UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

March 21, 2019

MEMORANDUM

SUBJECT: Ethics Review of Completed AHETF Study AHE600 on Determination of Dermal and Inhalation Exposure to Workers during Mixing, Loading and Application of Pesticides in Managed Horticultural Facilities using Powered Handgun Equipment

FROM: Michelle Arling, Human Research Ethics Review Officer
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TO: Dana Vogel, Director
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Charles "Billy" Smith, Acting Director
Pesticide Re-evaluation Division, OPP

REF: Cañez, Victor and Baugher, Douglas (2019) Determination of Dermal and Inhalation Exposure to Workers during Mixing, Loading and Application of Pesticides in Managed Horticultural Facilities using Powered Handgun Equipment. Study Number AHE600, 1918 p., February 15, 2019. (MRID 50803701)

Bruce, Eric D. and Holden, Larry R. (2019) Agricultural Handler Scenario Monograph: Mixing/Loading/Application using Powered Handgun Equipment in Managed horticultural Facilities (i.e., greenhouses and nurseries). Report Number AHE1023, 287 p., **[date]**. (MRID)

Baugher, Douglas (2019) IRB Correspondence Report for Study AHE600. Related Submissions. Study Report AHE600 and Scenario Monograph Report No. AHE1023. 811 p., February 19, 2019. (MRID 50803702)

I have reviewed the available information concerning the ethical conduct of the research reported by the Agricultural Handler Exposure Task Force (AHETF) in the referenced documents. The documents describe the implementation and results of a field study, the objective of which was to develop data to determine the potential dermal and inhalation exposure for workers who perform open pour mixing, loading and application activities, and where

appropriate associated equipment clean up activities, using powered handgun equipment to make foliar applications in managed horticultural facilities. The monograph report summarizes the dermal and inhalation exposure data collected through study AHE600 for the open pour mixing, loading and application using powered handgun equipment in managed horticultural facilities scenario.

Based on the information available, study AHE600 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. Therefore, if study AHE600 and scenario monograph report AHE1023 are determined to be scientifically acceptable, I find no barrier in regulation to EPA's reliance on them in actions under FIFRA or §408 of FFDCA.

In addition, under 40 CFR 26.1604, EPA is required to seek input from the Human Studies Review Board (HSRB) for intentional exposure human studies covered by EPA's human studies rule that are initiated after April 7, 2006. EPA will share study AHE600, scenario monograph report AHE1023, the associated support documents, and EPA's science and ethics reviews of the study with the HSRB for their review. This memorandum and its attachments constitute EPA's ethics review.

Summary Characteristics of the Research

Study AHE600's objective "was to develop data to characterize the potential exposure of workers who perform open pour mixing, loading and application activities using powered handgun equipment in managed horticultural facilities." (AHE600 Study Report, p. 11). In addition, workers who normally also performed equipment clean up following such applications were also monitored during these activities. The research was conducted in greenhouses and nurseries, and the study involved applications to both ornamental and vegetable plantings. The dermal and inhalation exposure information was collected from workers conducting these tasks while wearing inner dosimeters (long underwear and socks) under regular work clothes and air sampling pumps. In addition, researchers collected face and hand wipe samples from the subjects at the end of the workday as well as at other points during the monitoring events.

A monitoring unit or MU refers to a single subject (worker) who is carrying out activities using a particular pesticide formulation under a specific scenario, on a particular day. For each MU in this study, the subjects conducted at least three loading events consisting of open pour loading of granules into application equipment. MUs also included other non-study work-related tasks, as well as breaks. Every MU provides an estimate of a single handler-day of exposure to the worker who open poured granular products into application equipment through measurement of the dermal and inhalation exposure potential for a single subject for a time period that represents a typical workday. A cluster is a group of MUs that are performed close together in terms of location and time. The AHE600 protocol, approved by Independent Investigational Review Board (IIRB), specified 30 MUs to be conducted, three MUs in each of ten geographic monitoring areas. The protocol was amended (AHE600 Study Report, p. 428-430; Amendment 6) to expand the geographic monitoring areas and to allow more than 3 MUs to be collected in a single monitoring area. Although a total of 30 subjects were enrolled in the study and monitored,

the study resulted in only 27 valid MUs. The first MU was conducted in October 2013 and the last MU was conducted in April 2017.

The table below identifies the monitoring areas for the 30 MUs and the number of workers/MUs per monitoring area.

Monitoring Area Number/ID Code	**States Included in Monitoring Area**	**Monitoring Units Conducted**
1/601	Lower New England	2
2/602	Mid-Atlantic	2
3/603	North Carolina-South Carolina-Tennessee	5*
4/604	Northern Florida	4
5/605	Southern Florida	2
6/606	Ohio-Pennsylvania	3
7/607	Indiana-Michigan	3
8/608	Illinois-Wisconsin	5*
9/609	Louisiana-Texas	1
10/610	Oregon-Washington	3*

* The AHE600 Study Report notes that "[a] single MU from each of these monitoring areas was considered invalid, leaving a total of 27 valid MUs." (AHE600, p. 28)

Required Reviews of Protocol and Ethics-Related Chronology

A draft of the protocol for study AHE600 was submitted to the Independent Investigational Review Board, Inc. (IIRB) on September 29, 2011 approved. The IIRB-approved protocol and associated materials were submitted to EPA for review by EPA and the HSRB. The HSRB discussed the protocol and EPA's scientific and ethics review[1], dated December 30, 2011, at a meeting on January 26, 2012 and responded with support for the study to move forward after the AHETF addressed comments from EPA and the HSRB. With regard to ethics, the HSRB's final meeting report concluded that, "the protocol submitted for review, if modified in accordance with EPA (Evans, Sarkar and Sherman 2011) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."[2] The AHETF made revisions based on feedback from EPA and HSRB, submitted the revised documents to IIRB on April 25, 2012 and received approval on May 1, 2012 (IIRB Correspondence Report, p. 329). A summary of EPA's and HSRB's recommendations and how the AHETF addressed them is included in Attachment 1.

[1] Evans, J., Sarkar, B., and Sherman, K. Science and Ethics Review of AHETF Scenario Design and Protocol AHE600 for Exposure Monitoring of Workers during Mixing, Loading and Application of Pesticides in Managed Horticultural Facilities using Powered Handgun Equipment. December 30, 2011.

[2] Philpott, Sean. January 26, 2012 EPA Human Studies Review Board Meeting Report. April 11, 2012. https://archive.epa.gov/osa/hsrb/web/pdf/hsrb_meeting_final_report_january_2012.pdf

Oversight of the protocol was handled initially by IIRB, which was registered with the Office of Human Research Protections (OHRP). On October 24, 2012, the AHETF was notified that as of October 1, 2012, IIRB "was absorbed into its parent company Schulman Associates Institutional Review Board, Inc…." (IIRB Correspondence Report, p. 375). Schulman IRB maintained IIRB's registration with the OHRP, and subsequent review of study AHE600 was performed by Schulman IRB #3. Schulman IRB's written policies and procedures were reviewed and are on file with EPA. On November 7, 2017, Schulman IRB notified the AHETF "that Chesapeake IRB and Schulman IRB have merged to created Advarra" (IIRB Correspondence Report, p. 727-729). At this point, all MUs had been conducted. Schulman IRB conducted the last annual continuing review of the study (IIRB Correspondence Report, p. 726). Advarra IRB's oversight of the study included receipt of protocol deviation 3, approval of amendment 9 to the protocol, and receipt of the study close-out report (IIRB Correspondence Report, p. 797-811). Advarra IRB is registered with OHRP and provided EPA with its written policies and procedures. All necessary documentation for each of the IRBs involved in review of this study were provided to EPA.

A summary of the ethics-related protocol amendments and deviations is included below.

Completeness of Submission

The checklist used by EPA to verify fulfillment of the requirements of §26.1303 as they apply to this research is provided in Attachment 2. This ethics review considers the study materials referenced above, the AHETF's responses to EPA questions which were integrated into this memorandum, and IRB correspondence.

Grower Recruitment

With regard to recruitment of growers, the protocol references SOPs 11.K. and 11.M. The recruitment process outlined in the protocol and these SOPs appears to have been followed in study AHE600.

According to the protocol and completed study report, recruitment activities occurred in three phases, summarized as follows:

- Phase 1: Create GUL from commercial grower lists. Employ professional call center to determine whether growers make handgun applications; those that do are included in the qualified grower list (QGL).
- Phase 2: Have a member of the research team contact all growers on the QGL. According to the study report, "[t]he researcher confirmed the type of spray equipment that the grower typically uses to spray their greenhouse or nursery, explained the nature of the study and the study requirements, and asked if the qualified grower would consider participating in the study." (AHE600 Study Report, p. 26) When growers who were qualified and tentatively agreed to participate were identified by researchers, their contact information was provided to the Study Director or his designee.
- Phase 3: "Contact and visit potentially eligible employers, confirm eligibility and then schedule and conduct monitoring of workers that volunteer and have experience making handgun applications in greenhouses or nurseries." (AHE600 Study Report, p. 27)

The report notes that "[t]he AHETF Study Director or recruiting personnel made an effort to contact and/or visit potentially eligible growers in order to locate growers that might participate in a timeframe and schedule to allow the monitoring to be conducted efficiently. Initial contacts were made by telephone. When promising situations arose (i.e., willing growers, suitable handler activity, and researcher availability), arrangements were made to visit the growers, inspect their equipment, and recruit participants for the study. During site visits, the research was discussed with each grower (e.g., typically the facility owner or a supervisor) and a recruitment meeting was usually held with at least one potential participant." (AHE600 Study Report, p. 27)

The protocol was amended related to grower recruitment twice. Amendment 6 expanded the monitoring areas (expanding to recruit in additional counties within already designated states and contiguous states) and re-opened recruitment in monitoring areas where 3 MUs had already been collected to allow for more than 3 MUs per monitoring area. Amendment 7 added the option for researchers to contact potential growers referred by growers contacted as part of the recruitment process. Both of these amendments were reviewed and approved by the IRB prior to implementation.

The table below is taken from page 28 of the AHE600 study report. It summarizes the extent of the lists and numbers of monitoring units (MUs) for each monitoring area. The study report provides specific details about the recruitment details by monitoring area (AHE600 Study Report, pp. 26-59)

Monitoring Area	**Grower Universe List**	**Qualified Grower List**	**Potentially Eligible Grower List**	**Eligible Employer List**	**MUs Collected**
601	1,744	213	40	2	2
602	1,156	161	36	4	2
603	1,311	176	40	5	5*
604	1,429	202	49	8	4
605	758	108	27	2	2
606	1,553	224	52	4	3
607	1,217	237	55	4	3
608	1,685	206	47	5	5*
609	1,663	186	53	2	1
610	751	116	15	5	3*
Total	**13,267**	**1,829**	**414**	**41**	**30**

* The AHE600 Study Report notes that "[a] single MU from each of these monitoring areas was considered invalid, leaving a total of 27 valid MUs." (AHE600, p. 28)

A poll of horticultural and agricultural experts conducted after all MUs for Study AHE600 were completed was taken "to evaluate the representativeness of the grower/applicators

and greenhouse/nursery facilities participating in the study." (AHE600 Study Report, p. 59) Overall, the surveys returned to the AHETF indicated the experts' belief that the growers and their facilities were representative of the industry as a whole. Of 72 surveys completed, only 2 indicated that the MUs were not representative. One respondent indicated that the MUs were not representative because the expert's facility used different application equipment (backpack sprayer vs. powered handgun). The other respondent noted that in their experience most applications are conducted by an employee rather than the grower/operator.

Subject Recruitment and Consent

Subject recruitment, selection, and consenting were carried out according to the protocol and relevant SOPs (11.B., 11.C., 11.D., 11.J.). During the grower recruitment phase and prior to recruitment of subjects, employers signed a non-coercion statement (Employer Cooperation Statement – see SOP 11.M) agreeing that they would not coerce or influence their employees' decision about whether to participate in the study and that workers' employment would not be affected regardless of their participation. They also agreed to provide alternate work for those employees who choose not to participate in the study. This step was not carried out when the grower was also the prospective subject.

Following SOP-11.B., workers were recruited through meetings with research staff, without employers present (where applicable). The researchers provided the IRB-approved recruitment flyer and informed consent materials, either in advance or at the time of the recruitment and consent meeting. The meeting covered "the goals of the research study, the procedures used in exposure monitoring, and the risks and benefits to subjects." (AHE600 Study Report, p. 390). Either as part of this meeting or following it, all interested and qualified subjects completed the consent process. In obtaining consent from each subject, the AHETF followed SOP-11.J. and the protocol. All meetings were held one-on-one between the researcher and the subject, in a private location where the discussion could not be overheard by anyone else. After reviewing the consent form and the product label (if available at the time of consent), and answering any questions, the researcher asked a series of questions (see SOP-11.J) to confirm the worker's understanding of the materials covered prior to obtaining the worker's informed consent.

Materials and meetings were offered in English and Spanish. The protocol noted that for subjects who preferred to conduct the meeting in Spanish, a bilingual researcher would be available on site both during the consent meeting and during the MU (see SOP 11.I). A total of 3 subjects requested that interactions be conducted in Spanish, and the AHETF confirmed that in each instance a bilingual researcher conducted the consent meeting and participated during the MU. The IRB reviewed and approved translations of all materials. Note, there was an error in the Spanish consent form – the hours of the IRB's call line were incorrect. This did not affect the consent process for the Spanish-speaking subjects. The AHETF's translator corrected the error and the IRB approved the amended the consent form.

Subjects met the inclusion criteria outlined in AHETF SOP 11.B. Subjects had experience handling pesticides as part of their job, were trained in safe pesticide handling procedures, provided proof that the were at least 18 years old, confirmed that they were not an

employee of a pesticide company, were in good health and had no medical conditions that would affect their ability to participate in the study. Subjects confirmed that they usually wore the personal protective equipment (PPE) required by the label, and were willing to wear the long underwear/inner dosimeter. Subjects also met the study-specific criteria listed in the protocol:

- "Have experience within the past year with open pour mixing and loading of solid or liquid formulations, and with spraying the diluted product using a powered handgun in nurseries or greenhouses, including the type of equipment to be used.
- Agree to wear chemical-resistant gloves even if the label does not require them.
- Agree to wear chemical-resistant headgear during applications involving either overhead only' spray situations or a mix of 'overhead' and 'nonoverhead' spray situations, even if the label does not require it." (AHE600 Study Report, p. 366)

The AHETF verified the age of each subject through a government-issued photo identification. The AHETF followed the protocol and SOP-11.D. to ensure that no pregnant women participated in the research. Each of the six female study participants took a pregnancy test on the day of their MU and a female member of the research team verified that the result was negative prior to the MU beginning.

Across the 10 monitoring areas, a total of 34 persons attended a consent meeting. In most instances, only one worker was eligible and consented. In the single situation where multiple workers attended the recruitment meeting, selection of the worker to enroll in the study was done by coin toss. Of the 30 subjects who completed MUs, 6 were female and 24 were male. Subjects ages ranged from 22 years old to 63 years old. The AHE600 Study Report includes additional information about the subjects who completed MUs on pp. 97-108.

Product-Specific Information for Subjects

The protocol called for providing each subject with the identity of the substance that he or she would be monitoring, in addition to reviewing a copy of the labeling and discussing required personal protective equipment (PPE) and potential health effects (see also SOP-11.E.). Because the specific product to be used was selected by the grower, the product identity was not always known to the researchers at the time of the consent meeting. The protocol was amended to specify that prior to monitoring (rather than during the consent meeting), information about the products to be used would be provided to the subject and to add that researchers would specifically discuss pertinent sections of the directions for use with subjects (AHE600 Study Report, pp. 424-427).

The AHETF confirmed that all participating subjects were informed of the active ingredient and the end-use product before monitoring began. The AHETF also confirmed that field staff reviewed the label information with the subjects prior to participating in the study consistent with the protocol, SOP-11.E. and the informed consent form.

Personal Protective Equipment and Work Clothing

The protocol called for subjects to wear the PPE required by the labeling. The protocol also noted that SOP 11.E. would be followed, which requires researchers to monitor subjects'

compliance with the labeling requirements. A summary of the clothing and PPE worn by each subject can be found in tables 4 and 5 of the AHE600 Study Report (pp. 109-119). The AHETF confirmed that the subjects participating in study AHE660 wore the required PPE as specified on product labeling and in the approved protocol (i.e., chemical resistant hat when making overhead spray applications), along with the outer clothing prescribed in the protocol. The clothing and PPE worn by workers was consistent with the requirements of the U.S. EPA Worker Protection Standard. All subjects wore their own long-sleeved shirts and long pants (or in one instance, coveralls), over the whole-body dosimeters provided by the AHETF. The AHETF confirmed that all work clothing was laundered prior to the day of the MU. In addition, the AHETF provided the required chemical-resistant new gloves worn by all participating workers. Subjects wore their own shoes and socks. Some workers wore protective eyewear (e.g. goggles or protective glasses) and respiratory protection as required by the pesticide label or based on their own preference.

The study report notes that for 4 MUs, subjects' clothing had a small hole or tear (MUs 9, 18, 28, 30). The AHETF acknowledged that neither the SOPs nor the protocol considered how to address problems with the worker-provided garments. Faced with the choice of repairing the clothing with tape that was generally less than 1 square inch, or replacing the clothing with new garments that would be more resistant to penetration and less representative of workers' clothing, the Study Director determined that taping the holes was the preferred path forward. The AHETF noted that the taping did not impact the dosimetry. The small patching of clothing did not impact subjects' safety.

Heat Stress Monitoring

The AHETF has SOPs related to subject safety and monitoring weather conditions to avoid heat-related illness (SOP 11.G., 11.N). The protocol originally referenced SOP 11.G. and was amended to also reference SOP 11.N. (AHE600 Study Report, p. 423) These SOPs were followed during the study to minimize the risks of heat-related illness. All researchers were trained to recognize the symptoms of heat-related illness, a medical professional (nurse, certified first responder, or emergency medical technician) was on-site for each monitoring event and checked subjects for signs of heat-related illness. Observers closely watched subjects, reminded them to take breaks as necessary, and offered fluids. Table 11 of the AHE600 Study Report summarizes the weather conditions, including heat index, during each MU. In two instances, the heat index exceeded 105° (AHE600 Study Report, pp. 275-284). In one instance (MU 23), the heat index was just above 105° inside an enclosed greenhouse, which was not reflective of the application occuring in a greenhouse with doors opened at both ends and sides rolled up. No cooling action was taken in this instance. In the second instance (MU 18), the heat index reached 117° and two cooling periods were used to safely manage heat exposure. Apart from these two situations, no other MUs were stopped due to heat-related symptoms. There were no reports of heat-related illness during this study.

Subject Compensation

The protocol indicated that subjects would be compensated $20 for attending a consent meeting and $80 for participating in a monitoring event. The AHETF confirmed that all 34

subjects who participated in a consent meeting received $20, and that all workers who were dressed for a monitoring event were compensated $80.

Provision of Personal Exposure Results to Subjects

The protocol (AHE600 Study Report, p. 407), consent form (IIRB Correspondence Report, p. 97), and AHETF SOP 11.J., all indicate that subjects may request their personal study results. The AHETF noted that of the 30 subjects who were monitored, 28 requested their personalized monitoring results. The letters were all dated February 11, 2019 and were mailed by the Study Director. Letters were prepared in the language used during the consent meeting; three letters were in Spanish and the remainder were in English.

Protocol Amendments and Deviations

The protocol was amended 9 times and 4 deviations were reported to the overseeing IRBs. This section discusses the amendments and deviations related to the ethical conduct of the study.

Additional Surrogate Chemicals

The protocol was amended twice to add additional surrogate chemicals. Submitted and approved in May 2015, Amendment 3 added an additional active ingredient (acephate) to the list of surrogate chemicals that could be used in the study (IIRB Correspondence Report, pp. 464-468). This protocol amendment did not include a corresponding edit to the consent materials, which also list all potential surrogate chemicals. Neither the AHETF nor the overseeing IRB (Schulman) caught the error during the amendment submission and approval process. The AHETF became aware of this omission of acephate from the consent form during a consent meeting where acephate was to be used during the study. The AHETF researcher wrote in acephate on the consent form, and corrected the error by revising the consent form and submitting it to the IRB for approval (IIRB Correspondence Report, pp. 474-489). Because the subject to be exposed to acephate was informed of its identity, the consent form was amended by hand to note the product, and researchers reviewed the product's labeling, including precautions, PPE, and directions for use, with the subject prior to initiating the monitoring, this deviation did not adversely impact the subject's safety or welfare.

Submitted and approved in February 2017, Amendment 8 revised both the protocol and the informed consent materials to include an additional active ingredient (mefenoxam) to the list of surrogate chemicals that could be used in the study (IIRB Correspondence Report, pp. 621-688).

Heat-Related Illness/Weather Condition Monitoring

Submitted and approved in May 2015, Amendment 4 revised the protocol to allow for heat stress management using the "wet bulb/globe/dry bulb temperature (WBGT) method as described in SOP AHETF-11.N.0." (IIRB Correspondence Report, p. 472). This amendment allowed for an additional method for ensuring subjects' safety when the heat index reached levels of concern. This amendment did not adversely impact subjects' safety or welfare.

Worker Training and Product-Specific Information

Submitted and approved in September 2016, Amendment 5 revised the protocol and consent form to revise the criteria regarding training under the Worker Protection Standard and added a requirement for researchers to review the product label, including the section "Directions for Use", with subjects prior to initiating the monitoring (IIRB Correspondence Report, pp. 545-611). In July 2016, EPA reviewed another AHETF study (AHE120), and recommended that the AHETF revise its description of worker eligibility based on satisfying the training requirements under the Worker Protection Standard, and to clarify that researchers would discuss the relevant portions of the directions of use with subjects. Based on this feedback, the AHETF amended the protocol and consent forms for ongoing studies, including study AHE600. This amendment did not adversely impact subjects' safety or welfare.

The AHETF reported four protocol deviations (AHE600 Study Report, pp. 435-440). Two of the deviations were related to the methods for collection and analysis of samples, and did not affect the ethical conduct of the study. One of the deviations was related to recruitment in expanded geographical areas prior to amending the protocol to explicitly acknowledge that the areas could be expanded to adjacent states.

One reported deviation related to MU 11. The subject used an approved surrogate material (imidacloprid). However, the product was in a water-soluble package (WSP). The report notes that

> [t]he Monitoring Unit Selection and Construction Plan for this scenario states 'Exposure monitoring for this scenario will only include open-pouring situations since open pouring is most common and is expected to represent a higher exposure potential than the use of closed systems (which includes water-soluble packets).' In addition, the study protocol states that the 'objective of this study was to develop data to characterize the potential exposure of workers who perform open pour mixing, loading and application activities using powered handgun equipment in managed horticultural facilities.' (AHE600 Study Report, p. 64)

WSPs are engineering controls designed to reduce worker exposure to pesticides while loading them into application equipment and preparing tank mixes. Therefore, the protocol deviation did not adversely affect the subject's safety or welfare. However, the deviation does mean that this MU is considered invalid although the full day of monitoring was completed.

The AHETF reported two non-compliance deviations to the IRBs. The first non-compliance report noted that a researcher obtaining consent crossed out the witness signature block, which is to be used in instances where the researcher reads the consent materials to a subject who is unable to read and understand the materials on his or her own. The witness certifies that what the researcher presented was accurate. This section is only relevant for subjects who are illiterate or low literacy. The researcher scratched out the witness section because the subject read the materials on his/her own and did not need a witness to certify the accuracy of the researcher's presentation. The IRB became aware of this practice through the submission of the most recently completed consent forms as part of the continuing review of the study (IIRB Correspondence Report, pp.

399-402). The AHETF acknowledged the deviation and proposed corrective action (instructing all researchers to leave the witness section blank if not relevant) the day after submitting their continuing review form (IIRB Correspondence Report, pp. 403-404). This protocol deviation did not adversely affect the subject's safety or welfare.

The second non-compliance deviation reported two issues discussed previously in this memo: the omission of acephate as a surrogate chemical from the consent forms and the incorrect start time for the IRB in the Spanish translation of the materials (IIRB Correspondence Report, p. 474). The AHETF corrected both of these errors through submission of revised consent forms to the IRB for approval. Neither of these errors impacted subjects' safety or welfare.

There was also an unreported protocol deviation. The protocol notes that on the day of monitoring, subjects will "have their hands washed again, with the assistance of a researcher, in mild surfactant and water before they eat anything or smoke…" (AHE600 Study Report, p. 381). For MU 13, the researchers failed to collect a handwash sample prior to the subject smoking a cigarette (AHE600 Study Report, p. 214). The observations for MU 13 note that prior to be observed smoking, the subject left the monitoring area and went to the office. Because the subject lit the cigarette before the observer noticed, no handwash sample was collected. The subject did not report any adverse effects from participation in the study. In the future, EPA recommends that observers and subjects are reminded of the conditions requiring a handwash sample to be collected at the beginning of the monitoring day.

Applicable Ethical Standards

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

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

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

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

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

40 CFR §26.1703 prohibits research involving intentional exposure of pregnant or nursing women or of children under 18. All subjects who participated in study AHE600 were at least 18 years old. With subject screening and pregnancy testing on the day of monitoring, the AHETF confirmed that no female subjects were pregnant or lactating. Therefore, 40 CFR §26.1703 does not prohibit reliance on this research.

Substantial compliance with 40 CFR 26 subparts A through L

40 CFR §26.1705 requires that EPA have "adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." Within this range, only subparts K and L are directly applicable to the conduct of third-party research such as this. The AHE600 study was conducted in substantial compliance with subparts K and L.

Compliance with 40 CFR §26 subpart M

As documented in Attachment 2 to this review, the central requirements of 40 CFR §26 subpart M, §26.1303 to document the ethical conduct of the research were addressed.

Compliance with FIFRA §12(a)(2)(P)

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

Conclusion

This study reports research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L. In its conduct, study AHE600 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. From EPA's perspective, if this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA's reliance on it in actions under FIFRA or §408 of FFDCA. This research will also undergo review by the Human Studies Review Board.

cc: Rick Keigwin
Matt Crowley
David Miller
Dana Friedman

Attachment 1: EPA and HSRB ethics-related comments on protocol & AHETF responses
Attachment 2: §26.1303 Completeness checklist for AHE600 Study

Attachment 1
Ethics Comments from January 2012 HSRB Meeting & AHETF Actions

EPA Comments on AHE600 Protocol	AHETF Actions to Address Comments
Revise the discussion "psychological risks" to identify the risk of a breach of confidentiality associated with photographs or video as a potential risk.	AHETF revised the protocol to note that: "Participating in AHETF exposure monitoring studies involves activities that are unusual and might cause subjects psychological distress. These include: • Performing an over-the-counter pregnancy test prior to participation (females only) • Allowing a researcher to assist with removing long underwear • Breaching of confidentiality associated with photographs or video." (AHE600 Study Report, p. 369)
Clarify in the protocol that the most significant psychological risk associated with pregnancy testing is the unwanted disclosure of test results, rather than embarrassment associated with administration of the test.	AHETF revised the protocol to read as follows: "Minimizing the risk of psychological harm related to pregnancy tests involves providing a private place for women to take the test and following procedures outlined in SOP AHETF-11.D to ensure the confidentiality of a positive result, along with maintaining the confidentiality of the results." (AHE600 Study Report, p. 369)
Add to the consent form the risks of breach of confidentiality and unwanted disclosure of pregnancy results.	AHETF did not make this revision. The HSRB recommended against including these specific risks in the consent form because it might give subjects the erroneous impression that the risks are particularly significant or that appropriate steps have not been taken to mitigate these risks.
In the protocol, describe the types of locations where recruitment discussions will occur.	The protocol was revised to explain that "The consenting process will take place in a private setting where the volunteer cannot be seen by, or heard by, anyone other than the authorized participants in the consenting session. "Private settings" may be on site or off site and may include (but not be limited to) private office space, conference rooms, break rooms, automobiles, and, private outdoor areas. A description of the private setting will be maintained with the consenting documents." (AHE600 Study Report, p. 378)
HSRB Comments on AHE600 Protocol	**AHETF Actions to Address Comments**
Revise the consent form as follows: "~~If you do~~ **In order to** take part in this study, you must read and sign this consent form."	Revised as recommended. See IIRB Correspondence Report, p. 302.

Revise the consent form to note that pregnancy test will be taken before the beginning of the monitoring period.	Revised as recommended. See IIRB Correspondence Report, p. 305.
Add to the consent form a line indicating the name and contact information of the Study Director or other individual to be contacted if the participant experiences an adverse event within 24 hours.	Revised as recommended. See IIRB Correspondence Report, p. 308.

Attachment 2
§ 26.1303 Checklist for Completeness of AHE600 Submitted for EPA Review

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

Requirement			Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y	
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	
	§1115(a)(3): Records of continuing review activities.		Y	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	
	§1115(a)(5): • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution		Y	
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		Y	Procedures on file for IIRB, Schulman IRB, and Advarra IRB.
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		n/a	Subjects were offered the option to request personal exposure results. Provided to 28/30 subjects.
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	
		(2) The measures proposed to minimize risks to the human subjects;	Y	
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	
		(5) The balance of risks and benefits of the proposed research.	Y	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.		Y	
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.			n/a	