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

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

March 17, 2011

MEMORANDUM

SUBJECT: Ethics Review of Completed AEATF II Wipe 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: Selim, S. (2011) A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using Trigger Spray and Wipe or Ready-to-Use Wipes for Cleaning Indoor Surfaces. Unpublished study prepared by Golden Pacific Laboratories, LLC, under Project No. AEA02, Report No. 070264. 2000 p. (MRID 48375601)

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 wiped indoor surfaces with a liquid antimicrobial pesticide product containing didecyl dimethyl ammonium chloride (DDAC). 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).

Background and Chronology

The scenario design and protocol for this study, identified by the investigators as Protocol #070264, was approved by the overseeing investigational review board (IRB), the Independent Investigational Review Board, Inc. (IIRB), and submitted to EPA for review in February 2008. The protocol and EPA's review dated March 10, 2008, were discussed by the Human Studies Review Board (HSRB) on April 9, 2008. The HSRB review was generally favorable; their June 25, 2008, final report concluded, with respect to ethics, that "if the proposed mop and wipe scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, the research would meet the applicable requirements of 40 CFR part 26, subparts K and L."

Following the HSRB review, the protocol, consent form, and recruiting materials were revised to address EPA, HSRB, and California Department of Pesticide Regulation (CDPR) comments. The revised protocol was submitted to IIRB on February 5, 2009, and approved, along with certified Spanish translations, on February 11, 2009.

The protocol was subsequently amended eight times, with revised Consent Forms approved on May 5, 2009 (pp. 1352-1374, used in monitoring in Cluster 1), and August 21, 2009 (pp. 1467-1477, 1499-1509, used in monitoring at Clusters 2 and 3).

Final approval of the protocol and supporting materials was granted by CDPR on April 17, 2009. Subject recruitment began the following week on April 24, 2009. Initial response was slow, and Amendment 3 (pp. 1393-1401; approved 25 June 2009) revised the recruiting procedures. Subject enrollment began on July 1, 2009. Recruiting procedures were revised further to add recruiting by newspaper advertisements in Amendment 4 (pp. 1402-1420; approved 13 July 2009.) Initial enrollment of subjects was completed on July 24, 2009.

After random assignment of enrolled subjects to specific monitoring slots at each of the three sites, subjects were monitored at Site 1 from August 10-15, 2009; at Site 2 from August 24-29, 2009; and at Site 3 from September 28 through October 3, 2009. A more detailed chronology appears as Attachment 2 to this review.

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, together with the materials submitted for the initial protocol review, contains all required information.

Protocol Amendments:

Subsequent to IIRB approval of the revised protocol on February 11, 2009, it was amended eight times. A summary of the scope of all amendments appears as Attachment 3 to this review. Amendments 3 and 4 are of primary ethical interest. Both resulted from the discovery in the field that the planned approach to recruitment—approaching janitorial service providers and asking to post flyers in their premises—was unproductive. Revised procedures in Amendment 3 allowed enrollment of individual qualified candidates before the entire group of potential subjects had been identified, and Amendment 4 provided for recruiting through newspaper advertising. The choice of newspapers—three different newspapers, each serving a different community in the Fresno area—was an appropriate adjustment given the difficulties with the original recruitment plan. The change to the recruiting process is discussed in more detail on pages 4-5 of this review, in the section titled "Recruiting."

Protocol Deviations:

Reported Deviations

Two reports of protocol deviations were made to the IIRB, Inc. after completion of the research; they are summarized in Attachment 3. Two points raised in Deviation Report 1 (pp. 1562-1567) are of potential ethical interest. Most subjects reportedly declined to take rest breaks, or took less than the 10 minutes provided for in the protocol, and at one monitoring site photographs were taken showing subjects' faces. No images of subjects' faces were included in the report. I have concluded that neither of these deviations affected subject safety or jeopardized the informed consent process.

Unreported Deviations

I noted one unreported deviation. Three enrolled subjects (one who was monitored and two who were alternates) reported their general health as "fair." The protocol specifies that to be included, subjects must be "in good health" (p. 483). The consent form states that participants "must be healthy adults" (p. 1353, 1468). The "Subject Self-Reporting Demographic Form," Appendix D to the protocol (p. 529), offered candidates a choice in describing their health as 'Excellent,' 'Good,' 'Fair,' or 'Poor.' The decision to enroll subjects in only 'fair' health is not explained in the report.

The HSRB has considered this issue before, in connection with the AEATF Mop Study, the partner study to the AEAFT Wipe Study. In the Mop Study (which employed identical enrollment criteria with respect to participants' health), the investigators similarly enrolled 2 subjects who reported "fair" health. (One was monitored, and one was an alternate.) In its report of the October 2010 HSRB meeting, the Board did not conclude that this deviation rendered the results unacceptable under EPA's regulations,

but the Board recommended that the AEATF "clarify the criteria used to establish participants' health status prior to study enrollment." I agree with this conclusion.

The AEATF Wipe Study, which is being reviewed here, was conducted during the summer of 2009, before the October 2010 HSRB meeting. It therefore does not reflect the lessons learned from the October 2010 HSRB review process. However, before conducting future studies, the AEATF should develop an SOP that provides procedures for determining the general health status of potential subjects and whether potential subjects have any medical condition(s) which could impact their ability to participate in the research.

Recruiting:

Following approval of the protocol by CDPR, EPA, and IIRB, 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. A letter was then sent to those managers expressing willingness to post the flyers. The letter instructed the managers to attend an informational meeting and/or speak with research personnel before posting the flyers. The purpose of the meeting was to educate the managers about the monitoring process as well as impress upon them the need to remain neutral in their interactions with employees regarding study participation. English and Spanish versions of the flyers were approved by IIRB (Appendix C, D; p. 271, 273).

The recruiting process as initially designed proved unproductive. Very few service providers were willing to post flyers, and very few candidates responded to the flyers that were posted. A handful of candidates did respond, but the protocol did not provide for enrolling them until after the full complement of subjects had been recruited and randomized. The investigators were concerned that they would lose contact with the candidates who had been identified, so after discussion with EPA, the investigators submitted an amendment to IIRB (Amendment 3) to allow them to recruit and enroll subjects as they came forward, and randomly assign them to monitoring sites and slots after recruiting was completed. EPA endorsed this revision to the original plans for recruiting and randomization. IIRB approved the amendment on June 25, 2009.

Response to the recruiting flyers continued to be slow, and after further discussion with EPA, the AEATF submitted another amendment to IIRB (Amendment 4), to allow recruiting through newspaper advertisements. This change—and newspaper advertisements in English and Spanish— was approved by IIRB on July 13, 2009. Recruiting was completed on July 24, 2009.

A total of 72 subjects (primarily identified in response to the newspaper advertisements) came to Golden Pacific Laboratories (GPL) for the interview, signed the Informed Consent Forms, and filled out the Subject Demographic forms, enrolling them in the study. After the enrollment period ended, an attempt was made to contact all the subjects to verify contact information and confirm that they were still available and interested in participating. Sixteen of the 72 enrolled subjects were dropped – two because they reported taking a medication that, in the study director's judgment, could have increased their sensitivity to the test material – and 14 because they could not be contacted due to disconnected phone numbers or lack of response after three failed attempts to reach them via telephone.

An identification number was assigned to each of the remaining 56 subjects and the numbers were randomized. The first 48 randomized subjects were split into 6 groups of 8 subjects. In each of the 3 clusters, 8 subjects were randomly assigned to use trigger spray and wipe and the other 8 subjects were assigned to use RTU wipes. The remaining 8 subjects were held as extras for potential entry into the study in the sequence determined by the randomization process. Six wiping time durations (Monitoring Events) were assigned for each cluster ranging from 30 minutes to 210 minutes. In each cluster, six subjects completed the time durations using trigger spray and wipe and six subjects completed the time durations using ready-to-use wipes. The last two subjects of the 8 assigned to each cluster and each wiping scenario were considered alternates. The subjects were contacted and scheduled to come to one of the sites on a specific day and time. Below is a summary of the demographics of the 72 enrolled subjects (p. 71).

Table 1: AEATF II Wipe Study Subject Characteristics

	All Enrolled Subjects (72)	Monitored Subjects (36)	Alternate Subjects (20)	Dropped Subjects (16)
Male	41	20	12	9
Female	31	16	8	7
English	60	33	15	12
Spanish	12	3	5	4
Range of Experience	6 mos – 52 yrs	6 mos – 52 yrs	6 mos – 36 yrs	1 – 40 yrs
Mean Years Experience	11.9	13.5	9.7	10.9
Age Range	19 - 62	20 - 62	22 - 56	19 – 61
Mean Age	40.6	42.8	38.4	38.8
Health 'Excellent'	36	21	8	7
Health 'Good'	33	14	10	9*
Health 'Fair'	3	1	2	0
Requested Results	53 (74%)	26 (72%)	16 (80%)	11 (69%)

* The two subjects taking medication are included in this number. The protocol (p. 1518) states that subjects will not be allowed to participate if they are "taking medicines that might react with the test product."

Monitoring

Monitoring was conducted without noteworthy incident. There were four instances when a subject either spoke to the medical professional observing the study or reported feeling ill possibly due to inhaling fumes from the test material (details are provided in Table 2, below), but in all cases the workers continued working and none of these situations resulted in a report of an adverse event or other incident of concern. There was one report (RTU, Cluster 3, R4) of a subject leaving early because he was feeling ill. The observation log does not indicate whether the worker was feeling ill possibly as a result of his/her participation in the research, or whether his illness was unrelated to the study.

Table 2: Selected Subject Observations During Monitoring

Scenario/ Cluster	Subject	Date	Time	Notes Provided in Observation Log
RTU Wipe Cluster 1	R5	8/10/09	11:08 am	"Worker stops to show his finger tips to medical personnel. Finger tips he says look white. Worker takes break and describes finger skin is wrinkling possibly from being moist so long. EMT will notify Study Director. Worker says he is fine and wants to continue working." (p. 339)
RTU Wipe Cluster 2	R5	8/26/09	09:48 am-10:10 am	"Subject cut left hand on shelf; observed blood on pants and touched eyewear. Subject wanted to continue study regardless of cut hand…Subject sat with hands on his knees…Nurse checked left hand of subject…Subject wiped surface with right hand while keeping left hand on pants." (p. 344)
RTU Wipe Cluster 3	R4	9/29/09	"Summary"	"Subject had to leave before the designated time because he was feeling ill." (p. 349) It is not reported whether the subject was feeling ill possibly as a result of his participation in the study, or if he was feeling ill for other reasons.
Trigger Spray Cluster 1	T3	8/13/09	09:31 am	"Worker ends break and requests to move to another location. Spray fumes were making worker somewhat uncomfortable. Worker stated that she had not eaten this morning. EMT met with worker during break and asked her condition. Worker wanted to continue working in another location." (p. 355)
Trigger Spray Cluster 3	T5	10/2/09	"Summary"	"Subject reported allergies and asthma during work period. Study director was notified." (p. 370)

The observation log reports that many of the workers were sweating from their faces, a sign that they were feeling hot. But they were given the opportunity 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 – 69.9 °F to 76.6 °F.

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 March 10, 2008, EPA noted "the following specific [ethical] deficiencies should be corrected before the research is initiated:

- Better provision is need for ensuring that Spanish-speaking candidates are fully informed and fully comprehend what they have been told. It would be better for candidate interviews to be conducted by a member of the research team fluent in Spanish than to rely on a translator.

- References in the consent forms to "normal business hours" should be replaced by references expressed in California local time, and care must be taken to ensure that a Spanish-speaking responder can be reached at any telephone number cited as a source for further information."

In the revisions submitted to the IIRB, Inc. on February 5, 2009 (p. 931), all references in the protocol and consent form to translators were replaced by references to researchers fluent in Spanish, to whom the recruiting and consenting responsibilities of the principal investigator would be delegated when candidates preferred to interact in Spanish (pp. 956-7, p. 1107). The Consent Form and California Experimental Subject's Bill of Rights were revised to show hours for calling in Pacific (local) time (pp. 1113, 1003).

HSRB Protocol Review Comments

In its June 25, 2008 report of its April 2008 review of the AEATF Mop and Wipe Scenarios, the HSRB summarized its recommendations as follows:

> "The Board concurred with the initial assessment of the Agency that if the proposed mop and wipe scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, the research would meet the applicable requirements of 40 CFR part 26, subparts K and L."

In addition, the HSRB made several specific suggestions for refinements. A summary of these suggestions, and of how they were addressed by the AEATF, appears as Attachment 4 to this review.

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 comments were satisfactorily addressed, as were most of the HSRB's comments, in the revisions approved by the IIRB on February 11, 2009.

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, properly amended when necessary, and all amendments were approved by the overseeing IRB before they were implemented. 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 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.

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 Wipe Scenario Report
Attachment 2: Chronology of AEATF Wipe Study
Attachment 3: Summary of Amendments and Deviations to AEATF Wipe Study
Attachment 4: Responsiveness of AEATF to HSRB Comments on Wipe Study

§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
AEATF II Wipe Scenario Report: MRID 48375601

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 p. 1352-1374; 1467-1477; 1499-1509 p. 888
	§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. 888
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	p. 664-1574
	§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 –1352, 1467 Approved Spanish CF 1363, 1499
	§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; see also amendments 3 and 4
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	p. 664-1574
	§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. 674 Renewal p. 898 Post-HSRB approval p. 1117, 1130 Amendment 1, 2 p. 1351 Amendment 3 p. 1400 Amendment 4 p. 1411 Amendment 5 p. 1435

§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
AEATF II Wipe Scenario Report: MRID 48375601

Requirement	Y/N	Comments/Page References
		Amend 6 p. 1552 Amendment 7 p. 1466 Amendment 8 p. 1574
(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. 1352, 1467, 1363, 1499
(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	

Chronological Listing of Events: AEATF Mop Study

Based on Table 1 from AEATF Submission (pp. 121-122)

16 Jan 08	GPL submission of undated protocol and supporting materials to IIRB
16 Jan 08	GPL submission of protocol (dated 16 Jan 08) and supporting materials to CDPR
18 Jan 08	GPL re-submission of protocol with version date of 16 Jan 08 and supporting materials
22 Jan 08	IIRB approval of protocol and supporting materials
14 Feb 08	CDPR reviewed ICF submitted on 16 Jan 08 and provided summary of revisions to GPL
25 Feb 08	Submission of IIRB-approved protocol to EPA
10 Mar 08	EPA Science & Ethics Review of Proposal
9 Apr 08	HSRB Discussion of Proposal
11 Apr 08	CDPR submitted summary of revisions needed to be incorporated in protocol submitted on 16 Jan 08 and ICF
25 Jun 08	HSRB Final Report of April public meeting
12 Jan 09	GPL submission of annual progress report to IIRB
21 Jan 09	IIRB extension of approval through 19 Jan 10
23 Jan 09	GPL transmittal of undated protocol with appendices A through L to CDPR
27 Jan 09	GPL submission of responses to CDPR review of 11 Apr 08
02 Feb 09	CDPR provisionary approval of study, prior to final approval
05 Feb 09	GPL submissions of Spanish translated appendices A, B, C, D, F, G, and H and revised protocol titled “Final 02-03-09” with all appendices A through L) to IIRB with extensive changes from version of Jan 08, not characterized or tracked
10 Feb 09	GPL resubmission of 22 Jan 08 IIRB-approved CF with tracked changes
11 Feb 09	IIRB approval of English ICF (Ver. 11 Feb 09), protocol version 03 Feb 09, California Experimental Subject‘s Bill of Rights (ESBOR) and Print Ad version “Research Study Volunteers”
23 Feb 09	“Start of search for test site selection”
23 Mar 09	IIRB acceptance of certified Spanish translation of Informed Consent Form (Ver. 11 Feb 09, Approved 11 Feb 09), ESBOR (Approved) 11 Feb 09 and Print Ad “Research Study Volunteers” (Approved 11 Feb 09) and other Spanish translated protocol appendices H, A, G and D
7 Apr 09	GPL submission of final IIRB approved protocol (11 Feb 09) and all Spanish translated appendices to DPR
8 Apr 09	“Study Initiation” [Date on which study director signed protocol]
16 Apr 09	GPL submission of all English IIRB approved appendices to DPR
17 Apr 09	CDPR granted GPL final approval of study
4 May 09	GPL submission of protocol Amendments 1 and 2, English and Spanish appendices B, C, F, G, H to IIRB
5 May 09	IIRB approval of protocol Amendments 1 and 2, English/Spanish ICF (ver. 5/5/09), English/Spanish ESBOR (dated 05/05/09), revised Recruiting Flyers (appendices G and H) in English

Chronological Listing of Events: AEATF Mop Study

Based on Table 1 from AEATF Submission (pp. 121-122)

6 May 09	IIRB acceptance of certified Spanish translation of appendices G and H
24 Jun 09	GPL submission of Amendment 3 to IIRB. (Amendment text is a paraphrase of what might be changed in the protocol.)
25 Jun 09	IIRB email reports having faxed approval of Amendment 3
25 Jun 09	IIRB approval of Amendment 3
9 Jul 09	GPL submission of Amendment 4 and English/Spanish recruiting ads to IIRB
10 Jul 09	IIRB approval of Amendment 4
13 Jul 09	IIRB approval of English/Spanish recruiting ads
27 Jul 09	GPL submission of Amendment 5 to IIRB
27 Jul 09	IIRB approval of Amendments 5
10 Aug 09	First subject enrolled/monitored; “Experimental Start”
10-15 Aug 09	Monitoring at Site 1 (IRS Office Building)
21 Aug 09	GPL submission of Amendment 7 to IIRB
21 Aug 09	IIRB approval of Amendment 7
21 Aug 09	IIRB email reference to approval of revised CFs and supporting materials
24-29 Aug 09	Monitoring at Site 2
28 Sep-3 Oct 09	Monitoring at Site 3
3 Oct 09	Last subject monitored
3 Nov 09	Analyses completed for subject and field fortification samples
15 Jan 10	GPL submission of closeout report to IIRB
29 Jan 10	IIRB acceptance of closeout report
20 May 10	GPL submission of Amendment 6 to IIRB
24 May 10	IIRB acceptance of Amendment 6
4 Jun 10	GPL submission of Deviation Report 1 to IIRB
4 Jun 10	IIRB acceptance of Deviation Report 1
14 Nov 10	Analysis of three additional samples
15 Nov 10	“Experimental Termination” (p. 6) “Last day of data collection”
16 Nov 10	GPL submission of Amendment 8, Deviation Report 2 and the revised Closeout Report to IIRB
18 Nov 10	IIRB acceptance of Amendment 8, Deviation Report 2 and the revised Closeout Report
13 Jan 11	“Study Completion”
26 Jan 11	Submission of study to EPA

Summary of Amendments and Deviations
AEATF-II Wipe Study GPL Protocol # 070264

Amendment 1: (Submitted May 4, 2009; Approved May 8, 2009; p. 1249-1351)

1. Added minimum size of 10,000 square feet in definition of acceptable sites
2. Permitted use of "non-vacant" meeting spaces for hire
3. Added provision to send a copy of the recruitment flyer to employers before employers make a decision about posting a flyer

Amendment 2: (Submitted May 4, 2009; Approved May 8, 2009; p. 1249-1351)

1. Clarified that CF would be available in either English or Spanish
2. Added commitment to make MSDS available in both English and Spanish
3. Clarified that at least 7 days would elapse between monitoring at different clusters
4. Clarified that all recruiting materials and communication with subjects would be available in either English or Spanish
5. Clarified availability of 24-hr toll-free answering service in both English and Spanish
6. Committed to provide each subject with a copy of the label and MSDS
7. Harmonized descriptions of recruiting procedures in sections 9.1.2 and 9.3
8. Reflected name change of Grayson Research in exclusion criteria
9. Changed study procedures to permit discussion with subjects either individually or in a group
10. Changed study procedures to specify removal of shoes before removal of pants
11. Clarified procedure for weighing spray bottles
12. Clarified collection of sock dosimeters before WBDs
13. Clarified reporting of weights of spray bottles
14. Deleted unnecessary reference to QAU statements
15. Reflected name change of Grayson Research throughout protocol

Amendment 3: (Submitted June 24, 2009; Approved June 25, 2009; pp. 1393-1401)

1. Clarify the four-week recruiting period begins following completion of the janitorial firm manager meetings
2. Allow informed consent meetings and enrollment of individuals during the recruiting period
3. Require three attempts be made to reach and schedule informed consent meetings with all individuals on the primary call-in list
4. Randomly order all enrolled volunteers at conclusion of the enrollment process, and select the first (randomly ordered) forty eight volunteers for participation in the study. Use this same random order to assign participants to the trigger spray and wipe or ready-to-use scenarios, specific clusters within scenarios, and specific ME slots within clusters.

Summary of Amendments and Deviations
AEATF-II Wipe Study GPL Protocol # 070264

Amendment 4: (Submitted July 9, 2009; Approved July 13, 2009; pp. 1402-1420)

1. Added newspaper advertisements (English and Spanish) to recruiting process

Amendment 5: (Submitted and approved July 27, 2009; pp. 1421-1436)

1. Revised the protocol to provide that the diluted cleaning solution will be prepared at the study location on the day of use, rather than prepared at the laboratory the day before the study.
2. Revised method for assigning subjects to ME slots
3. Corrected reference to SOP
4. Revised §10.4 Re: Field Recovery Evaluation to be consistent with revised SOP

Amendment 6: (Submitted August 4, 2009; Approved May 24, 2010; pp. 1549-1552)

1. Further revised §10.4 Re: Field Recovery Evaluation
2. Revised §12.2 Re: Analytical Method

Amendment 7: (Submitted and approved August 21, 2009; pp. 1437-1511)

1. Changed Field Study Coordinator and Field Study Associate

Amendment 8: (Submitted November 16, 2009; Approved November 18, 2009; pp. 1569-1574)

1. Changed the address and management of the Study Director/Principal Investigator (the study director resigned from Golden Pacific Laboratories, but will continue to serve as Study Director as an independent contractor. The study director information has changed to reflect this status change.

Deviation Report 1: (Submitted and acknowledged June 4, 2010; pp. 1553-1565)

Dates of occurrence:
Cluster 1: August 10-15, 2009
Cluster 2: August 24-29, 2009
Cluster 3: September 28-October 3, 2009

1. Subjects washed hands with 50% IPA and water as well as with soap before monitoring
2. Light readings were not taken at monitoring sites as called for in the protocol
3. Subjects declined to take breaks at 30-minute intervals or took less than 10 minute breaks
4. The empty weight of each unique trigger spray bottle used by subjects was not documented as required by Protocol Amendment 2

Deviation Report 1 (continued):

5. The final concentration of test substance solution for clusters 2 and 3 was diluted to 1:63 rather than 1:64.
6. Subject face/neck wipe samples at sites 2 and 3 not collected as specified in Protocol §10.
7. Environmental measurements made less frequently at site 1 than required in Protocol §8.5 (measurements should have been made at a minimum of 10-minute intervals, but during cluster 1, some data logger measurements were only recorded every 15 to 30 minutes.
8. During cluster 1, the data logger in the test solution preparation area only recorded the temperature, not the humidity. During cluster 3, one of the data loggers that followed the subjects only recorded the temperature, not the humidity.
9. Researchers failed to record the serial number from certain data logger devices in cluster 1, making it difficult to determine which data loggers accompanied the concurrently monitored subjects for monitoring events R3 and R4.
10. Study personnel failed to record the RTU canister number in connection with the ready-to-use wipe sample collected, and as a result, the observational notes from cluster 1 do not indicate from which RTU canisters the ready-to-use wipe samples were pulled during monitoring events R5 and R6.
11. Field fortification samples of hand wash at site 1 were not collected at all prescribed times.
12. The diluted material aliquots were not collected from every trigger spray bottle used by the subjects during cluster 1, as specified in Protocol Appendix K.
13. Air pump flows were not recorded for subject T6 during cluster 1, and subjects R1 and R6 during cluster 2.
14. During Cluster 1, the documentation for the air pump calibration on August 11, 2009, was misplaced. Thus, there are no calibration records or before-pump flow rates from the T6 pump (contrary to Protocol §10.2.1)
15. During Cluster 1, subject W16 wiped for 165 minutes, 15 minutes short of the allotted time interval, and subject W10 wiped for 154 minutes, four minutes over the allotted time interval. In Cluster 2, subject W37 wiped for 61 minutes, one minute over the allotted time interval, and subject W18 wiped for 121 minutes, one minute over the allotted time interval.
16. During Cluster 1 monitoring event R5, the field study personnel responsible did not indicate on the appropriate form whether the subject washed with ivory soap, and rinsed with 50% IPA:50% water prior to the monitoring event. It is also unknown whether the hand examination procedure was completed.
17. Air sampling pumps malfunctioned in two instances.
18. On the first day of cluster 2, the subjects were only photographed from the front with faces included in the photograph. This was contrary to the protocol requirement that both the front and back should be photographed, and that faces should be excluded.
19. Temperature of walk-in cold locker in which samples were stored was not confirmed at site 2.

Summary of Amendments and Deviations
AEATF-II Wipe Study GPL Protocol # 070264

Deviation Report 1 (continued):

20. OVS tubes fortified at field site rather than at the laboratory at site 2.
21. Background air samples at site 3 collected at 3 feet instead of 5 feet above the floor.

Deviation Report 2: (Submitted November 16, 2010; acknowledged November 18, 2010; pp. 1568-1574)

Dates of occurrence:
Cluster 1: August 10-15, 2009
Cluster 2: August 24-29, 2009
Cluster 3: September 28-October 3, 2009

1. Some sample fortifications were at incorrect levels
2. Solvent blanks were not injected before all analytical runs as specified

Responsiveness to HSRB Ethics-Related Comments on AEATF-II Wipe Study Protocol

	HSRB Comment on Protocol	Response
Protocol	Although the risks to subjects from exposure to the test compound appear very low, . . . it might be possible to design scenarios in which instead of an antimicrobicide, some less toxic tracer substance might be used. It would be appropriate for protocols to discuss this possibility for further minimizing risks.	EPA believes tracer studies would raise more new issues, including issues of safety, than studies with registered antimicrobials used in approved use patterns.
	[T]he requirement for females under the age of 50 to take a pregnancy test could be refined. It would be possible to design criteria that created a better fit between which female subjects might be able to get pregnant, and which of them are being asked to take that test. By doing this, the researchers would be showing greater respect for this group of subjects.	Amended to require ALL females, regardless of age, to take pregnancy test. Investigators explained to EPA that they thought it would be less intrusive and more respectful to apply the requirement to all women than to inquire about their individual ability to become pregnant.
	[P]rovide a greater justification for why subjects older than 65 are excluded.	"Because this study may require physically strenuous activities, an upper age limit was imposed" (p. 958)
Consent Form	[M]ake sure that the consent forms are at an appropriate level of readability. . . . [T]here appears to be room for further simplification.	Negligible change (from 9.9 to 9.8) in reading level (Flesch-Kincaid Grade Level for CF.) F-KGL for some amended material is as high as 16+.
	[The consent form does not] describe adequately the procedures discussed in the protocol relating to (a) still photography of the subjects, (b) videotaping of the subjects, and (c) observation of the subjects by members of the study team.	Changed to state that photos and video will be taken by an assigned observer, and that subjects' faces will not be shown in any reports. "There were always 3 to 4 study personnel following the subject during a ME." (p. 46)
	[E]xplain [in CF] that the underlying purpose of the study will be to collect information that will be provided to the EPA, and that the EPA would use that information to determine the appropriate standards for allowable exposures to products such as the test compound.	Not addressed
	Replace the confusing term "same-sex person" in procedure step 4 in CF; replace with the descriptions used elsewhere in the form, such as "a researcher of your own sex."	Unchanged in #4 in consent form (p. 1109). In #11 in consent form, phrase changed to "researcher of your own gender." (p. 1110)
	Explain any known risks to subjects, such as eye irritation.	"Permanently" changed to "forever" in CF discussion of risk of eye irritation (p. 1111)
	Correct garbled sentence in IIRB-approved CF concerning risks to the unborn.	Corrected (p. 1112)
Recruiting Flyer	Explain in flyer that research will measure inhalation as well as dermal exposure	Not changed
	Correct garbled eligibility criterion in Flyer	Corrected
	Correct mischaracterization of how EPA will use the resulting data	Corrected
Other	Add reference to inhalation monitoring in phone dialogs	Already included in phone dialog; no change required
	Provide more detail about how community—including unions—will be engaged/involved	Revised in protocol and in Appendix H. Intention was to engage unions through pre-recruiting employer meetings, none of which took place.

Attachment 4

Responsiveness to HSRB Ethics-Related Comments on AEATF-II Wipe Study Protocol

	HSRB Comment on Protocol	Response
	Ensure appropriate dialect is used in translations, and clarify who is doing translations	Translations done by CA translator, who was part of research team. Protocol states "all documents . . . will be translated by an individual familiar with idioms and common dialects used in the Fresno area." (p. 955)