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

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

January 4, 2012

MEMORANDUM

SUBJECT: Ethics Review of Completed AEATF II Aerosol Scenario Worker Exposure Monitoring Study

FROM: Kelly Sherman
Human Studies Ethics Review Officer
Immediate Office of the Director
Office of Pesticide Programs

TO: Nader Elkassabany, PhD, Chief
Risk Assessment and Science Support Branch
Antimicrobials Division

REF: Testman, R.J. and Boatwright, M.T. (2011) A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using a Pressurized Aerosol Can for Indoor Surface Disinfecting. Unpublished study prepared by Golden Pacific Laboratories, LLC, under Project No. AEA04, Report No. 070270. 1851 p. (MRID 48659001)

Addendum 1: Protocol Amendment 4, dated February 8, 2011

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced document, which describes the execution and results of a study in which dermal and inhalation exposure of professional janitorial workers to antimicrobial pesticides was monitored as they applied a liquid antimicrobial pesticide product containing C14 alkyl dimethyl benzyl ammonium chloride (C14 ADBAC) using hand-held pressurized aerosol canisters. If it is determined to be scientifically acceptable, I find no barrier in regulation to the Environmental Protection Agency's (EPA's) reliance on this study in actions under the Federal Insecticide, Fungicide, or Rodenticide Act (FIFRA) or the Federal Food, Drug, and Cosmetic Act (FFDCA).

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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. The report and Addendum 1, together with the materials submitted for the initial protocol review, contain all required information.

Background and Chronology

The scenario design and protocol for this study was approved by the overseeing institutional review board, the Independent Investigational Review Board, Inc. (IIRB), and submitted to EPA for review in August 2009. The protocol and EPA's review dated September 21, 2009, were discussed by the Human Studies Review Board (HSRB) on October 21, 2009. The HSRB review was generally favorable; the December 16, 2009, final report concluded, with respect to ethics, that "the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."

Following the HSRB review, the protocol, consent form, and recruiting materials were revised to address EPA and HSRB comments, and were submitted to the California Department of Pesticide Regulation (CDPR) on February 9, 2010. On March 17, 2010, CDPR requested revisions to those documents, and the researchers at Golden Pacific Laboratory (GPL) completed those revisions in early April 2010.

The revised protocol (dated 3-31-10), revised informed consent form, revised Subject's Bill of Rights, and revised advertisements and Qualification Questionnaire were submitted to IIRB on April 6, 2010, and approved, along with certified Spanish translations, on April 7-9, 2010. The versions approved by IIRB were submitted to CDPR on April 16, 2011, and CDPR granted final approval on April 19, 2010.

Study "Hold"

Subject recruitment began shortly after CDPR approval, and the first subject was enrolled on April 27, 2010. During the recruitment process, some subjects expressed a desire to wear a respirator when performing their task. After consulting with the EPA and IIRB, the AEATF decided to offer subjects the option of wearing a half-mask respirator fitted with organic vapor cartridges. A protocol amendment and revised consent documents covering the use of respirators was approved by IIRB in May 2010. The revised consent form was signed by subjects prior to their participation. A copy of the approved protocol amendment was sent to CDPR for review.

After random assignment of enrolled subjects to the three different clusters, four subjects in Cluster 1 were monitored on June 7-8, 2010 at TownePlace Suites by

Marriott in Fresno, CA. Shortly thereafter, CDPR contacted the Study Director and requested that GPL conduct a further review of its procedures for respirator use. As a result of CDPR's request, the AEATF placed the study on hold pending this review.

On August 16, 2010, a meeting was held between representatives from EPA, the AEATF, and the Study Director. At the conclusion of that meeting, the AEATF approved continuation of the study and decided to proceed with offering subjects the option of wearing a respirator. The protocol amendment and supporting documents, as well as a copy of the "Respirator Protection Plan for GPL" (pp. 1799-1823) was submitted to CDPR for review. Approval was received from CDPR prior to initiating additional monitoring events (the CDPR approval letter dated May 11, 2011, appears on pp. 1825-8).

All 18 monitored subjects ultimately requested to wear a respirator. They were fitted for the respirator by a trained study investigator, and they wore the respirator under the supervision of the study registered nurse.

New Study Director/Principal Investigator

Shortly after the meeting to discuss respirator use, the original Study Director/Principal Investigator, Dr. Sami Selim, resigned from GPL and was no longer available to oversee the study.

A new Study Director/Principal Investigator, Dr. Robert Testman, was authorized via protocol amendment 2. Dr. Testman, in consultation with the AEATF and IIRB, implemented a revised Informed Consent Form to inform subjects of the change in Study Director/Principal Investigator, as well as to further clarify procedures if a subject chose to use a respirator. The protocol amendment also included revised recruiting materials reflecting the change in Study Director/Principal Investigator. The revised recruiting materials would have been necessary in case an insufficient number of previously enrolled subjects were available to continue the study.

Study Resumption

When the study resumed in spring 2011, subjects were contacted to confirm interest and availability with a resulting loss of nine subjects from the original 34. Five of those nine had originally been assigned into a cluster. The subjects held as extras were then assigned into the clusters in the sequence determined by the randomized process.

The two remaining subjects for Cluster 1 were monitored on May 16, 2011 at TownePlace Suites by Marriott in Fresno, CA. Subjects in Cluster 2 were monitored on June 6-8, 2011 at Piccadilly Inn Shaw in Fresno, CA; and subjects in Cluster 3 were monitored on June 27-29, 2011 at Homewood Suites by Hilton in Fresno, CA. A more detailed chronology appears as Attachment 2 to this review.

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Protocol Amendments:

Subsequent to IIRB approval of the revised protocol on April 8, 2010, the protocol was amended four times. Details about the scope of each of the amendments appears as Attachment 3 to this review. Amendments 1 and 3 are of primary ethical interest. Both amendments were made to accommodate preferences voiced by the study subjects.

Protocol Amendment 1 was submitted to IIRB during the early stages of recruiting, after some subjects expressed a desire to wear a respirator when performing the monitored task, even though the product label does not require use of a respirator. After consulting with EPA and IIRB, the AEATF submitted Protocol Amendment 1 amending several sections of the protocol to allow subjects the option of wearing a respirator. All 18 subjects wore respirators during monitoring.

Protocol Amendment 2 extended the proposed experimental termination date and the proposed final report issue date, changed the Study Director and Principal Investigator from Sami Selim to Robert Testman, and made several changes that are not ethically significant.

Protocol Amendment 3 revised the procedures for sample collection to allow subjects to keep their socks on, but roll them down – rather than remove their socks – during dosimeter collection. The reason for this change was that some subjects in Cluster 1 were not comfortable with removing their socks. The sample collection procedures outlined in Section 10(d) of the protocol were adjusted to respect the subjects' preference, while minimizing, to the greatest extent possible, the potential for cross-contamination.

Protocol Amendment 4, which updated the address of the Study Sponsor due to a move in office location, was not timely reported to IIRB due to an oversight by GLP. Researchers at GPL submitted the protocol amendment to IIRB on January 4, 2012, after they were alerted to the oversight by EPA. IIRB's approval/acknowledgement of the amendment is expected, but was not available at the time that this review was finalized. Given the routine and administrative nature of Protocol Amendment 4, I have concluded that the oversight is inconsequential.

I have reviewed all four amendments and have concluded that they did not negatively affect subject safety or jeopardize the informed consent process. In particular, I have concluded that Amendments 1 and 3 were appropriate because they accommodated subject preferences while not jeopardizing other aspects of the research. I defer to the EPA science reviewer on the impact of these amendments on the scientific aspects of the research.

Deviations:

Protocol Deviations

Four reports of protocol deviations were made to the IIRB, Inc. after completion of the research; they are summarized in Attachment 3. Deviations noted in Deviation Report 1 (p. 397 of 1851) and Deviation Report 3 (p. 399 of 1851) are of potential ethical interest.

As reported in Protocol Deviation Report 1, some subject's socks were not removed prior to outer and inner dosimeter collection, as required in Section 10(d) of the protocol (p. 235 of 1851). The reason for this deviation is that several of the subjects indicated that they were not comfortable removing their socks. In order to respect the subjects' preferences, the researchers allowed the subjects to keep their socks on, but folded them down, before removing the inner dosimeter that was tucked underneath the socks. Folding the socks down minimized the potential for cross contamination. I have concluded that this deviation was appropriate and did not negatively affect subject safety or jeopardize the informed consent process. I defer to the EPA science reviewer about the potential impacts on the scientific results of the study.

As reported in Protocol Deviation Report 3, a subject who reported fair health on the demographic questionnaire was enrolled and randomized into the study. The protocol specifies that to be included, subjects must be "in good health" (p. 227 of 1851). The "Subject Self-Reporting Demographic Form," Appendix D to the protocol (p. pp. 286-7 of 1851), offered candidates a choice in describing their health as 'Excellent,' 'Good,' 'Fair,' or 'Poor.' This subject who reported fair health was not monitored because he could not be reached for scheduling (disconnected phone number).

The HSRB has considered this issue twice before, in connection with the AEATF Mop and Wipe Studies. In both of those studies, which employed identical enrollment criteria with respect to participants' health, the investigators similarly enrolled subjects who reported "fair" health. In the reports of the October 2010 and April 2011 HSRB meetings, the Board concluded that this deviation did not render the results unacceptable under EPA's regulations, but recommended that the AEATF "clarify the criteria used to establish participants' health status prior to study enrollment." I think that the HSRB's previous conclusion applies equally for this study.

The enrollment of the subject reporting fair health occurred on May 7, 2010, which was prior to the October 2010 HSRB meeting (the first occasion during which this issue was brought to the AEATF's attention), and therefore does not reflect the lessons learned from the October 2010 and April 2011 HSRB reviews. More recently, the AEATF developed an SOP that clarifies the AEATF's health status reporting and inclusion criteria

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(AEATF-II SOP-11J.0). This new SOP was included with the AEATF Liquid Open Pour Protocol, which was reviewed favorably by the HSRB in October 2011.

Method Deviations

Two method deviations are summarized in Appendix 3. Neither of these deviations is of ethical significance. Consistent with IIRB procedures and policies, these deviations were not reported to IIRB because these deviations were unanticipated and accidental divergences from established laboratory methods that did not increase the risk to research participants. I defer to the EPA science reviewer about any potential impacts on the scientific results of the research.

SOP Deviations

Eight SOP deviations are summarized in Attachment 3. One of these deviations is of potential ethical significance. The ethics training certifications of the Study Director/Principal Investigator, Dr. Sami Selim, and the field coordinator, Ms. Megan Boatwright, were more than three years old during the period in which they enrolled and interacted with subjects while conducting four monitoring events in June 2010. This was an SOP deviation because SOP AEATF-II-11-G.0 states that all researchers working on behalf of the AEATF II who interact with or have the potential to interact with the study subjects must have completed a training course for protection of human subjects and must be re-certified every three years.

Only four monitoring events were conducted by these two researchers while their ethics training re-certification was overdue. Ms. Boatwright was re-certified before the study resumed in April 2011, and Dr. Selim was replaced by Dr. Robert Testman as the Study Director/Principal Investigator in April 2011.

Given that this deviation involved researchers who had received ethics training in the past, but their re-certification was overdue, I have concluded that the deviation did not negatively affect subject safety or jeopardize the informed consent process.

The other seven SOP deviations are not of ethical significance. I defer to the EPA science reviewer about the effect of these deviations on the results of this research.

Consistent with IIRB procedures and policies, these deviations were not reported to IIRB because they were unanticipated and accidental divergences from the SOPs that did not increase the risk to research participants.

Unreported Deviations:

I did not note any unreported deviations.

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Recruiting:

Following approval of the protocol by EPA, IIRB, and CDPR, a randomized list of janitorial service providers in Fresno County was generated from telephone directories, the Chamber of Commerce, and information given from janitorial service providers themselves. Phone calls were placed to the janitorial service providers, and they were asked if they would be willing to post flyers soliciting study subjects. An IIRB-approved script was used during these phone calls and is provided in the study report in Appendix B (English) and Appendix C (Spanish dialect; Mexican) (pp. 402-409 of 1851). A letter was then sent to those managers expressing willingness to post the flyers. The letter contained the flyer or flyers in the language they requested. Copies of the IIRB-approved flyers in both English and Spanish are shown in Appendix D and E of the study report (pp. 410-413 of 1851). Follow-up calls to confirm receipt of the letter were attempted approximately four days after the letter and flyer were sent in the mail. The follow-up call also gave the managers a chance to ask any further questions they might have after seeing the flyer. Out of 228 janitorial companies, 34 agreed to have the flyers sent to them for posting. Fifteen companies requested flyers in English, one company requested flyers in Spanish, and eighteen companies requested flyers both in English and Spanish. Of the flyers that were sent to the businesses, it is unknown how many were actually posted.

In addition to flyer distribution, a newspaper advertisement was placed in three local newspapers: the Fresno Bee, the California Advocate, which is widely circulated in the African-American community, and Vida en el Valle, which is widely circulated in the Spanish-speaking community. The advertisements were approved by IIRB and copies are provided in Appendix F and G in the study report (pp. 414-417 of 1851). The advertisements included a brief description of the study and directed interested volunteers to contact the Study Director or a Spanish-speaking Coordinator for more information. An IIRB-approved script, provided in Appendix B and C of the study report (pp. 402-409 of 1851) was used at the time of call-in.

Interested callers were phone-interviewed to determine whether they met the inclusion criteria. Callers were screened for janitorial experience by asking if they were currently employed as a janitor, had previously worked as a janitor or currently own and operate a janitorial firm providing services to commercial buildings within Fresno County in the last 18 months. Callers were asked if they were at least 18 years of age and resided in Fresno County. During the phone call, volunteers were given a brief overview of the study and told that they would need to present a government-issued identification card, and then asked if they were still interested in participating. For those who met the inclusion criteria and were still interested, an Informed Consent Meeting was scheduled.

Informed Consent Meetings were held at GPL. Potential subjects were asked to bring a government-issued, picture identification card to the meeting. The meetings

were one-on-one unless the subject wished to have family members/spouses attend the meeting as well. Potential subjects met with either the Study Director and/or a Spanish-speaking Field Research Associate. The Study Director or Spanish-speaking Field Research Associate checked the government-issued picture identification card to verify identity and age. Each volunteer was then given the Subject Self-Reporting Demographic Form, the Informed Consent Form, a copy of the product label, a copy of the Material Safety Data Sheet (MSDS), and the California "Experimental Subject's Bill of Rights." The potential subject was asked to first fill out part 1 (the Health Questionnaire) of the Self-Reporting Demographic Form. The Study Director or Field Research Associate read the questions with the subject and inquired about the subject's health, including if the subject was taking any medication. If none of the answers disqualified the subject from participation, the Study Director or Field Research Associate read the Informed Consent Form and the "Experimental Subject's Bill of Rights" to the potential subjects. The study procedures and the inclusion and exclusion criteria were described to each volunteer in detail, and potential subjects were encouraged to ask questions or request clarification during the meeting and at any point during the rest of the study. Potential subjects were also encouraged to take the forms and information home with them to discuss the study with family and friends. The Study Director or Field Research Associate explained to potential subjects wishing to remain in consideration that they could withdraw from the study at any time without penalty.

If an eligible potential subject met the inclusion criteria, and was still interested in enrolling in the study, he or she was asked to sign and date the Informed Consent Form and fill out the second part of the Subject Self-Reporting Demographic Form. Although a few meetings were sometimes held as a group, these documents were signed in a one-on-one setting with the Study Director. Once these forms were fully completed, the subject was considered officially enrolled in the study.

A total of 42 people came to GPL for a consent interview, and 34 people were enrolled in the study during the four-week enrollment period. An identification number was assigned to each of the 34 subjects and the numbers were randomized. The first 24 randomized subjects were split into 3 groups of 8 subjects. The first set of eight subjects was grouped into Cluster 1, the second set of eight subjects was grouped into Cluster 2, and the third set of eight subjects was grouped into Cluster 3. Within each group of eight, the first six subjects (primary subjects) were assigned to the various spray durations listed in the protocol. The last two subjects in each group of eight were considered alternates and remained on site in case any subject did not show up or was unable to complete the task. As additional subjects beyond the 24 initially selected were required, subjects were contacted in the order of assigned numbers (i.e., subject 25 was contacted first, followed by 26 and so on).

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Demographics

Below is a summary of the demographics of the 34 enrolled subjects (summarized from p. 66 of 1851).

Table 1: AEATF II Aerosol Study Subject Characteristics				
	All Enrolled Subjects (34)	**Monitored Subjects (18)**	**Alternate Subjects (4)**	**Dropped Subjects (12)**
Male	19	11	2	6
Female	15	7	2	6
English	29	16	4	9
Spanish	5	2	0	3
Range of Experience	1 - 23 yrs	1 - 20 yrs	2 - 23 yrs	1 - 20 yrs
Mean Years Experience	8	7.5	12	8
Age Range	19 - 57	19 - 57	47 - 52	20 - 57
Mean Age	43	46	49	39
Health 'Excellent'	18	11	3	5
Health 'Good'	15	7	1	6
Health 'Fair'	1	0	0	1
Requested Results	14 (41%)	6 (33%)	2 (50%)	4 (33%)

Both male and female subjects were monitored in all three clusters. The language preference was predominately English, but five out of 34 subjects requested the Informed Consent documents in Spanish. Subjects' ages ranged from 19 years old to 57 years old. The subjects' experience working in the janitorial field ranged from 1 year to 23 years.

One enrolled subject considered himself to be in "fair" health. Although originally assigned to a monitoring event, this subject was not able to be contacted after the study "hold" and therefore was not monitored.

Monitoring

Upon arrival at the study location, the subjects were offered food and beverages, and were reminded that they could withdraw from the study at any time. The subjects met privately with the Study Director/Principal Investigator to review the study procedures and ask questions. Subjects had previously signed the modified Informed Consent Form and been informed about the voluntary use of a respirator.

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All subjects chose to wear a respirator. Following their meeting with the PI, each subject met privately with the on-site nurse. The nurse verbally queried each subject about their health as necessary to qualify the subject to wear the respirator. The nurse signed a form indicating approval for the subject to wear a respirator, and no records were made of subject answers. Subjects who were not comfortable speaking English were offered the option of having a Spanish speaking study investigator present to assist with the discussion. The nurse also inspected the subject's hands to ensure that there were no disqualifying skin conditions. Female subjects were taken to a private area by a female researcher and asked to self-administer an over-the-counter urine pregnancy test.

Qualified subjects were taken to a private area to wash their hands and face with Ivory soap and water. The subjects were then taken to the dosimeter assembly room by a same gender member of the research team and asked to don inner and outer dosimeters for the exposure monitoring. Two air sampling pumps, each connected to Tygon tubing, were attached to the belt of the subject. One pump was attached to an air sampling tube containing XAD sorbent which was placed in the subject's breathing zone. The other pump was attached to a RespiCon™ Particle Sampler attached to a harness over their chest. The subjects were donned with a half-mask respirator, given safety glasses and photographed; care was taken not to photograph their faces.

There were three to four study personnel following a subject during a given monitoring event. One researcher was assigned as the "observer" and remained with the subject throughout the duration of the monitoring period. The observer recorded observational notes of the subject's activities and guided the subject from room to room. A second researcher was assigned to assist the observer. This researcher provided the subject with the canister, weighed and recorded the canisters weights, determined when a new canister was necessary, and kept a running tally of the amount of solution sprayed. The researcher pushed the mobile cart that contained the temperature and humidity data logger, timed the spraying duration with a stop watch, and logged the locations and types of surfaces sprayed. A study assistant operated the digital camera and video camera during the monitoring period. A registered nurse was always on site to monitor the well-being of the subject. During the monitoring period, the nurse held the drink for subject during breaks and collected the face wipe samples generated from wiping sweat off a subject's face. The observational notes are provided in Appendix L of the study report (pp. 474-507 of 1851).

Subject monitoring was conducted without noteworthy incident. Subjects were periodically offered rest breaks during the monitoring, and six of the eighteen monitored subjects did take a break. During the rest breaks, workers generally sat in a plastic-covered chain in the next room to be sprayed and drank water or a sports drink. There were a few instances where subjects wearing respirators asked for assistance with adjusting the respirator, but there were no instances of subjects reporting feeling injured or ill during the monitoring.

The observation log reports that several of the subjects were sweating from their faces. As mentioned above, all subjects were given frequent opportunities to take breaks and drink their choice of water or a sports drink. It does not appear that any of the subjects was in danger of suffering heat-related illness. The range of maximum recorded temperatures during monitoring was relatively low – 68.2 °F to 76.4 °F – and the work periods were relatively short (the longest work period was 2 hours and 5 minutes). Study personnel were also instructed to observe subjects for possible signs of heat stress.

The procedures provided in the protocol and SOPs 10.C.1, 11.B.1, 11.C.1, 11.E.1, and 11.F.1 related to recording observations, minimizing risks, and protecting the subjects were followed.

Applicable Ethical Standards

Because this study was initiated after 7 April 2006, prior submission of the protocol and supporting materials to EPA was required by 40 CFR §26.1125. 40 CFR §26.1601(c) required EPA to review the protocol and present it to the HSRB for review. These requirements were satisfied.

EPA Protocol Review Comments

In its Science and Ethics review dated September 21, 2009, EPA noted "If the deficiency noted above is addressed and the amended protocol is approved by the overseeing IRB, this research should meet the ethical standards of FIFRA §12(a)(2)(P) and 40 CFR 26 subparts K and L." The EPA comment, and how the AEATF addressed that comment, is provided in Attachment 4.

HSRB Protocol Review Comments

In the December 16, 2009 report of its October 2009 review of the AEATF aerosol scenario and protocol, the HSRB summarized its recommendations as follows:

> "The Board concluded that the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."

In addition, the HSRB made several specific suggestions for refinements. A summary of the HSRB's comments and how they were addressed by the AEATF is provided in Attachment 4.

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Regulatory and Statutory 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. . . .

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

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

Findings

Responsiveness to EPA and HSRB reviews

EPA's and HSRB's comments were satisfactorily addressed in the revisions approved by the IIRB in April 2010.

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

All enrolled subjects were at least 18 years old. All female subjects, regardless of age, self-administered over-the-counter pregnancy tests on the day of monitoring; all such tests were negative. The prohibition in 40 CFR §26.1703 of research involving intentional exposure of pregnant or nursing women or of children under 18 was satisfied.

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.

I identified no noteworthy deficiencies in the ethical conduct of the research. The protocol was faithfully executed and properly amended when necessary. The protocol amendments were approved by the overseeing IRB before they were implemented, with the exception of Protocol Amendment 4, which was administrative in nature (updated the address of the Study Sponsor due to a move in office location).[1] Given the routine and administrative nature of Protocol Amendment 4, I have concluded that the oversight is inconsequential.

The deviations reported 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. I conclude that 40 CFR §26.1705 does not prohibit EPA reliance on this study.

Compliance with 40 CFR §26 subpart M

As documented in Attachment 1 to this review, the 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.

Conclusions

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. All requirements for documentation of ethical conduct of the research were also satisfied. 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.

Attachment 1: §26.1303 completeness check for AEATF Aerosol Scenario Report
Attachment 2: Chronology of AEATF Aerosol Study
Attachment 3: Summary of Amendments and Deviations to AEATF Aerosol Study
Attachment 4: Responsiveness of AEATF to HSRB Comments on Aerosol Study

[1] Protocol Amendment 4 was not timely reported to IIRB due to an oversight by GLP. Researchers at GPL submitted the protocol amendment to IIRB on January 4, 2012, after they were alerted to the oversight by EPA. IIRB's approval/acknowledgement of the amendment is expected, but it was not available at the time that this review was finalized.

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§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
AEATF II Aerosol Scenario Report: MRID 48659001

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 n/a Y Y	Initially addressed in protocol pp. 418-459 pp. 1246-1274
	§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.		N	All post-HSRB IIRB reviews were under expedited procedures; no minutes were made.
	§1115(a)(3): Records of continuing review activities.		Y	p. 1246-1274
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	pp. 642-1486
	§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, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		N	Provided separately 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	Provided separately 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	Original – in protocol submission Approved English CF –419, 440 Approved Spanish CF 429, 450
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	Initially satisfied in protocol. Flyers & Ads in English & Spanish
	§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	Initially satisfied in protocol
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 642-1486
	§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	IRB approvals: Initial p. 896 Revised p. 1668; Renewal p. 1319 Amdmt 1: p. 1215; Amdmt 2: p. 1374 Amdmt 3: p. 1438; Amdmt 4: p. 1760
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	pp. 418-459
(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	

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Chronological Listing of Events: AEATF Aerosol Study

Based on Table 1 from AEATF Submission (pp. 107-108)

14 July 2009	GPL submission of protocol 070270 and AEATF Scenario Design, Submission Letter, Site Questionnaire and Study Set-up Form to IIRB
27 July 2009	IIRB approval of protocol and supporting materials
4 Aug 2009	Submission of IIRB-approved protocol to EPA
21 Sept 2009	EPA Science & Ethics Review of Research Proposal
21 Oct 2009	HSRB Meeting during which research proposal/protocol is discussed
16 Dec 2009	HSRB Final Report of the October 2009 meeting
9 Feb 2010	Submission of protocol 070270 to CDPR
17 Mar 2010	CDPR provides GPL with a summary of requested revisions
6 April 2010	GPL re-submission of revised protocol 070270 dated 3/31/2010, revised Informed Consent Form, revised Subject's Bill of Rights, revised advertisements and Qualification Questionnaire to IIRB
7 April 2010	IIRB approval of advertisement flyers
8 April 2010	IIRB approval of revised protocol 070270 dated 3/31/2010, Informed Consent Form version 4/8/2010 (English and Spanish), revised Subject's Bill of Rights (English and Spanish) version 4/8/2010, and Qualification Worksheet and final print ad.
9 April 2010	IIRB acknowledgement of certified translations of the approved Qualification Worksheet, Employer Contract Script and Community Flyer included in the protocol approved on 4/8/2010.
16 April 2010	GPL submission of IIRB approval packets from April 7, 2010 through April 9, 2010 to the CDPR
19 April 2010	CDPR grants final approval for protocol 070270
21 April 2010	"Study Initiation" (p. 6) [Date on which study director signed protocol]
28 April 2010	Start of search for test site selection
27 April 2010	First subject enrolled into the study
14 May 2010	GPL submission to IIRB of Amendment 1 adding the use of respirators as an option
21 May 2010	IIRB approval of Amendment 1 and Informed Consent Forms version 5/21/2010 in both English and Spanish.
4 June 2010	GPL submission of Amendment 1 and IIRB approval letter and packet to CDPR
7 June 2010	First subject monitored; "Experimental Start"
7-8 June 2010	Monitoring of Cluster 1, Day 1 and Day 2 (4 subjects)
7 June 2010	CDPR acknowledgement of receipt of Amendment 1 and IIRB approval

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Chronological Listing of Events: AEATF Aerosol Study

Based on Table 1 from AEATF Submission (pp. 107-108)

8 June 2010	CDPR informed GPL that voluntary subject use of a respirator requires further review by GPL to ensure compliance
10 June 2010	AEATF formally puts study on hold
7 July 2010	GPL submission of annual progress report to IIRB
14 July 2010	IIRB extension of Approval for Ongoing Research
16 Aug 2010	Conference call between Biocides Panel AEATF II and EPA to convey background information on use of respirators in the study and steps taken by the AEATF II to address the CDPR questions; AEATF II obtains EPA approval to resume study and relayed the approval to GPL
14 April 2011	GPL submission of Amendment 2, revised Informed Consent Form and Experimental Subject's Bill of Rights (versions April 8, 2011) as well as revised versions of appendices F, G and H and the newspaper advertisement to IIRB
22 April 2011	IIRB approval of Amendment 2, English/Certified Spanish Translated Informed Consent Form version 8-Apr-2011, English/Certified Spanish Translated Experimental Subject's Bill of Rights dated 8-Apr-2011 and revised versions of appendices F, G and H and the newspaper ad
27 April 2011	IIRB Certified Spanish Translations of the Notice version 4/8/2011 and Notice to Hotel/Motel Guests version 4/8/2011
29 April 2011	GPL submission of Amendment 2 and the IIRB approval letter and packet to CDPR
10 May 2011	CDPR grants final approval of Protocol Amendment 2
16 May 2011	Monitoring of Cluster 1, Day 3 (2 subjects)
5 June 2011	GPL submission of Protocol Amendment 3 and Protocol Deviation 1 to IIRB
6-8 June 2011	Monitoring of Cluster 2 (6 subjects)
7 June 2011	IIRB approval of Protocol Amendment 3 and acknowledgement and review of Protocol Deviation 1
14 June 2011	GPL submission of Protocol Amendment 3 and Protocol Deviation 1 and the approval and acknowledgement letters from the IIRB to CDPR
21 June 2011	CDPR acknowledges receipt and review of Protocol Amendment 3 and Protocol Deviation 1
27-29 June 2011	Monitoring of Cluster 3 (6 subjects)
29 June 2011	Last subject monitored
1 July 2011	GPL submission of closeout report to IIRB
5 July 2011	IIRB acceptance of closeout report (letter dated July 12, 2011)

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Chronological Listing of Events: AEATF Aerosol Study

Based on Table 1 from AEATF Submission (pp. 107-108)

26 Oct 2011	"Experimental Termination" (p. 6) "Last day of data collection"
31 Oct 2011	GPL submission of Protocol Deviations 2, 3 and 4 to IIRB
1 Nov 2011	IIRB acknowledgement of Protocol Deviations 2, 3 and 4 and acknowledgement of no further action required
3 Nov 2011	GPL submission to CDPR of Protocol Deviations 2, 3 and 4 along with IIRB acknowledgement letter to GPL
14 Nov 2011	"Study Completion"
4 Jan 2012	GLP submission to IIRB of Protocol Amendment 4

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Summary of Protocol Amendments and Deviations for AEATF-II Aerosol Study Protocol

Amendment 1: (dated May 13, 2010 [p. 368]; approved May 21, 2010 [p. 1215])

1. Allowed subjects to choose to wear a respirator during monitoring events

Amendment 2: (dated April 18, 2011 [p. 370]; approved April 22, 2011 [p. 1374])

1. Extended the proposed experimental termination date from August 2010 to July 2011
2. Extended the proposed final report issue date from October 2010 to December 2011
3. Changed the Study Director and Principal Investigator from Sami Selim to Robert Testman
4. Incorporated into the study the GLP analysis of the test substance and formulated product (BTC 885) for C14 ADBAC concentration to be conducted by GPL.
5. Corrected the length of the cited freezer storage stability study from 6 months to 18 months showing that over the time samples were in storage C14 ADBAC is stable.
6. Changed the person to whom the Quality Assurance Unit report from Sami Selim to Robert Testman
7. Updated the personnel section of the protocol (section 20) to identify Robert Testman as the study director/principal investigator, not Sami Selim
8. Updated the Quality Assurance Unit contact information to add an additional name and indicate that Anantdeep Kang is no longer employed with GPL
9. Completed additional revisions to address the change to the Study Director/Principal Investigator name and contact information

Amendment 3: (dated May 26, 2011 [p. 396]; approved June 7, 2011 [p. 1438])

1. Revised the procedure for removing the subjects' socks during sample collection to respect the subjects' preference.

Amendment 4: (dated February 8, 2011 [see addendum]; submitted to IIRB on January 4, 2012**)

1. Updated the sponsor's contact information, address, and phone number due to a move in office location from Arlington, VA to Washington, DC

*** Due to an oversight by GPL, this protocol amendment was prepared in February 2011 but never submitted to IIRB. This issue was noticed during EPA's ethics review and discussed with GPL. The amendment was immediately thereafter submitted by GPL to IIRB (on January 4, 2012). IIRB's approval/acknowledgement of the protocol amendment is fully expected, given the routine nature of this protocol amendment. However, IIRB's approval/acknowledgement was not available at the time that this review was finalized.*

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Summary of Protocol Amendments and Deviations for AEATF-II Aerosol Study Protocol

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Deviation Report 1: (dated June 1, 2010 [p. 397]; stamped "received" June 5, 2010 [p. 1437])

Dates of occurrence: June 7-8, 2010 and May 16, 2011

1. Some subjects' socks were not removed prior to removing and collecting the outer dosimeter and inner dosimeter
2. During the field fortification event, 5 mL of 50% isopropyl alcohol/50% water was used to moisten the dressing sponges for the face/neck wipe samples instead of 4 mL of 50% IPA/50% water

Deviation Report 2: (dated October 19, 2011 [p. 398]; acknowledged November 1, 2011; p. 1486)

Dates of occurrence: April 28-29, 2011 and May 20, 2011

1. During sample analysis, several analytical sets were analyzed without a solvent blank included in the analytical run

Deviation Report 3: (dated October 14, 2011 [p. 400]; acknowledged November 1, 2011 [p. 1486])

1. A subject enrolled and randomized into the study marked "fair health" on the demographic questionnaire. This was contrary to the inclusion/exclusion criteria which state that "good health" is an inclusion criterion. The subject did not participant in any monitoring event or as an alternate. [date of occurrence: May 7, 2010]
2. The first four subjects in Cluster 1 were not assigned to the MEs as directed in the protocol. They were assigned to spraying durations in the opposite order. [date of occurrence: May 26, 2010]
3. Fortification samples for each matrix/level combination were fortified, however not all of the three samples were analyzed. [dates of occurrence: June 7, 2010 – September 29, 2011, throughout the analytical phase]

Deviation Report 4: (dated October 19, 2011 [p. 401]; acknowledged November 1, 2011 [p. 1486])

1. During Cluster 1, the subjects which completed A1 and A5 were not provided with a half full canister to be used first as directed in Section 8C of the protocol. [dates of occurrence: June 7-8, 2010]
2. Air samples were to be collected for a fifteen-minute period; however, sample collection times were routinely longer. [dates of occurrence: June 7-8, 2010; May 16, 2011; June 6-8, 2011; June 27-29, 2011]

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Responsiveness to EPA and HSRB Ethics-Related Comments on AEATF-II Aerosol Study Protocol

EPA Comment on Aerosol Protocol	Has comment been addressed?
In the statement about compensation for research-related injuries in the consent form, please make the following clarifying revision: Current language: "We will pay for needed medical treatment that is not paid for by your own insurance or by someone else." Change to: "We will pay for needed medical treatment that is not paid for by your own insurance or by the insurance of a third party under which you are covered."	Yes. The revised language requested by EPA appears in both of the IIRB-approved versions of the consent form that were used during the study (pp. 425-6 of 1851; p. 447 of 1851).
HSRB Comment on Aerosol Protocol	**Has comment been addressed?**
As some possible subjects for this study may be undocumented immigrants, recruitment materials should more explicitly state that a valid government-issued form of identification is necessary for enrollment.	Yes. The recruitment flyer for posting in janitorial businesses clearly indicates that a government-issued photo identification card is required. The newspaper advertisement does not indicate the requirement for an ID card, but the newspaper advertisement is very short and it would not be appropriate to include that level of detail. The telephone scripts specify that potential subjects will be told during the initial telephone conversation about the requirement for a government-issued ID.
Ensure that documents in Spanish are reviewed by someone familiar with the dialects written and spoken in the target community.	Yes. The documents were translated by an individual familiar with idioms and common dialects used in the Fresno area.
The protocol provides for use of a community notification flyer. However, one neglected community includes persons who might be staying in the hotels where the study is conducted. The flyer should be revised so that it communicates the goals of the study and risks to that group. These flyers, in both English and Spanish, should also be posted in locations so that hotel guests are likely to see it. Alternatively, the researchers should consider conducting the research in areas away from hotel guests.	Yes. A flyer will be distributed to hotel/motel guests explaining the purpose of the study and providing individuals with phone numbers of the principal investigator and field coordinators to contact if they have any questions or want additional information. This flyer is available in both English and Spanish, and was submitted to IIRB along with Protocol Amendment 2. See Appendix H, p. 302-305, and pp. 1374-5.
The exclusion criteria should be revised to eliminate some groups that might be at higher risk of physical harm but are not presently excluded. This might include subjects who might be immunosuppressed for a variety of reasons, those with severe diabetes, and those with other conditions that pose a health risk.	Yes. In response to this comment, the following exclusions were added to the protocol: severe diabetes; immunologically suppressed (e.g., undergoing chemotherapy, transplant patients). The protocol also excludes subjects with skin conditions on the surface of the hands; subjects with allergies to household chemical-based products, including soaps or isopropyl alcohol; subjects with severe respiratory disorders; and subjects with cardiovascular disease.

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