during Study AHE120

Table 4. Description of Worker Outer Clothing for MUs

MU	Long-Sleeve Shirt			Long Pants		
	Style	Material	Condition	Style	Material	Condition
Monitoring Area 122: Florida						
M3	Long sleeve pull over	Cotton knit	Good	Jeans	Cotton denim	Good
M10	Long sleeve knit pullover	Cotton	Good	Jeans	Cotton	Good
M21	Long sleeve button down with collar and button cuffs	Cotton	Good	Blue jeans	Cotton	Good
M22	Long sleeve polo shirt with no collar	Cotton	Good	Blue jeans	Cotton	Good
Monitoring Area 123: Louisiana						
M12	Long sleeve button up shirt	Cotton	Good	Jeans	Cotton	Good
M15	Long sleeve button up shirt with collar	Cotton	Good	Blue jeans	Cotton	Good
M18	Long sleeve button up shirt with collar	Polyester	Good	Work pants	Cotton / polyester	Good
Monitoring Area 124: North Dakota						
M6	Long sleeve shirt	100% cotton	Good	Jean type	100% cotton	Good
M7	Long sleeve button up shirt	Cotton	Good	Jeans	Cotton	Good

MU	Long-Sleeve Shirt			Long Pants		
	Style	Material	Condition	Style	Material	Condition
M14	Long sleeve crew neck t-shirt	Cotton	Good	Blue jeans	Cotton	Good [1]
M20	Long sleeve pull over without collar	Polyester / cotton	Good	Blue jeans	Denim	Good [2]
Monitoring Area 125: California						
M11	Long sleeve button up shirt	Cotton	Good	Jeans	Cotton	Good
M13	Long sleeve button up shirt	Cotton	Good	Blue jeans	Cotton	Good
M23	Long sleeve shirt	Cotton	Good	Blue jeans	Cotton	Good
M24	Long sleeve button up shirt	Cotton	Good	Blue jeans	Cotton	Good
M25	Flannel button up long sleeve shirt	Cotton	Good	Jeans	Cotton	Good

[1] Two holes were present on the workers pants: a quarter- size frayed area at the left front pocket with a dime-size hole, and a small vertical tear at the cuff area over the boot and sock. Both holes were considered by the Study Director to be WPS-compliant.

[2] Repaired an approximately ¾-inch slit at right outer knee with a small piece of duct tape.

Table 5. PPE (Personal Protective Equipment) and Additional Clothing or Items

MU	Clothing or PPE by Body Area for MUs						
	Head	Face/ Neck	Respirator	Hands (glove type)	Upper Body	Lower Body	Feet (shoes)
Monitoring Area 122: Florida							
M3	Baseball cap	Eye glasses	None	CR gloves	Longsleeve shirt	Long pants	Socks and leather boots
M10	None	Protective glasses	None	Rubber Sol-Vex 37-175	Longsleeve shirt	Long pants	Socks and leather boots
M21	Baseball cap	Sun glasses	None	Nitrile 15 mil	Longsleeve shirt	Long pants	Socks and leather boots
M22	None	Sun glasses [1] and goggles	None	Nitrile 15 mil	Long sleeve shirt	Long pants	Socks and leather boots
Monitoring Area 123: Louisiana							
M12	Baseball cap	None	None	Nitrile 15 mil	Long sleeve shirt	Long pants	Socks and leather boots
M15	None	Goggles	None	Nitrile 15 mil	Long sleeve shirt	Long pants	Socks and 14" high rubber boots
M18	Baseball cap	Eye/sun glasses	None	Nitrile 15 mil	Long sleeve shirt	Long pants	Socks and leather shoes
Monitoring Area 124: North Dakota							
M6	Baseball cap	Eye glasses	None	CR gloves (Best 727-11 Nitri-Solve)	Long sleeve shirt	Long pants	Socks and leather boots
M7	Wide brim hat [2]	Eye glasses	None	CR gloves, nitrile rubber, McMaster Car (727-10 MC)	Long sleeve shirt	Long pants	Socks and leather boots
M14	None	Sunglasses	None	Nitrile 15	Long	Long pants	Socks and

MU	Head	Face/ Neck	Respirator	Hands (glove type)	Upper Body	Lower Body	Feet (shoes)
		or goggles [3]		mil	sleeve shirt		leather boots
M20	None	None	None	Nitrile 15 mil	Long sleeve shirt	Long pants	Socks and leather boots
Monitoring Area 125: California							
M11	None	None	None	Nitrile 15 mil	Long sleeve	Long pants	Sock and sport
M13	Baseball cap	Goggles	None	Nitrile 15 mil	Long sleeve shirt	Long pants	Socks and leather boots
M23	Baseball cap	Goggles	None	Nitrile Sol-vex brand 12”	Long sleeve shirt	Long pants	Socks and leather boots
M24	None	Goggles	None	Nitrile Solvex brand 12”	Long sleeve shirt	Long pants	Socks and leather boots
M25	Baseball cap	Goggles	None	Solvex nitrile 15 mil	Long sleeve shirt	Long pants	Socks and leather boots

[1] Sunglasses not worn during mixing/loading events.

[2] Only worn during the last mixing/loading event.

[3] Goggles only when the worker handled the additional tank mix products.

Excerpt from Table 3 – Page 95 of Monograph Scenario Report AHE1014

Table 3. PPE (Personal Protective Equipment) and Additional Clothing or Items Worn by Workers

Monitoring Area	MU ID	Head	Face/Neck	Hands (glove type)
Site 122 Florida (FL)	M3	Baseball cap	Eye glasses	CR gloves
	M10	---	Protective glasses	Rubber
	M21	Baseball cap	Sunglasses [1] & goggles	Nitrile
	M22	---	Sunglasses [1] & goggles	Nitrile
Site 123 Louisiana (LA)	M12	Baseball cap	---	Nitrile
	M15	---	Goggles	Nitrile
	M18	Baseball cap	Eye/sun glasses	Nitrile
Site 124 North Dakota (ND)	M6	Baseball cap [2]	Eye glasses	CR gloves
	M7	Wide brim hat	Eye glasses	Nitrile
	M14	---	Sunglasses or goggles [3]	Nitrile
	M20	---	---	Nitrile
Site 125 California (CA)	M11	---	---	Nitrile
	M13	Baseball cap	Goggles	Nitrile
	M23	Baseball cap	Goggles	Nitrile
	M24	---	Goggles	Nitrile
	M25	Baseball cap	Goggles	Nitrile

Attachment 10 - Assigned observers for each MU for AHE120

AHETF provided the following chart in response to a request from EPA.

"AHE120 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--LPN	SDD-1
7	CRO--LPN	SDD-1
8	CRO--First Responder	SD
9	CRO--First Responder	SD
10	CRO--First Responder	SD
11	CRO--First Responder	SDD-1
12	CRO--First Responder	SDD-2
13	CRO--First Responder	SDD-2
14	CRO	SD
15	CRO--First Responder	SDD-2
16	CRO--First Responder	SDD-2
17	CRO--First Responder	SD
18	CRO--First Responder	SD
19	CRO--LPN	SD
20	CRO--LPN	SD
21	CRO--First Responder	SD
22	CRO--First Responder	SD
23	CRO--First Responder	SDD-2
24	CRO--First Responder	SDD-2
25	CRO--First Responder	SDD-1

CRO = Contract Research Organization Researcher
SD = AHE120 Study Director
SDD-1 = AHETF Study Director on other exposure studies
SDD-2 = Qualified Study Director Designee"

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 11

APPROVED INCLUSION CRITERIA FOR STUDY PARTICIPATION in AHE120

Note: This is the approved inclusion criteria from SOP 11.B.7 with AHE120 revisions incorporated into criterion "a." The IRB approved the revisions prior to implementation as part of AHE120 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. By discussion with the volunteer, the Study director will determine if the previous experience with other formulations or WSPs is sufficient.
b. Handle pesticides as part of their job.
c. 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.
d. 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.
e. Confirm they do not work for a pesticide company (that is, a manufacturer or pesticide registrant or a contractor of the AHETF.
f. 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).
g. Not be pregnant or nursing (See SOP AHETF-11.D).
h. 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.
i. Have a private meeting with a researcher to review and discuss the consent form.
j. Understand English or Spanish (see SOP AHETF-11.I for detailed discussion of this topic).
k. Understand and sign the consent form, and if in California, the California Experimental Research Subject's Bill of Rights.

Attachment 12 - Summary of Excluded MU Work Practices

The excluded work practices of the nine MUs and the reasons for nonconformance are excerpted from the study and summarized below:

MU ID	State	Date Collected	Reason for Excluded Work Practice as Identified in Study
M1	FL	8/2/11	Basket in tank opening. Overhead water recirculation. Water directed onto WSPs.
M2	NY	10/20/11	Basket in tank opening. Overhead water recirculation. Water directed onto WSPs.
M4	NY	5/14/12	Basket in tank opening. Overhead water recirculation. Water directed onto WSPs.
M5	NY	5/17/12	Basket in tank opening. Water directed onto WSPs.
M8	NY	7/12/12	Water directed onto WSPs.
M9	NY	7/13/15	Water directed onto WSPs.
M16	MS	7/30/14	Loaded WSPs after other product(s)--poor dissolution--nozzle clogging
M17	LA	8/5/14	WSPs broken before being loaded. Manufacturing issue.
M19	ND	8/20/14	WSPs broken before being loaded. Rough handling of boxes in the field.

Please note: Additional information on each of these MUs is included in Appendix G on pages 8-9.

Attachment 13 – Information provided by AHETF on Experience of MUs M1, 2, 4, 5, 8, 9

WSP Experience

1. MU 1 10 years
2. MU 2 10 years of experience loading any product, per protocol amendment. WSP loading experience was unknown but likely.
3. MU 4 35 years
4. MU 5 15 years
5. MU 8 12 years
6. MU 9 20 years

Attachment 14 – Revised procedures for proper use of water soluble packets

Note: This is an excerpt from page 99 of Appendix G to study AHE120.

Best Practice Mixing/loading Instructions for WSPs:

- Do not handle cartons or packages of WSPs roughly.
- Remove any basket/strainer from the tank hatch.
- Fill tank to approximately one-third to one-half of the desired final volume of spray.
- Stop adding water and any agitation.
- Add WSPs to the surface of the water in the tank.
- Start mechanical and recirculation agitation from the bottom of tank without using any overhead recirculation.
    - If overhead recirculation cannot be turned off, close the hatch before starting agitation.
    - Do not direct water from a hose or fill pipe to break the bags.

- Dissolving the WSPs may take up to 5 minutes or longer, depending on water temperature, hardness and intensity of agitation. Check periodically, avoiding any dusts or recirculating spray mix.
- When the bags have fully dissolved and the powder has gone into suspension in the water, other products may be added.
- Resume filling the tank with water to the desired level.
- Maintain agitation while filling and driving/flying to the spray site and during application.
- Follow all other label instructions regarding the handling of WSPs.

Attachment 15 – Protocol Amendments – Pages 11 – 12 of Study AHE120

Amendment 1:

- Assigned Dr. Baugher as Study Director and identified Mr. Lange as a Principal Field Investigator (PFI).

Amendment 2:

- Eliminated the requirement for the participant to have experience loading WSPs within a year of participation. Any open pour mixing / loading experience within a year of participation is acceptable.
- Allowed for less efficient collection of MU samples without impacting the study design. Multi-MU efficient configurations were allowed by protocol for economic reasons but were not required by the statistical design.
- Identified a new Principal Analytical Investigator (PAI) and analytical facility.
- Allowed the use of the manufacturer's certification of the active ingredient concentration when a GLP-sourced reference substance is not readily available.

Amendment 3:

- Removed the requirement for the participant to have experience loading the particular equipment to be used in the study.

Amendment 4:

- Expanded the list of Principal Field Investigators to allow scheduling flexibility.
- Expanded the monitoring areas to include the entire state.
- Included the process for getting names of qualified employers from local agricultural specialists, referred to as primary sources.
- Allowed commercial application companies (in addition to just growers) to provide secondary sources of qualified names, if needed.
- Combined certain lists of employers for this study and a similar study, AHE80, involved with open pour mixing / loading of wettable powder (WP) products. This is consistent with past practice, now formalized in this amendment.
- Changed references of ‘grower’ and ‘growers’ to ‘employer’ and ‘employers’ since recruiting now may include commercial application companies.

Amendment 5:

- Replaced the PAI for Ricerca Biosciences.

Amendment 6:

- Disallowed the use of suspended baskets inside tank openings that prevent the WSPs from going directly into standing water in the tank. AHETF identified the use of suspended baskets as an unanticipated cause of higher exposure. The AHETF does not want to include the use of baskets as part of the definition for the WSP mixer/loader scenario.

Amendment 7:

- Allowed participants to handle more than 400 lb AI of thiophanate-methyl (TPM), which was previously the highest amount that could be handled in a day for this study. Only the highest strata for TPM was changed.

Amendment 8:

- Provided specific mixing instructions for the use of WSP to address the use of overhead addition of water, filling order, and the use of baskets.

Amendment 9:

- Added or changed contact information for PFI and PAI
- Discontinued reviewing the Material Safety Data Sheets. The brand of product or qualified active ingredient may change between the informed consent process and monitoring. Reviewing the label on the day of monitoring is a standard practice.
- Expanded the Louisiana monitoring area to the Mississippi counties of Hinds County, north to the Tennessee border (DeSoto and Marshall Counties), east to Webster and Calhoun Counties, and west to the Mississippi River.

Amendment 10:

- Replaced the PAI for Morse Laboratories.

Amendment 11:

- Identified a new PAI. Morse Laboratories LLC was purchased by ABC Laboratories and the essential equipment and personnel were relocated to ABC Laboratories in Columbia, Missouri during November 2013.

Amendment 12:

- Allowed the use of the Wet Bulb Globe Temperature approach, which follows established academic, government, military, and industry occupational health management practices that allow work in warm environments while better protecting the health and safety of the worker

Amendment 13:

- Modified the WSP mixing / loading instructions to reflect best practice techniques over a wide range of equipment and loading configurations.

Amendment 14:

- Change the company name, email address, and phone number for the study quality assurance (QA) personnel and add an additional QA contact.
- Replaced the PAI for JRF America and Jai Research Foundation.

Amendment 15:

- Replaced the PAI for ABC Laboratories.

Attachment 16 – Example of Compilation of QEL

Excerpt from study AHE120 – Page 29. The compilation of the QEL per monitoring area can be found on pages 29, 33, 37 and 41 of AHE120.

In summary, the Qualified Employer List for the Florida monitoring area was compiled as follows:

2011:
Farm Market ID (used a subset of 107) 4,960
Meister Media Worldwide (used a subset of 1,499) 4,000
Sod growers via internet search 77
Less grower duplicates 31

2012:
Meister Media Worldwide (used remaining 2,501 growers from 2011) 0

2014:
Meister Media Worldwide (used a subset of 1,868) 2,932
Sod growers via internet search 52
National Agricultural Aviation Association (NAAA) 27
Commercial applicators, Florida Dept. of Ag custom applicator list 442
Less duplicates 307

Employer Universe List 12,152

Less: 2011 Farm Market ID Growers not used 4,853
2012 Growers with missing phone numbers 1,045
2012 Growers with missing phone numbers found but duplicate 14
2014 Meister Media growers without phone not used 1,064

Master Employer List 5,176

Less: Not contacted (no answer, disconnected, etc.) 3,041
Refusal to talk to interviewer 1,089
Not qualified (does not use water soluble packages or wettable powders) 690
Total number of respondents completing survey 356
Respondents not wanting to be further contacted 1

Qualified Employer List 355

Attachment 7 – 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.