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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

*January 7, 2010*

**MEMORANDUM**

**SUBJECT:** Ethics Review of Completed AHETF Closed Cab Airblast Scenario Worker Exposure Monitoring Study

**FROM:** Kelly Sherman
Human Research Ethics Review Officer
Office of Pesticide Programs

**TO:** Steve Knizner, Associate Director
Health Effects Division

**REF:** Smith, Larry D. (2010) Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment in Florida Citrus. Study Number AHE55. 377 p. (MRID 48289601) **[Volume 1]**

Smith, Larry D. (2010) IIRB Correspondence Report for Cluster Report AHE55. 287 p. (MRID 48303503) **[Volume 2]**

Smith, Larry D. (2010) Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment in Georgia Pecans. Study Number AHE56. 379 p. (MRID 48289602) **[Volume 3]**

Smith, Larry D. (2010) IIRB Correspondence Report for Cluster Report AHE56. 295 p. (MRID 48303504) **[Volume 4]**

Smith, Larry D. (2010) Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment in Michigan Stone Fruit. Study Number AHE57. 377 p. (MRID 48303501) **[Volume 5]**

Smith, Larry D. (2010) IIRB Correspondence Report for Cluster Report AHE57. 172 p. (MRID 48289608) **[Volume 6]**

Bruce, Eric D. (2010) Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment in California Trellis Crops. Study Number AHE58. 282 p. (MRID 48289604) **[Volume 7]**

Bruce, Eric D. (2010) IIRB Correspondence Report for Cluster Report AHE58. 357 p. (MRID 48289609) **[Volume 8]**

Bruce, Eric D. (2010) Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Closed Cab Equipment in Washington Pome Fruit. Study Number AHE59. 220 p. (MRID 48303502) **[Volume 9]**

Bruce, Eric D. (2010) IIRB Correspondence Report for Cluster Report AHE59. 195 p. (MRID 48289610) **[Volume 10]**

I have reviewed the available information concerning the ethical conduct of the research reported in the referenced documents, which describe the execution and results of a series of five field studies in which dermal and inhalation exposure of professional pesticide applicators was monitored as they applied liquid pesticides to orchard and trellis crops using an airblast sprayer drawn by a vehicle with an enclosed cab. If these studies are determined to be scientifically acceptable, I find no barrier in regulation to EPA's reliance on them in actions under FIFRA or FFDCA.

## 1.0 Background and Ethics-related Chronology

Five separate field studies were conducted, each monitoring workers while they sprayed tree or trellis crops in five different states in the U.S where closed cab airblast equipment is commonly used in production agriculture. The studies are summarized in Table 1.

**Table 1. Study Summary**

| Study ID | State | Crop | Number of Monitored Workers | Gender | Ages |
|---|---|---|---|---|---|
| AHE55 | FL | Orange, Tangerine | 5 | All male | 20-70 |
| AHE56 | GA | Pecan | 5 | All male | 43-68 |
| AHE57 | MI | Cherry | 5 | 4 males, 1 female | 21-58 |
| AHE58 | CA | Grape | 5 | All male | 27-49 |
| AHE59 | WA | Apple | 4 | All male | 26-62 |

The background and ethics-related chronology for each field study is summarized below.



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## 1.1 AHE55

The scenario design and protocol for AHE55 were approved by the overseeing IRB, the Independent Investigational Review Board, Inc. (IIRB), of Plantation, Florida, in March 2008 and submitted to EPA for review in April 2008. The protocol and EPA's review dated May 27, 2008 were discussed by the Human Studies Review Board (HSRB) at its June 2008 meeting. The HSRB review was generally favorable, and the Board's November 14, 2008 final report of the June 2008 meeting concluded, with respect to ethics, that "with a number of required revisions, [the protocols] appear likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L."

Following the HSRB review, the protocol, consent form, and recruiting materials for AHE55 were revised to address EPA and HSRB comments. The revised protocol was submitted to IIRB on July 18, 2008, and approved on July 21, 2008. There are no other amendments to the protocol documented in the IIRB correspondence volume for AHE55 (Vol 2).

Subject monitoring for AHE55 took place in late October 2008. Five male subjects between the ages of 20 and 70 were monitored for dermal and inhalation exposure while applying pesticide sprays using closed-cab airblast equipment to orange and tangerine crops in Florida. There was one reported deviation during the field phase of the research, and there were no reported deviations during the analytical phase. I noted 4 unreported deviations.

A detailed chronology of the ethics-related study activities for AHE55 is provided in Table A in Attachment 1. A summary of amendments and reported and unreported deviations from all studies is provided in Table 2, on page 18.

## 1.2 AHE56

The scenario design and protocol for AHE56 was approved by IIRB in March 2008 and submitted to EPA for review in April 2008. The protocol and EPA's review dated May 27, 2008 were discussed by the Human Studies Review Board (HSRB) at its June 2008 meeting. The HSRB review was generally favorable, and the Board's November 14, 2008 final report of the June 2008 meeting concluded, with respect to ethics, that "with a number of required revisions, [this protocol appears] likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L."

Following the HSRB review, the protocol, consent form, and recruiting materials for AHE56 were revised to address EPA and HSRB comments. The revised protocol was submitted to IIRB on July 18, 2008, and approved on July 21, 2008. There are no other amendments to the protocol documented in the IIRB correspondence volume for AHE56 (Vol 4).

Subject monitoring for AHE56 took place in August 2008. Five male subjects between the ages of 43 and 68 were monitored while applying pesticide sprays using closed-cab airblast equipment to pecans in Georgia. There were five reported deviations during the field phase of the research, and three reported deviations during the analytical phase. I noted one unreported deviation. EPA presented preliminary recruiting results from AHE56 at the October 2008 HSRB meeting.

A detailed chronology of the ethics-related study activities for AHE56 is provided in Table B in Attachment 1. A summary of amendments and reported and unreported deviations from all studies is provided in Table 2, on page 18.

### 1.3 AHE57

The scenario design and protocol for AHE57 was approved by IIRB and submitted to EPA for review in August 2008. The protocol and EPA's review dated September 23, 2008 were discussed by the HSRB at its October 2008 meeting. The HSRB review was generally favorable; the Board's December 30, 2008 final report of the October 2008 meeting concluded, with respect to ethics, that "if revised as suggested by the Board, the research described in these three protocols is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L."

Following the HSRB review, the protocol, consent forms, and recruiting materials for AHE57 were revised to address EPA and HSRB comments. The revised protocols, consent forms, and recruiting materials for AHE57 were submitted to IIRB on January 16, 2009, and approved on January 19, 2009. There are no other amendments to the protocol documented in the IIRB correspondence volume for AHE57 (Vol 6).

Subject monitoring for AHE57 took place in May 2009. Four male subjects and one female subject between the ages of 21 and 58 were monitored while applying pesticide sprays using closed-cab airblast equipment to cherries in Michigan. There was one reported deviation during the field phase of the research and four reported deviations during the analytical phase. I noted two unreported deviations.

After monitoring, an amendment to the purity analysis section of the protocol (Section 7.5.3) was submitted to IIRB. This Amendment was not acknowledged by IIRB until after the study was closed, but IIRB concluded that the amendment was "administrative in nature, did not affect subject safety, and would not have received a revision to the consent form."

A detailed chronology of the ethics-related study activities for AHE57 is provided in Table C in Attachment 1. A summary of amendments and reported and unreported deviations from all studies is provided in Table 2, on page 18.



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### 1.4 AHE58

The scenario design and protocol for AHE58 was approved by IIRB and submitted to EPA for review in August 2008. The protocol and EPA's review dated September 23, 2008 were discussed by the HSRB at its October 2008 meeting. The HSRB review was generally favorable; the Board's December 30, 2008 final report of the October 2008 meeting concluded, with respect to ethics, that "if revised as suggested by the Board, the research described in these three protocols is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L."

Following the HSRB review, the protocol, consent forms, and recruiting materials for AHE58 were revised to address comments from EPA, HSRB, and the California Department of Pesticide Regulation. The revised protocol, consent form, and recruiting materials for AHE58 were submitted to IIRB on March 26, 2009, and approved on April 1 and April 6, 2009. Two subsequent amendments were approved by IIRB in June and July 2009.

Subject monitoring for AHE58 took place in June and July 2009. Five male subjects between the ages of 27 and 49 were monitored while applying pesticide sprays using closed-cab airblast equipment to grapes in California. There were four reported deviations in the field phase of the study, and one reported deviation in the analytical phase. I noted three unreported deviations.

A detailed chronology of the ethics-related study activities for AHE58 is provided in Table D in Attachment 1. A summary of amendments and reported and unreported deviations from all studies is provided in Table 2, on page 18.

### 1.5 AHE59

The scenario design and protocol for AHE59 was approved by IIRB and submitted to EPA for review in August 2008. The protocol and EPA's review dated September 23, 2008 were reviewed by the HSRB at its October 2008 meeting. The HSRB review was generally favorable; the Board's December 30, 2008 final report of the October 2008 meeting concluded, with respect to ethics, that "if revised as suggested by the Board, the research described in these three protocols is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L."

Following the HSRB review, the protocol, consent forms, and recruiting materials for AHE59 were revised to address EPA and HSRB. The revised protocol, consent form, and recruiting materials for AHE59 were submitted to IIRB on January 16, 2009, and approved on January 19, 2009. There was one additional amendment in May 2009 to add two additional carbaryl products to the list of approved test substances.

Subject monitoring for AHE59 took place in late April and early May 2009. Four male subjects between the ages of 26 and 62 were monitored while applying pesticide

sprays to apple crops in Washington using closed-cab airblast equipment. A fifth subject was not monitored because of a series of logistical difficulties.[1]

There were two reported field phase deviations, and one reported analytical phase deviation. I noted three unreported deviations.

A detailed chronology of the ethics-related study activities for AHE59 is provided in Table E in Attachment 1. A summary of amendments and reported and unreported deviations from all studies is provided in Table 2, on page 18.

## 2.0 Completeness of Submission:

The checklist used by EPA to verify satisfaction of the requirements of §26.1303 as they apply to the report of this research appears as Attachment 1 to this review. This review considers the 10 study volumes identified on pages 1-2, plus Supplement 1 related to AHE57.

## 3.0 Protocol Amendments:

### 3.1 AHE55

Following EPA's and HSRB's reviews, the protocol, consent form, and recruiting materials were revised to address EPA and HSRB comments. The revised materials were submitted to IIRB on July 18, 2008, and approved on July 21, 2008. No further amendments are documented in the IIRB Correspondence Report (Volume 2). The study report (Volume 1) indicates that the protocol was amended three times prior to execution of the field phase, but the report does not summarize these changes. The discrepancy in the reporting of amendments between Volume 1 and Volume 2 is not resolved or explained elsewhere in the AHETF's submission.

### 3.2 AHE56

Following EPA's and HSRB's reviews, the protocol, consent form, and recruiting materials were revised to address EPA and HSRB comments. The revised materials were submitted to IIRB on July 18, 2008, and approved on July 21, 2008. No further amendments are documented in the IIRB Correspondence Report (Volume 2). The study

[1] One subject was enrolled and signed the consent form, but he was not ultimately monitored because a research team was not available on the day that he needed to make his application. Researchers attempted to enroll and monitor an alternate grower, but that grower's air conditioned closed cab tractor was not functioning on the day that the application needed to take place, so the grower applied the pesticide with an open cab tractor and the research did not take place. The timing of carbaryl apple-thinning application is dependent on crop growth state and weather, and as a result, the applications could not be pre-scheduled; researchers needed to be available when the grower intended to make an application. Several attempts were made to find a fifth subject by re-contacting the other Potentially Eligible Growers, but none was found before the use season ended.



US EPA ARCHIVE DOCUMENT

report (Volume 1) indicates that the protocol was amended two times prior to execution of the field phase, but the report does not summarize these changes. The discrepancy in the reporting of amendments between Volume 3 and Volume 4 is not resolved or explained elsewhere in the AHETF's submission.

### 3.3 AHE57

Following EPA's and HSRB's reviews, the protocol, consent form, and recruiting materials were revised to address EPA and HSRB comments. The revised materials were submitted to IIRB on January 16, 2009, and approved on January 19, 2009.

In June 2009, the AHETF submitted to IIRB an amendment to the purity analysis section of the protocol (Section 7.5.3). The IIRB Correspondence Report (Volume 6) shows that the amendment was emailed to IIRB on June 7, 2009. In September 2010, after the study was closed, AHETF realized that it did not have documentation of IIRB's approval of the amendment, and requested copies of IIRB's records on the amendment. AHETF was informed at that time that IIRB did not have a record of the amendment. On September 14, 2010, IIRB acknowledged receipt of the amendment, and noted that the amendment was "administrative in nature, did not affect subject safety, and would not have received a revision to the consent form." In EPA's view, this amendment did not affect subject safety or subject autonomy, and therefore the documentation issues are not important in evaluating the ethical conduct of this research.

There is agreement between the study report (Volume 5) and IIRB Correspondence Report (Volume 6) that there were two amendments to AHE57 prior to execution of the field phase of the research.

### 3.4 AHE58

Following EPA's and HSRB's reviews, the protocol, consent forms, and recruiting materials were revised to address EPA, HSRB, and California Department of Pesticide Regulation comments. The revised protocol, consent form, and recruiting materials for AHE58 were submitted to IIRB on March 26, 2009, and approved on April 1 and April 6, 2009.

In early June 2009, the AHETF consulted EPA about three changes to the AHE58 protocol, and EPA ultimately approved the changes. On June 19, 2009, the AHETF submitted to IIRB an amendment encompassing the three changes, and IIRB approved the amendment on June 23, 2009. Each of the three changes is discussed below.

1) The first change was to amend the inclusion criteria to allow participation by individuals who normally wear two layers of clothing (the inclusion criteria previously stated that only workers who normally wear one layer of clothing would be eligible to participate). The change was in response to a discovery by the AHETF that many airblast applicators in Fresno County normally wear two layers of clothing (for example, a typical shirt and pants under a cloth



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coverall). To accommodate these workers and increase the pool of potentially eligible workers, the AHETF sought to amend the inclusion criteria. EPA approved the change provided that the workers who normally wear two layers agree to substitute their normally-worn inner layer of clothing for the long underwear dosimeter provided by the AHETF. The change was acceptable to EPA from an ethics perspective because it neither requires participants to wear less clothing than they normally would, nor results in subjects wearing a third layer of clothing, which could increase risks of heat-related illness.

2) The second change was to expand the permissible recruitment area to any county in California or Washington if the county previously specified in the protocol (Fresno County, California) does not provide a sufficient number of eligible growers. The change appeared to be necessary because many potential subjects might not be eligible to participate because they normally wear Tyvek coveralls, or because their Pest Control Advisor, winery, or raisin packer might not approve the use of either of the two surrogate compounds.

3) The third change was to remove the efficient configuration requirement if the recruitment area is expanded.

On July 22, 2009, the AHETF submitted an additional amendment to IIRB to add to the list of approved test substances a malathion end-use product preferred by some growers. IIRB approved the amendment on July 22, 2009.

There is agreement between the study report (Volume 7) and IIRB Correspondence Report (Volume 8) for AHE58 that there were three amendments to AHE58.

### 3.5 AHE59

Following EPA's and HSRB's reviews, the protocol, consent form, and recruiting materials were revised to address EPA and HSRB comments. The revised materials were submitted to IIRB on January 16, 2009, and approved on January 19, 2009.

In April 2009, while preparing to conduct the monitoring for AHE59, the AHETF learned that two eligible growers wanted to use carbaryl products that were not on the list of approved surrogate products. In order to expand the list of surrogates to include these two products, AHETF submitted to IIRB new product risk statements (PRSs) for the two carbaryl end-use products on April 24, 2009; IIRB approved the new PRSs on April 29, 2009. On May 11, 2009, the AHETF submitted to IIRB an amendment, which had previously been approved by EPA, to add two carbaryl end-use products to the list of possible products for this study. IIRB approved this amendment on May 19, 2009. This amendment was not timely, however, because two subjects were monitored using the two new carbaryl products on May 7 and 9, 2009. This situation was later reported to IIRB as a deviation. Please refer to the discussion on page 16 of this review for more information.



US EPA ARCHIVE DOCUMENT

There is agreement between the study report (Volume 9) and IIRB Correspondence Report (Volume 10) that there was one amendment to AHE59 after the protocol was signed by the study director.

## 4.0 Protocol Deviations:

### 4.1 AHE55

#### 4.1.1 Reported Deviations

There was one reported deviation during the field phase of AHE55. On two occasions, a subject was selected for monitoring from two potential subjects by coin flip rather than by drawing a name as required by the protocol. This deviation occurred on October 28 and October 30, 2008, and was reported to IIRB on November 16, 2008. On November 17th, IIRB acknowledged the deviation and concluded that it did not place subjects at increased risk. In EPA's view, this deviation is not significant from an ethics perspective because it did not place subjects at increased risk and was consistent with the general intent of the protocol that subjects be selected randomly if more than one eligible individual is available for monitoring. I defer to the EPA science reviewer about whether this deviation is important from a science perspective.

There were no reported deviations in the analytical phase of the research.

#### 4.1.2 Unreported Deviations

There were four unreported deviations during the field phase of AHE55.

1) Section 2.4 of the protocol states that growers will be reimbursed for the pesticide used in the study, but for AHE55, the Local Site Coordinator purchased the product and delivered it to the application sites. Notwithstanding the study director's failure to report this deviation to IIRB, it raises no ethical issues. I defer to the EPA science reviewer on whether the deviation raises science issues.

2) One subject was a non-reader who required a witness for the consent process. Section 2.7 of the protocol states that "Witnesses must have no association with AHETF, its member companies, researchers, growers, or workers." (Vol 1, p 348). In this study, the non-reading worker selected the witness ("The witness was selected by the participant and monitored the informed consent procedure." [Vol. 1, p. 10]) This is an unreported protocol deviation because the witness had an association with the worker. This deviation does not raise concerns about the consent process for this worker, however, because even though the protocol for AHE55 states that the witness should not have an association with the worker, the protocols for AHE57, AHE58, and AHE59



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specify that the witness should be selected by the non-reading prospective subject. Moreover, SOP 11.I.1 states that subjects may choose a witness, and only specifies that "the witness must be unassociated with the conduct of the research (i.e., not employed by the Sponsor or any of its contractors.)"

The HSRB, in its December 18, 2007, report of the June 2007 HSRB meeting, stated the following on the topic of witnesses:

> "The Board expressed support for the Agency's proposal to have impartial third-party witnesses observe the consent process when a research subject is unable to read relevant study documents. As specific studies are proposed, however, it will be important for investigators to describe the procedures to be employed in recruiting these witnesses. It would be inappropriate, for example, to ask translators to serve as witnesses (as suggested in the materials reviewed by the Board), because one of the main purposes of employing a witness is to ensure that the communication of study-related materials is adequate (and the translator would be conflicted with regard to that assessment). If feasible, the Agency may wish to consider using impartial "consent monitors" or "research subject advocates" as witnesses, as is increasingly done in certain clinical studies." (p. 64-5 of 67)

Although this protocol deviation should have been reported to IIRB, it raises no ethics issues. It is appropriate, in EPA's view, for the non-reading subject to select the witness. The important restriction that the witness not be associated with the researchers or study sponsors was not violated in this case.

3) One subject touched the cab door while not wearing gloves, and later opened the cab door with bare hands. There is no record that the observer reminded the worker to wear his gloves or reported the behavior to the study director, which violated protocol section 2.3.2 and SOP AHETF-10.C.4. These protocol and SOP violations were not reported to IIRB. These deviations are discussed in greater detail in sections 8.1 and 10.0 of this review.

4) Four of the five subjects in this study did not spray for a minimum of 4 hours, as required in Section 7.8 of the protocol ("Each MU shall consist of a period of at least 4 hours of spraying and at least 3 tank loads of the spray mixture.") See Table F in Appendix 2 for individual spray times for each subject. Although this protocol deviation should have been reported to IIRB, it raises no ethics issues. I defer to the EPA science reviewer on whether this deviation raises science issues.

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## 4.2 AHE56

### 4.2.1 Reported Deviations

There were five reported deviations during the field phase of AHE56.

1) In the summer of 2008, the AHETF identified potential eligible pecan growers in southwest Georgia (located in the five counties adjacent to Tift County), in accordance with Section 4.0 of the AHE56 protocol (Vol 3, p 347 of 379). By mid-August, the AHETF had identified 22 eligible growers who agreed to participate in the study by providing the closed-cab equipment and allowing their pecan trees to be sprayed with one of the surrogate products. In the final phase of recruitment, the study director made telephone contact with and/or visited the 22 eligible growers to select at least five growers who could participate in a timeframe and schedule to allow the study to be conducted efficiently. During the course of conducting the telephone conversations with eligible growers, the study director was informed of two additional pecan growers who might be candidates for participation in the study. One of these referrals appeared on the original grower list, but was eliminated because he was no longer growing pecans and was now working as a commercial applicator; the other referral did not appear on the original grower list because his farm was not located in one of the five counties adjacent to Tift County.

   During the week of August 18, 2008, the AHETF had six growers ready to participate (five were needed; one was to serve as a back-up). The research team assembled in Tifton, Georgia on August 19, and they planned to begin monitoring on August 21st. However, a tropical storm struck on August 20th, making the field work impossible for several days. When the research was ready to proceed during the week of August 25th, three of the six growers were either no longer willing to participate or unable to be rescheduled within the necessary timeframe to efficiently conduct the research. In order to find the additional two needed growers, the AHETF contacted the two "referrals," and these two growers eventually agreed to participate. This was a deviation since the protocol does not provide for recruitment beyond the eligible growers list, and because one of the subjects was not located in a county directly adjacent to Tift County.

   The decision to use the two referred growers in the study was made during the week of August 25th. The deviation was reported to IIRB on September 5, 2008. On September 15, IIRB acknowledged the deviation and concluded that it did not place subjects at increased risk. I note that the deviation was reported to have occurred on August 18th, but the field notes show that the monitoring took place on August 25-28. In EPA's view, this deviation is not significant from an ethics perspective because after the initial identification of the two referred growers, they were recruited using the procedures that are

outlined in the protocol and SOP AHETF-11.B.3. I defer to the EPA science reviewer on whether this deviation affects the scientific integrity of the data.

2) The second reported deviation involved a departure from Section 2.7 of the protocol, which says that informed consent must be obtained before a subject participates in the research. In this instance, one of the subjects dressed in the dosimeter before he signed the consent form. He is reported to have given oral consent prior to donning the dosimeter, but he signed the consent form shortly after putting on the dosimeter. The reason for the deviation was that the subject (A5) arrived at the field site just before another subject (A1) was expected to return to the staging area to remove his dosimeter and have his samples collected. To avoid the possibility of contamination of subject A5's clean dosimeter while subject A1 was having his samples collected, subject A5 was quickly dressed in his dosimeter before subject A1 entered the staging area.

   Based on the field observation records, the deviation occurred on August 25, 2008, the first day of monitoring. However, the deviation was mistakenly reported to IIRB as having occurred on August 18th. The deviation was reported to IIRB on September 17, and IIRB acknowledged it on September 23rd and concluded subjects were not at increased risk. In EPA's view, this deviation is not significant from an ethics perspective because the subject gave verbal consent before putting on the dosimeter, and he signed the consent form shortly after putting on the dosimeter. It is questionable whether this is indeed a deviation since the subject gave oral consent prior to putting on the dosimeter, but the AHETF wisely erred on the side of caution by reporting this deviation.

3) The third reported deviation for AHE56 was that travel fortification samples, which should have been prepared on day 1, were not prepared until monitoring day 4. The deviation was reported to IIRB on September 17, and IIRB acknowledged it on September 23rd and concluded subjects were not at increased risk. I note that the deviation report erroneously indicates that the deviation occurred on August 18-21. Based on the field notes providing the dates that subjects were monitored, this deviation occurred on August 25-28, 2008. This deviation has no effect on the ethical conduct of the research. I defer to the EPA science reviewer on whether this deviation affects the scientific integrity of the study.

4) The fourth reported deviation for AHE56 was that one subject (subject A4) took a bathroom break without first washing his hands and without handwash samples being taken. The subject stepped away from the tractor to relieve himself behind a tree while his spray tank was being refilled. The worker was out of sight of the observer at that time. When the observer realized what had happened, he reminded the worker to follow label directions advising that users should wash hands before using the bathroom. This was a violation of



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label directions, and also a deviation from SOP AHETF-8.B.4 (section 5.2). From an ethics perspective, the observer responded appropriately to the situation by reminding the worker of label directions, but he should have also reported the occurrence to the study director in accordance with SOP AHETF-10.C.3. The deviation was reported to IIRB on September 17, and IIRB acknowledged it on September 23rd and concluded that subjects were not at increased risk. I note that the deviation report erroneously indicates that the deviation occurred between August 18-21, 2008. Based on the field notes providing the dates that subjects were monitored, this deviation occurred on August 28, 2008. This deviation raises no ethical issues, but I defer to the EPA science reviewer on whether this deviation affects the scientific integrity of the data.

5) The fifth reported deviation for AHE56 was that the air pump and sampling train were removed from subjects before the final air flow rate was measured with a calibrated rotometer. This was a deviation from SOP AHETF-8.D.2 (Section 4.11). The deviation was reported to IIRB on September 17, and IIRB acknowledged it on September 23rd and concluded that subjects were not at increased risk. I note that the deviation report erroneously indicates that the deviation occurred between August 18-21, 2008. Based on the field notes providing the dates that subjects were monitored, this deviation occurred on August 28, 2008. This deviation raises no ethical issues, but I defer to the EPA science reviewer on whether this deviation affects the scientific integrity of the data.

There were four deviations in the analytical phase of the research that were reported to IIRB. These deviations raise no ethical issues, but I defer to the EPA science reviewer on whether these deviations affect the scientific integrity of the data.

#### 4.2.2 Unreported Deviations

1) None of the five subjects in this study sprayed for a minimum of 4 hours, as required in Section 7.8 of the protocol ("Each MU shall consist of a period of at least 4 hours of spraying and at least 3 tank loads of the spray mixture.") See Table F in Appendix 2 for individual spray times for each subject. Although this protocol deviation should have been reported to IIRB, it raises no ethics issues. I defer to the EPA science reviewer on whether this deviation raises science issues.

### 4.3 AHE57

#### 4.3.1 Reported Deviations

There was one reported deviation during the field phase of AHE56. Subject A1, who was assigned to the lowest stratum of amount active ingredient handled (AaiH) –



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5 to 9 pounds – actually handled 10.68 pounds. In addition, this subject was monitored for only 2 hours and he applied only 2 tank loads, contrary to the protocol requirement in Section 7.8 that subjects are monitored for a minimum of 4 hours and apply at least 3 tank loads. The reason given for applying an amount outside of the limits of the stratum was that the grower needed the pesticide applied at a higher rate to achieve effective control of the target pest. The minimum application time and minimum number of loads specified in the protocol could not be achieved because of the grower's preference to use his normal tractor speed and spray volume. The deviation occurred on May 22, 2009, and was reported to IIRB on June 4, 2009. On June 10, 2009, IIRB acknowledged the deviation and indicated that no additional action is required. The deviation does not raise ethical issues because the expected exposure as a result of this deviation is not out of the range of safe exposures based on pre-study evaluations of risk. I defer to the EPA science reviewer on whether this deviation raises science issues.

There were 4 deviations in the analytical phase of the research that were reported to IIRB. These deviations raise no ethical issues, but I defer to the EPA science reviewer on whether these deviations affect the scientific integrity of the data.

#### 4.3.2 Unreported Deviations

1) None of the five subjects in this study sprayed for a minimum of 4 hours, as required in Section 7.8 of the protocol ("Each MU shall consist of a period of at least 4 hours of spraying and at least 3 tank loads of the spray mixture.") See Table F in Appendix 2 for individual spray times for each subject. Although this protocol deviation should have been reported to IIRB, it raises no ethics issues. I defer to the EPA science reviewer on whether this deviation raises science issues.

### 4.4 AHE58

#### 4.4.1 Reported Deviations

There were four reported deviations during the field phase of AHE58.

1) The first deviation was that on Study Day 2, inner whole body dosimeters were inadvertently not folded over after field fortifications were conducted and prior to covering with cloth as specified in SOP AHETF-8.E.5. The deviation occurred on July 1, 2009, and was reported to IIRB on September 2, 2009. On September 3rd, IIRB acknowledged the deviation and concluded no further action was required. This deviation raises no ethical issues. I defer to the EPA science reviewer on whether it raises science issues.

2) The second deviation was that low level field fortifications for the hand wash and face/neck wipes were conducted in duplicate on day 4 instead of in triplicate. The deviation occurred on August 7, 2009, and was reported to IIRB on September 2, 2009. On September 3rd, IIRB acknowledged the



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deviation and concluded no further action was required. This deviation raises no ethical issues. I defer to the EPA science reviewer on whether it raises science issues.

3) The third deviation was that subject A5 was monitored for 3 hours 8 minutes, contrary to the requirement in Section 7.8 of the protocol that subjects apply for a minimum of 4 hours. The deviation occurred on August 10, 2009, and was reported to IIRB on September 2, 2009. On September 3rd, IIRB acknowledged the deviation and concluded no further action was required. This deviation raises no ethical issues. I defer to the EPA science reviewer on whether it raises science issues.

4) The fourth deviation was that the field fortifications were done at levels different than those specified in protocol. The deviation was discovered upon inspection of the laboratory records, which showed that the laboratory technician preparing the fortification vials and tubes made several dilution errors that resulted in the field researchers using incorrect fortification levels. The deviation occurred on June 10 and 11, 2009, and it was reported to IIRB on December 7, 2009. On December 15th, IIRB acknowledged the deviation and concluded no further action was required. This deviation raises no ethical issues. I defer to the EPA science reviewer on whether it raises science issues.

There was one deviation in the analytical phase of the research that was reported to IIRB. This deviation raises no ethical issues, but I defer to the EPA science reviewer on whether the deviation affects the scientific integrity of the data.

#### 4.4.2 Unreported Deviations

There were four unreported deviations during the field phase of AHE58.

1. One subject touched the equipment while not wearing gloves. There is no record that the observer reminded the worker to wear his gloves or that the observer reported the behavior to the study director, which violated protocol section 2.3.2, SOP AHETF-10.C.4, and SOP AHETF-11.E.1. These protocol and SOP violations were not reported to IIRB. These deviations are discussed in greater detail in sections 8.1 and 10.0 of this review.

2. Protocol section 7.8 states that "a single MU will be conducted in this study from each of the five strata" (Vol 7, p. 253). In the conduct of the study, however, two subjects applied amounts from the highest stratum (56-100 lbs) and no worker applied from the second stratum (10-17 lbs) (Vol 7, p 43). This deviation was not reported to IIRB. Notwithstanding the investigator's failure to report the deviation to IIRB, I conclude that the deviation does not raise ethics issues. I defer to the EPA science reviewer on whether the deviation raises science issues.



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3. At least one of the five subjects in this study failed to spray for a minimum of 4 hours, as required in Section 7.8 of the protocol ("Each MU shall consist of a period of at least 4 hours of spraying and at least 3 tank loads of the spray mixture.") It is not possible to calculate spray times from the observer logs for this study. However, the dermal monitoring time for one of the workers was less than four hours, which means that spray time was indeed below 4 hours for this subject. It is possible that other subjects in AHE58 also sprayed for less than 4 hours. See Table F in Appendix 2 for individual spray times for each subject. Although this protocol deviation should have been reported to IIRB, it raises no ethics issues. I defer to the EPA science reviewer on whether this deviation raises science issues.

## 4.5 AHE59

### 4.5.1 Reported Deviations

There were two reported deviations during the field phase of AHE59.

1) Two subjects were monitored on May 7 and May 9, 2009 while applying carbaryl products that were not on the list of approved surrogate products in Section 7.5 of the protocol. The reason for the deviation was that two of the growers would agree to participate only if they could use carbaryl products which were not on the list of approved surrogates in the protocol. When the AHETF learned of the two growers' preferences for these two particular carbaryl products, the Task Force contacted EPA and provided copies of Product Risk Statements (PRSs) for the two carbaryl products. EPA reviewed the products and approved their addition to the list of possible test substances. The AHETF next submitted the new PRSs to IIRB on April 24, 2009, and IIRB approved the new PRSs on April 29, 2009. However, the AHETF erred in not simultaneously submitting an amendment to add the products to the protocol. The AHETF recognized the error, and submitted an amendment to IIRB on May 11, 2009, which was approved on May 19, 2009. But the amendment approval was granted after two subjects were monitored using the two new carbaryl products. This situation was reported to IIRB as a deviation on June 16, 2009. IIRB acknowledged the deviation on June 24, 2009 and concluded that no further action is required. In EPA's view, this deviation does not raise ethics concerns. Before the subjects used these two products, EPA reviewed and approved their use in this study. IIRB had also reviewed and approved PRSs for these products, and was aware that these two products may be used in the study. The error of not submitting a timely amendment was careless, but it is more of an administrative mistake than a substantive one. Both EPA and IIRB had approved the addition of the two carbaryl products to the list of approved surrogates, and the error of proceeding before a protocol amendment had been approved does not raise serious ethics issues.

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2) The second deviation was that researchers neglected to take photographs of the subjects' clothing after monitoring. This was a deviation from protocol Section 12 and SOP AHETF-10.C. This deviation occurred twice, on April 30, 2009, and May 7, 2009, and was reported to IIRB on May 12, 2009. On May 20, 2009, IIRB acknowledged the deviation and concluded that subjects were not at increased risk and that no further action was required. This deviation does not raise ethics issues. I defer to the EPA science reviewer on whether the deviation affects the scientific integrity of the data.

There was one deviation in the analytical phase of the research that was reported to IIRB. This deviation raises no ethical issues, but I defer to the EPA science reviewer on whether the deviation affects the scientific integrity of the data.

#### 4.5.2 Unreported Deviations

There were three unreported deviations during the field phase of AHE59.

1) All four subjects had instances of touching the cab door, equipment, or other treated surfaces while not wearing gloves. There is no record that the observer reminded the workers to wear their gloves or that the observer reported the behavior to the study director, which violated protocol section 2.3.2, SOP AHETF-10.C.4, and SOP AHETF-11.E.1. These protocol and SOP violations were not reported to IIRB. These deviations are discussed in greater detail in sections 8.1 and 10.0 of this review.

2) Protocol section 7.8 states that "a single MU will be conducted in this study from each of the five strata" (Vol 9, p. 201). In the conduct of the study, however, two subjects applied amounts from the second stratum (10-17 lbs) and no worker applied from the third stratum (18-30 lbs) (Vol 9, p 37).

3) Three of four subjects in this study failed to spray for a minimum of 4 hours, as required in Section 7.8 of the protocol ("Each MU shall consist of a period of at least 4 hours of spraying and at least 3 tank loads of the spray mixture.") See Table F in Appendix 2 for individual spray times for each subject. Although this protocol deviation should have been reported to IIRB, it raises no ethics issues. I defer to the EPA science reviewer on whether this deviation raises science issues.



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| Table 2. Summary of Protocol Amendments and Deviations | | | |
|---|---|---|---|
| **Study ID** | **Amendments** | **Deviations** | |
| | | **Field Phase** | **Analytical Phase** |
| AHE55 | 1. Amended once to incorporate comments from EPA and HSRB.<br><br>*Study report indicates that the protocol was amended 3 times prior to execution of the field phase, however it did not summarize these changes.* | Reported:<br>1. On two occasions, subjects were selected randomly using a coin flip rather than drawing names as required in protocol.<br><br>Unreported:<br>1. Rather than growers being reimbursed for the pesticide as required by section 2.4 of the protocol, the Local Site Coordinator purchased the product and delivered it to the application sites<br>2. The witness for the consent process for a non-reader was selected by the prospective subject, contrary to the protocol requirement that the witness should have no association with the grower or worker.<br>3. One subject touched the cab door while not wearing gloves, and later opened the cab door with bare hands. There is no record that the observer reminded the worker to wear his gloves or that the observer reported the behavior to the study director, contrary to the protocol (section 2.3.2) and SOP AHETF-10.C.4.<br>4. Four of five subjects did not achieve protocol-required 4-hour minimum spray time. | None reported |
| AHE56 | 1. Amended once to incorporate comments from EPA and HSRB.<br><br>*Study report indicates that the protocol was amended two times prior to execution of the field phase, however it did not summarize these changes.* | Reported:<br>1. The original list of eligible growers was exhausted before successfully recruiting enough subjects. Two growers ultimately monitored as subjects were referred to the AHETF by other growers, and did not appear on the eligible grower list. This was a deviation because the protocol did not provide for recruitment beyond the eligible growers list.<br>2. Informed consent form signed by one subject after donning inner dosimeter garment.<br>3. Travel fortification samples were not prepared until monitoring day 4.<br>4. One subject took a bathroom break without first washing his hands and having a handwash sample taken.<br>5. Air flow rotometer measurements taken after removal of sampling gear from workers.<br><br>Unreported:<br>1. None of the 5 subjects achieved the protocol-required 4-hour minimum spray time. | 1. OVS sampling tubes Set 2 was above 15% criteria (reported 22.02%) for back-calculation value at 5.0 ng/mL standard.<br>2. Travel spikes analyzed inadvertently.<br>3. For Set 2a OVS samples, 3.0 mL aliquot was used instead of 4.0 mL (deviation reported in IIRB correspondence [Volume 4], but not within Appendix B of AHE56 study report [Volume 3]). |

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| Table 2. Summary of Protocol Amendments and Deviations | | | |
|---|---|---|---|
| Study ID | Amendments | Deviations | |
| | | Field Phase | Analytical Phase |
| AHE57 | 1. Amended once to incorporate comments from EPA and HSRB.<br>2. Amended purity analysis section of the protocol (section 7.5.3). | Reported:<br>1. One subject applied 10.68 lbs (1.68 lbs above stratum 5-9 lbs); was monitored for 2 hours (the protocol prescribes a minimum of 4 hours of application time); and applied only 2 tank loads (the protocol prescribes a minimum of 3 tank loads).<br><br>Unreported:<br>1. Protocol section 7.8 states that "a single MU will be conducted in this study from each of the five strata" (Vol 5, p. 152). In the conduct of the study, however, two subjects applied amounts from the second stratum (10-17 lbs) and no worker applied from the lowest stratum (5-9 lbs) (Vol 5, p 31).<br>2. None of the 5 subjects achieved the protocol-required 4-hour minimum spray time. | 1. Inner dosimeter controls and LOQ concurrent recovery samples were diluted to 5 mL while field samples were diluted to 10 mL.<br>2. Protocol lists method titles not used.<br>3. Aliquot deviation in Method ARTF-0001 for 2-piece cotton inner dosimeters.<br>4. Back-calculated calibration standard values for the 0.001 ug/mL OVS sample and the 0.005 ug/mL face/neck wipe standard deviated from the theoretical value by > 20%. |
| AHE58 | 1. Amended once to incorporate comments from EPA, California Department of Pesticide Regulation, and HSRB.<br>2. • Inclusion criteria amended to allow participation of workers who normally wear two layers of clothing.<br>• Recruitment area expanded to allow any county in CA or WA.<br>• Removed efficient configuration requirement if recruitment area is expanded.<br>3. Added a new malathion product to possible test products (the active ingredient malathion was already an approved surrogate) | Reported:<br>1. On study day 2, inner dosimeters were inadvertently not folded over after field fortifications were conducted and prior to covering with cloth as specified in SOP AHETF-8.E.5.<br>2. Low level field fortifications conducted in duplicate on day 4, instead of triplicate.<br>3. One subject was monitored for only 3 hours 8 minutes (protocol prescribes a minimum of 4 hours of application time).<br>4. Field fortifications were done at (known) levels different than those specified in protocol.<br><br>Unreported:<br>1. One subject touched contaminated equipment while not wearing gloves. There is no record that the observer reminded the worker to wear his gloves or that the observer reported the behavior to the study director, contrary to the protocol (section 2.3.2) and SOP AHETF-10.C.4.<br>2. Protocol section 7.8 states that "a single MU will be conducted in this study from each of the five strata" (Vol 7, p. 253). In the conduct of the study, however, two subjects applied amounts from the highest stratum (56-100 lbs) and no worker applied from the second stratum (10-17 lbs) (Vol 7, p 43).<br>3. At least 1 of the 5 subjects did not achieve the protocol-required 4-hour minimum spray time. | 1. Concentrations of some field fortification solutions corrected for volume based on density, not gravimetrically, resulting in incorrect field fortification concentrations. |

US EPA ARCHIVE DOCUMENT

| Table 2. Summary of Protocol Amendments and Deviations | | | |
|---|---|---|---|
| **Study ID** | **Amendments** | **Deviations** | |
| | | **Field Phase** | **Analytical Phase** |
| AHE59 | 1. Amended once to incorporate comments from EPA and HSRB.<br>2. Two carbaryl products were added to possible test substances | Reported:<br>1. Two subjects were monitored using carbaryl products before those products were formally approved by IIRB for use in the research.<br>2. Post-monitoring photographs of worker clothing were inadvertently not taken.<br><br>Unreported:<br>1. Each of the four subjects contacted a contaminated surface at least one time while not wearing gloves. There is no record that the observer reminded the worker to wear his gloves or that the observer reported the behavior to the study director, which violated the protocol (section 2.3.2) and SOP AHETF-10.C.4.<br>2. Protocol section 7.8 states that "a single MU will be conducted in this study from each of the five strata" (Vol 9, p. 201). In the conduct of the study, however, two subjects applied amounts from the second stratum (10-17 lbs) and no worker applied from the third stratum (18-30 lbs) (Vol 9, p 37).<br>3. Only 1 out of 4 subjects achieved the protocol-required 4-hour minimum spray time. | 1. Curve standard off by 25.89% more than 15% criteria – (deviation reported in IIRB Corresp. Report (Vol 10) but not detailed in Appendix B of study report (Vol 9) |

## 5.0 Recruiting

The three-phase recruiting process outlined in the protocol and SOPs AHETF-11.K.O, 11.L.0, and 11.M.0 appears to have been generally followed in all five studies. In all studies, an initial grower universe list was generated from published lists or databases. Duplicate entries were suppressed and, for AHE55 and AHE56, growers not having sufficient acreage were removed, to produce the master grower list. For AHE55, the initial list was so large (1,381 names), even after suppression of duplicates and growers with less than 10 acres, that the master grower list was a randomly generated subsample of 425 contacts. After protocols were finalized and signed by the study director, qualifying calls were placed to the names on the master grower list, and the lists were narrowed by eliminating names based on responses to qualifying questions, being unreachable, or lack of interest in participating in the research. The resulting lists contained names of growers who were qualified and interested in participating in the research. For the final stage of recruiting, the study director contacted and/or visited all qualified growers, to identify growers who could participate in a timeframe and schedule to allow the study to be conducted efficiently. Table 2 in each of the Study Reports (Vol 1, p. 31; Vol 3, p. 31; Vol 5, p. 28; Vol 7, p. 39; Vol 9, p. 33) details the number of growers/workers in each stage of the recruitment process.

There was a reported deviation in recruiting for AHE56, when a tropical storm struck the day before monitoring was scheduled to begin. The storm necessitated the cancellation of the field work for several days. When the research was ready to proceed



US EPA ARCHIVE DOCUMENT

the following week, three of the six growers were either no longer willing to participate or unable to be rescheduled within the necessary timeframe to efficiently conduct the research. In order to find the additional two needed growers, the AHETF contacted two growers who had been referred to them by other growers on the master grower list, and those two growers ultimately participated in the research. This deviation is discussed in more detail on page 11 of this review.

### 5.1 Subject Representativeness

At the conclusion of the field phase of each of the studies, the AHETF conducted a survey of area experts to evaluate the representativeness of the growers/applicators participating in the study. These surveys were responsive to the HSRB's request that the AHETF attempt to characterize whether the monitored workers were typical of that type of worker/grower in the particular region. For AHE55, AHE56, and AHE57, all of the area experts that responded to the survey (4/4 for AHE55; 4/4 for AHE56, 5/5 for AHE57) agreed that study participants were typical of growers/applicators in the areas where the study was performed. For AHE58, four of five area experts agreed the growers/applicators were typical, and one stated that she was not familiar enough to provide an opinion. In AHE59, three of four area experts that responded to the survey opined that the growers/applicators were typical, whereas one responded that the monitored growers were not representative because their average farm size was below average and they did not use newer spray technologies that apply at lower gallons per acre.

## 6.0 Consent Process

The consent process outlined in the protocols and SOPs was closely followed in all studies. The only deviations related to the consent were in AHE55, where the witness for a non-reading subject was selected by the subject, contrary to the protocol requirement that the subject be unknown to the subject, and in AHE56, where one subject donned the inner dosimeter after giving verbal consent but before signing the consent form, although he signed the form shortly thereafter. The two deviations are discussed in detail in Sections 4.1.2 and 4.2.1 of this review.

## 7.0 Subject Demographics

Demographic information on the monitored subjects is summarized in Table 3 below.

### 7.1 Years of Experience

In AHE55, one worker listed his age as 20 years old, but self-reported that he had 10 years of experience (Vol 1, p. 32). Likewise, in AHE57, one subject listed her age as 21 years old, but self-reported that she had 6 years of experience. The unexpectedly large



US EPA ARCHIVE DOCUMENT

number of years of experience compared with the reported ages of these two subjects raises questions about the accuracy of these subjects' reporting of their age and/or years of experience.

### 7.2 Health Status

Prospective subjects were asked about their health status during the consent process, based on the procedures described in SOP AHETF 11.C.0/11.C.1. No prospective subjects were eliminated due reported health status. The inclusion criteria in the protocol state that subjects must report "good general health with no medication conditions that could impact their ability to participate in the study" in order to be eligible to participate (protocol section 2.1).

### 7.3 Pregnancy Testing

There was one female subject in AHE57; there were no female subjects in the other studies. Supplement 1 (email from D. Johnson to J. Evans and K. Sherman) confirms that the female subject took a pregnancy test, the test showed that she was not pregnant, and she stated that she was not nursing.

| | **Table 3: Subject Characteristics** | | | | |
|---|---|---|---|---|---|
| | **Number of Subjects** | | | | |
| | **AHE55** | **AHE56** | **AHE57** | **AHE58** | **AHE59** |
| Males | 5 | 5 | 4 | 5 | 4 |
| Females | 0 | 0 | 1 | 0 | 0 |
| Preferred consent process in English | 4 | Not reported | 5 | 3 | 4 |
| Preferred consent process in Spanish | 1 | Not reported | 0 | 2 | 0 |
| Self-identified as non-reader and used witness | 1 (in English) | 0 | 0 | 0 | 0 |
| Employment<br>Farm Employee | 5 | 0 | 2 | 3 | 3 |
| Farm Owner | 0 | 4 | 3 | 0 | 1 |
| Commercial Applicator | 0 | 1 | 0 | 2 | 0 |
| Years of Experience | 3-48 | 7-44 | 6-50 | 7-28 | 5-40 |
| Age Range | 20-70 | 43-68 | 21-58 | 27-49 | 26-62 |
| Requested Results | 5 | 5 | 5 | 4 | 4 |
| Withdrew | 0 | 0 | 0 | 0 | 0 |
| Removed from participation by AHETF | 0 | 0 | 0 | 0 | 0 |



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## 8.0 Monitoring

Exposure monitoring was conducted without incident. No subjects withdrew from the research. No adverse events or other incidents of concern were reported.

### 8.1 Instances of Failure to Wear Gloves

In AHE55, AHE58, and AHE59, the field notes report instances in which a subject, who was outside of his enclosed cab, contacted surfaces contaminated with pesticide residues while not wearing chemical-resistant gloves.

Below in Table 4 are the log entries, prepared by the study observers in each of the studies, documenting the observations of instances in which a subject contacted a contaminated surface while not wearing gloves.

**Table 4. Observations Noting Instances of Failure to Wear Gloves**

| Study ID | MU ID | Log Time | Observation |
|---|---|---|---|
| AHE55 | A3 | 11:44 | "…exits cab without gloves…shuts the door…contacting the side edge." |
| | | 12:14 | "…opens door with bare hands…" |
| AHE58 | A5 | 08:14 | "Turned off water near tank with bare hand…" |
| AHE59 | A1 | 08:58 | "Climbed back into cab, opened door with bare hands." |
| | A2 | Gen. obs. | "Door opened with bare hand." |
| | A3 | 09:56 | "Opened truck door with bare hands…" |
| | A4 | 11:02 | "…exited cab and with bare hands picked up a marker from ground…" |
| | | 13:20 | "Exited cab, walked back to sprayer and with bare hands, turned lever…" |
| | | 14:32 | "Walked to front of spray tank and with bare hand turned lever…" |
| | | 15:49 | "…walked back to sprayer and with bare hands, turned off a couple nozzles…" |

## 9.0 Applicable Ethical Standards

The following provisions of 40 CFR 26 Subpart Q, as amended effective August 22, 2006, 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 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 shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part. . . .



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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.

## 10.0 Findings

### 10.1 Responsiveness to EPA and HSRB reviews

EPA's and HSRB's comments on these protocols were satisfactorily addressed before the research was conducted. Please see Attachment 4 for details.

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

All enrolled subjects were at least 18 years old. There was one female subject; she tested negative for pregnancy and confirmed that she was not nursing. The prohibition in 40 CFR §26.1703 of research involving intentional exposure of pregnant or nursing women or of children under 18 was satisfied.

### 10.3 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. This research would not comply with Subpart L if any of the subjects was a child, or a pregnant or nursing woman. The study reports document compliance with subpart L.

#### 10.3.1 Subjects not wearing gloves when contacting treated surfaces

Based on the study report, I find that the AHETF violated the protocol by not ensuring that all study participants wore label-specified PPE when they contacted surfaces contaminated with pesticide residues. As summarized in Table 4, the log for AHE55 reports that there was one subject (A3), who exited and contacted contaminated surfaces twice. The log for AHE58 reports that there was one subject who exited and contacted a contaminated surface one time. The log for AHE59 reports that there were three subjects, each of whom exited and contacted a contaminated surface one time, as



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well as one subject (A4), who exited and contacted contaminated surfaces at least four times. [2]

In addition to the failure to enforce the use of PPE, as required by section 2.3.2 of the protocol, there is no documentation indicating that the observer(s) notified the study director, principal field investigator, or quality assurance unit of any of these occurrences as required by section 6.12 of SOP AHETF-10.C.4. Finally, the study reports do not indicate that any of these subjects were reminded by the observer of the gloves requirement. The failure to warn the subjects would also violate SOP AHETF-11.E.1 if deemed a "safety issue."

As noted above, section 2.3.2 of the study protocols provides that the AHETF will "enforc[e] the use of label-specified PPE (especially the use of gloves outside the cab if contacting contaminated surfaces) during participation." Two of the SOPs also contain language relevant to this situation. SOP AHETF-10.C.4 states:

> Section 6.12: "Observers should contact the Study Director, PFI or QAU if they observe any activity contrary to the study design, label requirements, or dangerous activities undertaken by the worker. Based on the event, the SD has the discretion to terminate the MU."

AHETF-11.E.1 states:

> Section 3.3: "During the study conduct, researchers will ensure compliance with safety requirements on the product label and with the Worker Protection Standard (WPS). For example, workers will be reminded to use the label specified PPE and to follow use directions on the label
>
> > "a. Each worker will be observed by a researcher during the entire monitoring period unless the worker travels out of sight of the observer (*e.g.*, aerial application, driving beyond view in a field).

---

[2] In examining the records, EPA has determined that none of the subjects violated either the labeling of the pesticides or EPA's Worker Protection Standard (WPS). The WPS states at 40 CFR 170.240(d)(5)(iv):

> "persons occupying an enclosed cab shall have all labeling-specified personal protective equipment immediately available and stored in a chemical-resistant container, such as a plastic bag. They shall wear such personal protective equipment if it is necessary to exit the cab and contact pesticide-treated surfaces in the treated area. Once personal protective equipment is worn in the treated area, it must be removed before reentering the cab."

The WPS requires gloves when contacting "pesticide-treated surfaces," whereas the protocol refers to "enforcing the use of label-specified PPE (especially the use of gloves outside the cab if contacting contaminated surfaces) during participation." In EPA's view, all of the surfaces contacted by subjects not wearing gloves (summarized in Table 4) were "contaminated" with pesticide residues, but, for WPS compliance purposes, were not "pesticide-treated surfaces."



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"b. Worker observers will not advise workers on how to perform their work unless a safety issue is involved. If the observer advises a worker about a safety issue and the worker does not comply, the observer will then immediately notify the Study Director and ask the worker to cease any activity."

In sum, the behavior of the research team related to the instances of subjects not wearing gloves violates section 2.3.2 of the protocol, section 6.12 of SOP AHETF-10.C.4, and possibly section 3.3 of SOP AHETF-11.E.1. Specifically:

1) The use of "label-specified PPE (especially the use of gloves outside the cab if contacting contaminated surfaces)" was not enforced, as required in section 2.3.2 of the protocols.

2) There is no documentation indicating that the observer(s) notified the study director, principal field investigator, or quality assurance officer of the label violations, as required by section 6.12 of SOP AHETF-10.C.4.

3) There is no documentation indicating how observers determined whether they needed to advise the non-glove-wearing workers to wear their gloves, as required by section 3.3 of SOP AHETF-11.E.1.

These protocol and SOP violations are deviations that should have been immediately reported to IIRB. The AHETF did not report these deviations.

### 10.3.2 Considerations regarding the compliance of AHE55, AHE58, and AHE59 with Subparts A through L

This section addresses additional considerations that I regard as relevant to making a decision about whether, in light of the deviations discussed in Section 8.1 related to glove usage, the reported research was "conducted in substantial compliance with subparts A through L" of 40 CFR part 26. See 40 CFR 26.1705.

*The ethical duty to warn arising from the principle of beneficence.* There is a recognized ethical obligation on researchers to intervene when they become aware of behavior of a participant in human research that endangers the safety of the subject. Under the prevailing understanding of the ethical principles governing the conduct of human research, a researcher has a duty to warn subjects and/or intervene when the subjects engage in behavior potentially dangerous to themselves. This duty arises from the principle of beneficence from the Belmont Report, which obligates the researcher to secure the well-being of all research participants and protect participants from harm while the research is being conducted. The safety of the subjects must be prioritized above the desire to gather data. In making my determination about the ethical acceptability of the reported research, I considered the following factors.



US EPA ARCHIVE DOCUMENT

US EPA ARCHIVE DOCUMENT

*Intent of the investigators.* There is no evidence to indicate that the investigators intended to place the participants at risk. In fact, all of the available information indicates the opposite, that the investigators were concerned about and took steps to reduce risks to the participants. These include their overall responsiveness to EPA's and the HSRB's comments and the concrete steps they took to minimize risks to subjects including:

- Selecting only experienced pesticide handlers
- Requiring experience operating the equipment to be used
- Reminding workers of safe chemical handling practices
- Identifying nearby hospitalization facilities in case of emergency
- Monitoring the heat index and stopping the study if conditions warrant
- Providing transportation to medical treatment and covering the costs of
- Treatment, if needed
- Having a medical professional on site to observe the workers and, if needed, to provide urgent care
- Observing study participants throughout the monitoring period
- Ensuring that all tank mix products were used according to approved label (s) and did not require any additional PPE.

*The extent to which the ethical deficiency jeopardized (or could have jeopardized) the subjects' safety.* By not intervening during the study, the investigators allowed certain subjects to continue to engage in behaviors that increased their exposure and thus their risk. There was some variety in both the kind of conduct and the frequency of the conduct that observers reported. For four of the workers (one in AHE55; three in AHE58), the behavior involved only a very brief contact with a contaminated surface (e.g. removing gloves before rather than after entering the closed-cab, or touching the door handle while not wearing gloves) and likely did not measurably increase exposure. In other instances, the behavior was of a nature that the subject was likely getting a measurable increased increment of exposure to his hands (i.e., subject A4 in AHE59 who was not wearing gloves while contacting items on the ground [milk carton, rock]) that were likely contaminated with freshly applied residues). Four workers only had one instance each where they were observed contacting a treated surface without gloves, one worker had two instances, and one worker had at four. None of the subjects' actions were atypical of the behavior that EPA would expect pesticide applicators to exhibit. The gradations of violations and the likely impact of the violations on the levels of exposure make it difficult for an observer to determine which, if any, of the behaviors would have risen to a point triggering the duty to intervene. It is worth noting that none of the subjects reported any discomfort or symptoms of illness. Further, although it could not have been known at the time, EPA analysis of the levels of exposure received by the individual subjects showed that all of them had acceptably safe levels of exposure.

*The extent to which the investigators knew or should have known how they should have responded.* As discussed above, observers noted a variety of actions that ranged from very brief contacts with contaminated surfaces to more serious and repeated instances of contact with contaminated surfaces. While the applicable sections of the SOPs describe a general obligation to ensure study subjects follow applicable safety requirements and otherwise ensure they avoid dangerous practices, the directions lack

specificity with respect to what kinds of behavior raises a "safety issue" triggering the requirement to provide a warning and/or halt the research. The researchers could quite reasonably have thought that they had and should exercise judgment about whether and how to address instances of subject noncompliance. Certainly, until now, neither EPA nor the HSRB has focused on the application of the protocol and SOPs to the kinds of situations described in this report.

### 10.3.3 Conclusion regarding the compliance of AHE55, AHE58, and AHE59 with Subpart K

I have determined that the researchers failed to follow the protocol and the SOPs in several different ways and on multiple instances, as discussed above. I identified a number of unreported deviations which were of a minor or technical nature. This reflects a lack of thoroughness on the part of the AHETF in comparing the actual conduct of the research with the requirements of the protocol. In the future, EPA will expect the AHETF to examine field reports for possible deviations and to report them promptly to the supervising IRB. Apart from the gloves deviations discussed in Section 10.3.1 above, I identified no other noteworthy deficiencies in the ethical conduct of these five studies. The protocols were faithfully executed, properly amended when necessary, and only one amendment was not approved by the overseeing IRB before it was implemented. The reported and unreported deviations are of the nature to be expected in complicated field research of this kind, and did not affect the welfare or safety of the subjects, or compromise their informed and voluntary consent.

Of the unreported deviations, I am most concerned that the observer(s) did not ensure that the subjects wore their gloves as required by the protocol, and that the observers did not alert the study director about these incidents and appear not to have advised the subjects to wear gloves. These violations resulted in some, generally minor increased exposure and increased risk for the subjects. In addition, the protocol and SOP deviations should have been promptly reported to IIRB. Failure to report deviations prevents the IRB from exercising oversight and making recommendations for corrective action. It is my view, however, that despite these violations, the research substantially complied with the applicable regulations.

With respect to evaluating the failure to ensure that subjects wore gloves against the requirements of subpart K, I find that the researchers' violation consisted of a failure to report the deviations from the protocol pursuant to the rules of IIRB. While this failure to report is not strictly a violation of the regulations, it is inconsistent with the intended protections of the rule (See 40 CFR 26.1108). As discussed above, I do not think the failure to report the deviations placed the subjects at significant risk. Further, there is no evidence of any attempt by the researchers to evade IRB review and oversight, and the researchers have a long and consistent history of instituting corrective actions when EPA and the HSRB identifies ethical deficiencies. Consequently, I think that there is sufficient information to conclude the researchers' conduct with respect to subjects' failure to wear gloves substantially complied with subpart K.



US EPA ARCHIVE DOCUMENT

With respect to whether the research was deficient under the more general ethical duty to warn or otherwise intervene to protect the safety of study participants, I note that neither EPA nor the HSRB has provided the researchers with guidance on their responsibilities under this ethical principle. Further, in assessing their actions, I note that the subjects' behavior was not plainly dangerous. In most cases, a subject failed to wear gloves only on a single occasion. While a warning might have helped to protect these subjects from additional higher exposure, the degree of increased exposure actually experienced by these subjects was quite minor. As for subject A4 in study AHE59, the subject who repeatedly failed to wear his gloves, I think it would have been reasonable for the research team also to conclude the subject's actions, although concerning, were not so dangerous that they required special warnings or intervention, such as termination of his participation in the study. This applicator's actions did not involve prolonged contact with pesticide treated surfaces and are not atypical of the behavior of at least some pesticide applicators. Certainly, there was no indication that any of the participants experienced any physical distress during the research. Finally, EPA's post hoc risk assessment, finding an acceptable level of exposure for all study subjects, supports the reasonableness of a judgment that the behavior of subjects, including A4, was not overly risky. In sum, in view of the researchers' likely understanding of their ethical duties and a reasonable view of the dangers posed by the subjects' behavior, I cannot find that the researchers violated the principle of beneficence in this study.

Taking into account the overall care with which the research was defined and conducted, these deficiencies noted in the conduct and documentation of the research fall far below the level of substantial non-compliance with subparts A through L of 40 CFR part 26. I conclude that 40 CFR §26.1705 does not prohibit EPA reliance on this study.

### 10.4 Compliance with 40 CFR §26 subpart M

As is documented in Attachment 3 to this review, the central requirements of 40 CFR §26 subpart M, §26.1303 to document the ethical conduct of the research were satisfactorily addressed.

### 10.5 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.

## 11.0 Conclusion

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



US EPA ARCHIVE DOCUMENT

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.

Attachment 1: Ethics-related study chronologies (Tables A-E)
Attachment 2: Time Spent Spraying (Table F)
Attachment 3: §26.1303 completeness checks
Attachment 4: Responsiveness to EPA and HSRB Comments on protocols (Tables G, H)

US EPA ARCHIVE DOCUMENT

## Ethics-Related Study Chronologies

| Table A: AHE55 | |
|---|---|
| **Date** | |
| 06/24-25/08 | HSRB reviewed protocol and approved with recommendations |
| 07/11/08 | Phase 1 recruiting (creation of grower list). 7/11/08 to 9/2/08 |
| 07/18/08 | Submitted documents to IIRB to amend protocol, consent form, and product risk statements (following June 2008 HSRB meeting) |
| 07/21/08 | IIRB approves revised documents |
| 07/28/08 | Protocol finalized and signed by Study Director |
| 09/03/08 | Phase 2 recruiting (calls to grower list). 9/3/08 to 10/7/08 |
| 10/08/08 | Phase 3 recruiting (site visits and participant selection) - 10/8/08 to 10/26/08 |
| 10/27/08-10/31/08 | Five subjects monitored 10/27/08 – 10/31/08 |
| 11/16/08 | Protocol Deviation 1 reported to IIRB **[see Volume 2, pp. 21-220]**<br>• Deviation occurred 10/28/08, 10/30/08<br>• On two occasions, subjects were selected by flipping a coin to select a worker to participate from among two possible workers, rather than by drawing names from a container as described in the protocol |
| 11/17/08 | IIRB concludes Protocol Deviation 1 did not place subjects at increased risk; no further action required |
| 03/02/09 | Annual progress report submitted to IIRB |
| 03/03/09 | IIRB approves ongoing research; extends approval of research from 3/3/09 to 3/2/10 |
| 02/04/10 | Close out report submitted to IIRB |
| 02/04/10 | IIRB accepts Study Completion Report; study considered closed |

US EPA ARCHIVE DOCUMENT

## Ethics-Related Study Chronologies

| Table B: AHE56 | |
|---|---|
| **Date** | |
| 06/24-25/08 | HSRB reviewed protocol and approved with recommendations |
| 07/11/08 | Phase 1 recruiting (creation of grower list). 7/11/08 to 7/24/08 |
| 07/18/08 | Submitted documents to IIRB to amend protocol, consent form, and product risk statements (following June 2008 HSRB meeting) |
| 07/21/08 | IIRB approves revised documents |
| 07/24/08 | Protocol finalized and signed by Study Director |
| 07/24/08 | Phase 2 recruiting (calls to grower list). 7/24/08 to 9/04/08 |
| 08/08/08 | Phase 3 recruiting (site visits and participant selection) - 8/8/08 to 8/23/08 |
| 8/25/08 | Five subjects monitored 08/25/08 – 08/28/08 |
| 09/05/08 | Protocol Deviation 1 reported to IIRB **[see Volume 4, pp. 227-231]**<br>• Two growers whose names did not appear on the list of eligible growers were referred to investigators. The two referred subjects volunteered, were selected, and were monitored as subjects. |
| 09/15/08 | IIRB concludes Protocol Deviation 1 did not place subjects at increased risk; no further action required |
| 09/17/08 | Protocol Deviations 2, 3 reported to IIRB **[see Volume 4, pp. 232-238]**<br>• Deviation 2 occurred on 8/18/10<br>- One subject was dressed in his inner dosimeter before signing his informed consent form<br>• Deviation 3 (three different deviations) occurred between 8/18/10 and 8/21/10<br>- Deviation: Travel fortification samples were not prepared until monitoring day 4.<br>- Deviation: During monitoring, a subject stepped away from the tractor to relieve himself behind a tree while the spray tank was being re-filled. He was out of sight of the observer at the time. After the deviation was recognized, the observer reminded the worker that he should follow label user safety recommendations, "users should was hands before…using the toilet." This was also a deviation from AHETF SOP 8.B.4, section 5.2, which requires hand samples to be collected prior to workers using the restroom.<br>- Deviation: Air flow rotometer measurements were taken after removal of sampling gear from workers; this is a deviation from AHETF SOP 8.D.2, section 4.11. |
| 09/23/08 | IIRB concludes Protocol Deviations 2, 3 did not place subjects at increased risk; no further action required |
| 01/02/09 | Analytical phase deviations reported (dated 12/16/10) reported to IIRB **[see Volume 4, pp. 239-244]**<br>• Deviation: The back-calculation value for the second lowest standard at 5.0 ng/mL was +22.02%, which does not meet the ±15% acceptance criteria in Protocol AHE56, Section 15.3.<br>• Deviation: The two travel spikes were analyzed along with the other field spikes. This deviates from Protocol AHE56, Section 11.1 where it states the travel spikes are only analyzed if deemed necessary by the Study Director.<br>• Deviation: For analysis of carbaryl in OVS air sampling tubes, Set 2a, a 3.0 mL aliquot was process through the method rather than a 4.0 mL aliquot, which then required a 0.6 mL (instead of 0.8 mL) final volume for HPLC analysis. This was a deviation from AHETF Analytical Method ARTF-AM-013, Revision #1. |
| 01/07/09 | IIRB concludes no further action required on protocol and method deviations dated 12/16/08 and reported on 1/02/09 |
| 03/03/09 | Annual progress report submitted to IIRB |
| 03/10/09 | IIRB approval of ongoing research |
| 02/15/10 | Close out report submitted to IIRB |
| 02/19/10 | IIRB accepts Study Completion Report; study considered closed |

US EPA ARCHIVE DOCUMENT

## Ethics-Related Study Chronologies

| Table C: AHE57 | |
|---|---|
| **Date** | |
| 10/21-22/08 | HSRB reviewed protocol and approved with recommendations |
| 01/16/09 | Submitted documents to IIRB to amend protocol, consent form, and product risk statements (following June 2008 HSRB meeting) |
| 01/19/09 | IIRB approves revised documents |
| 1/23/09 | Protocol finalized and signed by Study Director |
| 01/26/09 | Phase 1 recruiting (creation of Master Grower List and Qualified Grower List). 1/26/09 to 3/5/09 |
| 02/17/09 | Phase 2 recruiting (calls to grower list). 2/17/09 to 4/2/09 |
| 4/02/09 | Phase 3 recruiting (site visits and participant selection) – 4/2/09 to 5/22/09 |
| 5/15/09 | Subjects monitored 5/15/09 to 5/22/09 |
| 6/4/09 | Protocol Deviation 1 reported to IIRB **[see Volume 6, pp. 105, 106, 110, 111]**<br>• Deviation occurred 5/22/09<br>• The subject assigned to Stratum 1 (5.0 lbs a.i. to 9.0 lbs a.i.) sprayed 10.68 lbs a.i., which exceeded the stratum limit of 9.0 lbs a.i. In addition, this subject applied only 2 tank loads for a period of 2 hours, whereas section 7.8 of the protocol states that each subject shall spray at least 3 tank loads of spray mixture over a period of at least 4 hours. |
| 6/7/09 | AHETF submits to IIRB an Amendment to the purity analysis section of the protocol (Section 7.5.3) **[see Volume 6, pp. 107-109, 170-172]**<br>• This Amendment was emailed to IIRB on 6/7/09, but it was not immediately acknowledged by IIRB<br>• In September 2010, after the study was closed, AHETF requested copies of IIRB's records on the Amendment, and was informed at that time that IIRB did not have a record of the Amendment.<br>• On 9/14/10, IIRB acknowledged receipt of the Amendment after study closure, and noted that the change was "administrative in nature, did not affect subject safety, and would not have received a revision to the consent form." |
| 6/10/09 | IIRB concludes no further action required on Protocol Deviation 1 |
| 7/15/09 | IIRB provides notification of risk of study closure |
| 7/16/09 | Progress report submitted to IIRB |
| 8/04/09 | IIRB approves ongoing research; extends approval of research from 8/04/09 to 8/03/10 |
| 7/07/10 | Problems in Research Report submitted to IIRB for review **[see Volume 6, pp. 134-141, 144-145]**<br>• Reports four deviations from analytic procedures methodologies that occurred on 2/25/10, 3/1/10, 3/4/10, and 4/9/10. |
| 7/08/10 | IIRB notifies AHETF of risk of study closure |
| 7/13/09 | IIRB concludes no further action required on the four analytical protocol deviations reported on 7/7/09 |
| 07/21/10 | Close out report submitted to IIRB |
| 07/23/10 | IIRB accepts Study Completion Report; study considered closed |

US EPA ARCHIVE DOCUMENT

## Ethics-Related Study Chronologies

| Table D: AHE58 | |
|---|---|
| **Date** | |
| 10/21-22/08 | HSRB reviewed protocol and approved with recommendations |
| 03/26/09 | Submitted changes to protocol, consent form, California Bill of Rights , recruitment flyer, and product risk statements (following June 2008 HSRB meeting) |
| 04/01/09 | IIRB approves revised recruitment flyer |
| 4/06/09 | IIRB approves revised informed consent document, California Bill of Rights, and product risk statements |
| 4/20/09 | Protocol finalized and signed by Study Director |
| 04/21/09 | Phase 1 recruiting (creation of Master Grower List and Qualified Grower List). 4/21/09-7/27/09 |
| 05/12/09 | Phase 2 recruiting (calls to qualified growers). 5/12/09 to 8/14/09 |
| 6/01/09 | Phase 3 recruiting (site visits and participant selection). 6/01/09 to 8/09/09 |
| 6/19/09 | Amendment 1 submitted to IIRB<br>• Amend inclusion criteria to allow participation of workers who normally wear two layers of clothing<br>• Amend protocol to allow recruitment in any county in California or Washington<br>• Remove the efficient configuration requirement if recruitment area is expanded |
| 6/23/09 | Amendment 1 approved by IIRB |
| 6/26/09 | Two subjects monitored, 6/26/09 and 7/01/09 |
| 7/14/09 | IIRB provides notification of risk of study closure |
| 7/16/09 | Progress report submitted to IIRB |
| 7/22/09 | Amendment 2 (adding one malathion product) submitted to IIRB |
| 7/22/09 | Amendment 2 approved by IIRB |
| 07/25/09 | Supplemental information for progress report submitted to IIRB |
| 07/28/09 | Subject monitored |
| 07/29/10 | IIRB approves ongoing research; extends approval of research from 7/28/09 to 7/27/10 |
| 08/07/09 | Two subjects monitored, 08/07/09 and 08/10/09 |
| 9/02/09 | Protocol Deviations 1, 2, 3 reported to IIRB (deviations occurred 7/6/2009, 8/11/09, and 8/11/09) **[see Volume 8, pp. 307-314]**<br>• Deviation 1: Whole body dosimeter fortification samples not folded before covering<br>• Deviation 2: Some low level fortifications done in duplicate instead of triplicate on one day<br>• Deviation 3: Monitoring time for subject A5 was less than 4 hours |
| 9/03/09 | IIRB acknowledges Deviations 1, 2, and 3; no further action required |
| 12/7/09 | AHETF submits to IIRB Deviation 4 (deviations occurred 6/10/09 and 6/11/09) **[see Volume 8, pp. 315-318]**<br>• Some field fortification samples were incorrectly prepared in the laboratory, so the fortification levels were not correct. However, the researchers know the actual amounts fortified, so no field fortification samples are missing. |
| 12/15/09 | IIRB acknowledges Deviation 4; concludes no further action required |
| 2/24/10 | IIRB provides notification of risk of study closure |
| 02/21/10 | Close out report submitted to IIRB |
| 02/25/10 | IIRB accepts Study Completion Report; study considered closed |
| 4/19/10 | Two deviations reported to IIRB **[see Volume 8, pp. 354-357]**<br>• Field phase: Calculations were performed incorrectly in preparation of field fortification samples. The solution was prepared using volume corrected for density instead of gravimetrically.<br>• Analytical Phase: Concentrations of some field fortification solutions corrected for volume based on density, not gravimetrically, resulting in incorrect field fortification concentrations. |
| 4/20/10 | IIRB acknowledges two deviations that were reported after study closure |

US EPA ARCHIVE DOCUMENT

## Ethics-Related Study Chronologies

| Table E: AHE59 | |
|---|---|
| **Date** | |
| 10/21-22/08 | HSRB reviewed protocol and approved with recommendations |
| 01/16/09 | Submitted documents to IIRB to amend protocol, consent form, and product risk statements (following June 2008 HSRB meeting) |
| 01/19/09 | IIRB approves revised documents |
| 1/23/09 | Protocol finalized and signed by Study Director |
| 01/26/09 | Phase 1 recruiting (creation of Master Grower List and Qualified Grower List). 1/26/09 to 3/5/09 |
| 02/06/09 | Phase 2 recruiting (calls to grower list). 2/06/09 to 3/28/09 |
| 3/30/09 | Phase 3 recruiting (site visits and participant selection) – 3/30/09 to 5/30/09 |
| 4/30/09-5/09/09 | 4 Subjects monitored on 4/30/09, 5/07/09, 5/08/09, 5/09/09 |
| 5/11/09 | Protocol Amendment 1 and Deviation 1 submitted to IIRB **[see Volume 10, pp. 140-152]**<br>• Amendment 1: Adding 2 carbaryl products were added to the protocol<br>• Deviation 1: No photographs were taken of the subjects after monitoring, in violation of SOP AHETF-10.C.4 |
| 5/19/09 | IIRB approves Amendment 1 |
| 5/20/09 | IIRB acknowledges Deviation 1; concludes no further action necessary |
| 6/16/09 | Protocol Deviation 2 submitted to IIRB **[see Volume 10, pp. 153-156]**<br>• Deviation was the use by two monitored subjects of carbaryl products not previously approved by IIRB (deviation occurred on 5/07/09 and 5/09/09) |
| 6/24/09 | IIRB concludes no further action required on Protocol Deviation 2 |
| 7/14/09 | IIRB provides notification of risk of study closure |
| 7/16/09 | Progress report submitted to IIRB |
| 7/29/09 | IIRB approves ongoing research; extends approval of research from 7/28/09 to 7/27/10 |
| 02/22/10 | Close out report submitted to IIRB |
| 02/25/10 | IIRB accepts Study Completion Report; study considered closed |

US EPA ARCHIVE DOCUMENT

## Time Spent Spraying

| Table F. Amount of Time Reported Spraying (in Minutes) | | | | | |
|---|---|---|---|---|---|
| **MU ID** | **AHE55** | **AHE56** | **AHE57** | **AHE58*** | **AHE59** |
| A1 | 192 | 107 | 68 | *[345]* | 195 |
| A2 | 78 | 179 | 117 | *[299]* | 77 |
| A3 | 208 | 159 | 142 | *[255]* | 156 |
| A4 | 178 | 151 | 201 | *[360]* | 384 |
| A5 | 331 | 166 | 218 | *[188]* | --- |

**AHE58 spray times could not be determined from observation log. Dermal monitoring times are provided in the column for AHE58, as a substitute for spray time. Spray time is shorter than monitoring time, so AHE58/A5 clearly did not spray for 4 hours. It is unclear if the other MUs in AHE58 sprayed for at least four hours.*

Section 7.8 of the protocol states that: "Each MU shall consist of a period of at least 4 hours of spraying and at least 3 tank loads of the spray mixture."

Table F shows the number of minutes for which the subjects operated their sprayers. This time included moving from one application site to another with a tank of spray, but did not include break time or time spent mixing and loading and driving between the application site and the mixing/loading station.

Gray shading highlights the subjects who did not operate their sprayers for at least 4 hours, as required in Section 7.8 of the protocol. Only two of the 19 subjects for which spray time could be determined had their spray equipment on for "at least 4 hours."



US EPA ARCHIVE DOCUMENT

## § 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
## AHE55 (MRID 48303503 )

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<br>• all research proposals reviewed,<br>• scientific evaluations, if any, that accompany the proposals,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | Y<br>n/a<br>Y<br>Y | Initially addressed in protocol;<br>Approved English CFs:<br>p 259<br>Approved Spanish CFs:<br>272<br>Progress Rpt 223<br>Close Out Report 287 |
| | §1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution. | | N | All post-HSRB IIRB reviews were under expedited procedures; no minutes were made. |
| | §1115(a)(3): Records of continuing review activities. | | Y | 220, 223, 287 |
| | §1115(a)(4): Copies of all correspondence between the IRB and the investigators. | | Y | 13-287 |
| | §1115(a)(5):<br>• 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;<br>• any employment or other relationship between each member and the institution | | N | Already available to EPA |
| | §1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b). | | N | Already available to EPA |
| | §1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5). | | n/a | |
| (b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f) | §1125(a) A discussion of: | (1) The potential risks to human subjects; | Y | Addressed in protocol |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | Addressed in protocol |
| | | (3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue; | Y | Addressed in protocol |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | Addressed in protocol |
| | | (5) The balance of risks and benefits of the proposed research. | Y | Addressed in protocol |
| | §1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB. | | Y | 61-214 |
| | §1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used. | | Y | Flyers & Ads in English & Span |
| | §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 | Addressed in protocol |
| | §1125(e): All correspondence between the IRB and the investigators or sponsors. | | Y | 13-287 |
| | §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 | 163 |
| (c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research | | | Y | 259-268 English<br>272-281 Spanish |
| (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 | |

US EPA ARCHIVE DOCUMENT

## § 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
## AHE56 (MRID 48303504)

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<br>• all research proposals reviewed,<br>• scientific evaluations, if any, that accompany the proposals,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | Y<br>n/a<br>Y<br>Y | Initially addressed in protocol;<br>Approved English CF:167<br>Approved Spanish CF: 188<br>Progress report 246<br>Close-out report 294 |
| | §1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution. | | N | All post-HSRB IIRB reviews were under expedited procedures; no minutes were made. |
| | §1115(a)(3): Records of continuing review activities. | | Y | Progress report 246 |
| | §1115(a)(4): Copies of all correspondence between the IRB and the investigators. | | Y | 16-295 |
| | §1115(a)(5):<br>• 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;<br>• any employment or other relationship between each member and the institution | | N | Already available to EPA |
| | §1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b). | | N | Already available to EPA |
| | §1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5). | | n/a | |
| (b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f) | §1125(a) A discussion of: | (1) The potential risks to human subjects; | Y | Addressed in protocol |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | Addressed in protocol |
| | | (3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue; | Y | Addressed in protocol |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | Addressed in protocol |
| | | (5) The balance of risks and benefits of the proposed research. | Y | Addressed in protocol |
| | §1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB. | | Y | English versions 140<br>Spanish versions 188 |
| | §1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used. | | Y | Approval of Flyers & Ads in English & Spanish 218 |
| | §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 | Addressed in protocol |
| | §1125(e): All correspondence between the IRB and the investigators or sponsors. | | Y | 16-295 |
| | §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 | 224-225 |
| (c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research | | | Y | 251-259 English<br>No Spanish speakers enrolled |
| (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 | |

US EPA ARCHIVE DOCUMENT

**§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review**
**AHE57 (MRID 48289608)**

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<br>• all research proposals reviewed,<br>• scientific evaluations, if any, that accompany the proposals,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | Y<br>n/a<br>Y<br>Y | Initially addressed in protocol;<br>English 80, Spanish 90<br>Progress report 115<br>Close-out report 147 |
| | §1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution. | | N | 155-164 |
| | §1115(a)(3): Records of continuing review activities. | | Y | 105-145 |
| | §1115(a)(4): Copies of all correspondence between the IRB and the investigators. | | Y | 13-172 |
| | §1115(a)(5):<br>• 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;<br>• any employment or other relationship between each member and the institution | | N | 157 |
| | §1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b). | | N | Already available to EPA |
| | §1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5). | | n/a | |
| (b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f) | §1125(a) A discussion of: | (1) The potential risks to human subjects; | Y | Addressed in protocol |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | Addressed in protocol |
| | | (3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue; | Y | Addressed in protocol |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | Addressed in protocol |
| | | (5) The balance of risks and benefits of the proposed research. | Y | Addressed in protocol |
| | §1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB. | | Y | Addressed in protocol |
| | §1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used. | | Y | Addressed in protocol |
| | §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 | Addressed in protocol |
| | §1125(e): All correspondence between the IRB and the investigators or sponsors. | | Y | 13-172 |
| | §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 | Approval of all submitted documents 79 |
| (c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research | | | Y | English 120<br>No Spanish speakers enrolled |
| (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 | |

US EPA ARCHIVE DOCUMENT

**§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review**
**AHE58 (MRID 48289609)**

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<br>• all research proposals reviewed,<br>• scientific evaluations, if any, that accompany the proposals,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | Y<br>n/a<br>Y<br>Y | Initially addressed in protocol;<br>English 151, Spanish 176<br>Progress report 242<br>Close-out report 320 |
| | §1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution. | | N | Some approvals under expedited review, minutes on progress report 300 |
| | §1115(a)(3): Records of continuing review activities. | | Y | 301-318 |
| | §1115(a)(4): Copies of all correspondence between the IRB and the investigators. | | Y | 17-357 |
| | §1115(a)(5):<br>• 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;<br>• any employment or other relationship between each member and the institution | | N | 302 |
| | §1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b). | | N | Already available to EPA |
| | §1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5). | | n/a | |
| (b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f) | §1125(a) A discussion of: | (1) The potential risks to human subjects; | Y | Addressed in protocol |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | Addressed in protocol |
| | | (3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue; | Y | Addressed in protocol |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | Addressed in protocol |
| | | (5) The balance of risks and benefits of the proposed research. | Y | Addressed in protocol |
| | §1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB. | | Y | Addressed in protocol |
| | §1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used. | | Y | Addressed in protocol |
| | §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 | Addressed in protocol |
| | §1125(e): All correspondence between the IRB and the investigators or sponsors. | | Y | 17-357 |
| | §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 | Approval of all submitted documents 149 |
| (c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research | | | Y | English 257<br>Spanish 286 |
| (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 | |

US EPA ARCHIVE DOCUMENT

## § 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review AHE59 (MRID 48289610)

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<br>• all research proposals reviewed,<br>• scientific evaluations, if any, that accompany the proposals,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | Y<br>n/a<br>Y<br>Y | Initially addressed in protocol;<br>English 90, Spanish 77<br>Progress report 159<br>Close-out report 193 |
| | §1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution. | | N | 184-188 |
| | §1115(a)(3): Records of continuing review activities. | | Y | 140-182 |
| | §1115(a)(4): Copies of all correspondence between the IRB and the investigators. | | Y | 14-195 |
| | §1115(a)(5):<br>• 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;<br>• any employment or other relationship between each member and the institution | | N | 189 |
| | §1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b). | | N | Already available to EPA |
| | §1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5). | | n/a | |
| (b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f) | §1125(a) A discussion of: | (1) The potential risks to human subjects; | Y | Addressed in protocol |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | Addressed in protocol |
| | | (3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue; | Y | Addressed in protocol |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | Addressed in protocol |
| | | (5) The balance of risks and benefits of the proposed research. | Y | Addressed in protocol |
| | §1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB. | | Y | Addressed in protocol |
| | §1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used. | | Y | Addressed in protocol |
| | §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 | Addressed in protocol |
| | §1125(e): All correspondence between the IRB and the investigators or sponsors. | | Y | 14-195 |
| | §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 | Approval of all submitted documents 74 |
| (c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research | | | Y | English 164<br>No Spanish speakers enrolled |
| (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 | |

US EPA ARCHIVE DOCUMENT

# Responsiveness to Major EPA and HSRB Comments

| Table G. Responsiveness to Major EPA and HSRB Comments on Protocols for AHE55, AHE56 (reviewed at the June 2008 HSRB Meeting) | | |
|---|---|---|
| **EPA or HSRB Comment** | **Addressed before executing AHE55, AHE56?** | **Addressed before executing AHE57, AHE58, AHE59?** |
| 1. Characterize subject representativeness | Yes, information gathered for AHE55 and AHE56 | Yes, information gathered for AHE57, AHE58, and AHE59 |
| 2. Disallow participation by employees of Local Site Coordinator | Yes | Yes |
| 3. Use bilingual researchers rather than interpreters | Yes | Yes |
| 4. Explain how Study Director will determine understanding of subjects in consent interviews conducted in Spanish | Yes | Yes |
| 5. Provide toll-free English and Spanish information numbers | Yes | Yes |
| 6. Capture ethnicity and sex of participating workers | Yes | Yes |
| 7. Clarify intended purpose of photos/videos | Yes | Yes |
| 8. Minimize identifiable photos/videos | Yes | Yes |
| 9. Refer to "AHETF" consistently *vice* "AHETF" and "Sponsor" | Yes | Yes |
| 10. Drop reference to "cognitively impaired" from recruitment flyer | Yes | Yes |
| 11. Change "liquid pesticides" to "airblast application of liquid sprays" | Yes | Yes |
| 12. Minimize paraphrasing of SOPs in protocols | No | Yes |
| 13. Simplify submissions | No | Yes |
| 14. Explain voluntary nature of participation at the beginning of consent forms | No | No, but has been addressed in subsequent protocols |
| 15. Ensure accurate Spanish translations | No | No, but has been addressed in subsequent protocols |
| 16. Update SOPs to:<br>• Insure all materials provided to candidates are approved by IRB<br>• Insure label and MSDS summaries are approved by IRB<br>• Clarify role of impartial witness to consent interviews with non-readers<br>• Replace references to WIRB with generic references<br>• Account for number of workers associated with each grower<br>• Define processes of diversity selection of growers and construction of an efficient configuration of MUs in a new SOP | No | Yes |
| 17. Better justify judgments of infeasibility of incorporating additional elements of random selection | No | No, but has been addressed in subsequent protocols |
| 18. Considering restriction to monitoring no more than one worker per employer | Only 1 worker monitored per employer. Restriction added in subsequent protocols. | Only 1 worker monitored per employer. Restriction added in subsequent protocols. |

US EPA ARCHIVE DOCUMENT

# Responsiveness to Major EPA and HSRB Comments

| Table H. Responsiveness to Major EPA and HSRB Comments on Protocols for AHE57, AHE58, AHE59 (reviewed at the October 2008 HSRB Meeting) | | |
|---|---|---|
| **EPA or HSRB Comment** | **Addressed before executing AHE57, AHE58, AHE59?** | **Addressed in subsequent AHETF protocols?** |
| 1. Characterize representativeness of subjects | Yes | Yes |
| 1. 5 monitoring units in each cluster, each from a different farm, is needed to ensure that the design and analyses are scientifically sound. | Only 1 worker monitored per employer. | Yes |
| 2. Select of Local Site Coordinators with demonstrable training and expertise in survey implementation to ensure optimal recruiting and thereby enhance the usefulness of the data | Yes | Yes |
| 3. The Local Site Coordinator, the Principal Field Investigator, the Field Facility, the Analytical Facility, and the Principal Analytical Investigator must be identified in the protocol | Yes, addressed prior to study initiation | Yes, addressed prior to study initiation |
| 4. Any key members of the research team who will have contact with the research subjects or their identifiable data must receive and document their recent (not expired) training in human subjects' protection | Yes, and relevant SOP subsequently revised. | Yes. |
| 5. Revise subject recruitment plan to specifically address the probability that subjects may also be growers. | No | Yes; relevant SOP revised |
| 6. Remove risks of agricultural work from the listing of risks related to the research. | Yes | Yes |
| 7. Identify risks of pesticide products that are due to scripting. | Yes | Yes |

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