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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

4 Oct 2010

MEMORANDUM

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

FROM: John M. Carley
Human Research Ethics Review Officer
Office of Pesticide Programs

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

REF: Selim, S., and Taylor, M. (2010) A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using Bucket and Mop Equipment for Cleaning Indoor Surfaces. Unpublished study prepared by Golden Pacific Laboratories, LLC, under Project No. AEA03, Report No. 070265. 2116 p. (MRID 48210201)

Selim, S., and Taylor, M. (2010) A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using Bucket and Mop Equipment for Cleaning Indoor Surfaces: Supplement 1 to MRID 48210201. Unpublished study prepared by Golden Pacific Laboratories, LLC, under Project No. AEA03, Report No. 070265. 1146 p. (MRID 48231201)

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced documents, which describe the execution and results of a study in which dermal and inhalation exposure of professional janitorial workers to antimicrobial pesticides was monitored as they mopped indoor floors and disposed of the spent mop water. If it is determined to be scientifically acceptable, I find no barrier in regulation to EPA's reliance on this study in actions under FIFRA or FFDCA.

Background and Chronology

The scenario design and protocol for this study, identified by the investigators as Protocol #070265, was approved by the overseeing IRB and submitted to EPA for review in February 2008. The protocol and EPA's review of 10 March 2008 were discussed by the HSRB on 9 April 2008. The HSRB review was generally favorable; their 25 June 2008 final report of the April meeting 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 extensively revised to address EPA, HSRB, and California DPR comments. The revised protocol was submitted to the IIRB, Inc., of Plantation FL on 26 February 2009, and approved, along with certified Spanish translations, on 16 March 2008. The approved English-language consent form is in the first supplement (S1:382-392)[1], the Spanish-language consent form is at S1:442-454. A mark-up comparing the 26 Feb 09 protocol and attachments to the proposal reviewed by EPA and the HSRB in April 2008 appears at S1:6-159.

After 16 March 2009 the protocol was amended seven times, with revised Consent Forms approved on 5 May 2009 (S1:573-596, used in monitoring in Cluster 1), and 21 Aug 2009 (S1:691-701, 722-732, used in monitoring at Clusters 2 and 3.)

Final approval of the protocol and supporting materials was granted by the California DPR on 17 April 2009. Subject recruitment began the following week on 24 April 2009. Initial response was slow, and Amendment 3 (S1:601-601; approved 25 June 2009) revised the recruiting procedures. Subject enrollment began on 1 July. Recruiting procedures were revised further to add recruiting by newspaper advertisements in Amendment 4 (S1:604-607; approved 13 July 2009.) Initial enrollment of subjects was completed on 24 July.

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; at site 2 from August 24-29, and at site 3 from September 28 through October 3. A more detailed chronology appears as Attachment 2 to this review.

Scope of Review:

This review reflects consideration of the primary study report and supplement cited above, and the following additional documents:

[1] Throughout this review page references to the primary submission, MRID 48210201, will be shown as (V1:nn), where 'nn' is the page number or page range within the 2116 pages of this document. References to Supplement 1, MRID 48231201, will be shown as (S1:nn), where nn refers to the page number or page range within the 1146 pages of that document.

- EPA's 10 March 2008 Science and Ethics Review of the AEATF II Mop Scenario Design and Protocol

- The HSRB's 25 June 2008 report of its April 2008 discussion of the AEATF II Mop Scenario Design and Protocol

- A spreadsheet "Subject Info all 32" submitted in response to EPA's request on 30 September, and appearing as Attachment 5 to this memo.

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 initial report—MRID 48210201—was deficient in many ways. Appendix Q, containing IIRB Correspondence, spanned 1178 pages, entirely un-indexed, of which more than half contained irrelevant or redundant information. I noted the following major omissions from Appendix Q:

- Documentation of IIRB extension of approval after Jan 09
- Documentation of IIRB approval of revised protocol and supporting materials on 16 Mar 09
- Documentation of IIRB approval of translated materials on 3 Apr 09
- Documentation of IIRB approval of Amendments 3, 4, and 5

Appendix R, containing correspondence with the California DPR, was likewise un-indexed, with these major omissions:

- Correspondence with CDPR before 29 Jan 09, including CDPR review of 1 Apr 08 and GPL response
- CDPR response to submission of 29 Jan 09
- Documentation of CDPR final approval

In addition, the chronology provided in Table 1 (V1:100) was significantly incomplete, and the changes made to the protocol, consent forms and other materials to address EPA and HSRB comments were not tracked.

After being notified of these deficiencies by EPA, the AEATF corrected them with the submission of the cited supplement, MRID 48231201. It contains the protocol and supporting materials submitted to the IIRB on 26 Feb 09 tracking changes from the versions previously reviewed by EPA and the HSRB (S1:6-159), an expanded chronology (S1:160-162), and complete replacements for Appendices Q (S1:164-796) and R (S1:798-1116), correcting omissions, omitting redundant and irrelevant materials, and accompanied by indices based on those prepared by EPA in its initial review.

Much of the bulk in the correspondence files resulted from the failure of the investigators to maintain effective version control over the protocol, consent forms, and other documents, notwithstanding repeated requests from the IIRB to do so.

No minutes of IIRB, Inc., meetings were submitted; because all IIRB, Inc. reviews subsequent to the HSRB meeting were conducted under expedited procedures, as noted in the letters of approval, no minutes were taken under IIRB's procedures. In addition, neither the IIRB, Inc., roster nor the IIRB, Inc., procedures were submitted as part of the study.

Protocol Amendments:

Subsequent to IIRB approval of the revised protocol on 16 Mar 09 it was amended 7 times. A summary of the scope of all amendments appears as Attachment 3 to this review. Although Amendment 2 made minor adjustments in some procedures, 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 had been identified, and Amendment 4 provided for recruiting through newspaper advertising. The choice of newspapers—three in all, each serving a different community in the Fresno area—was appropriate.

Protocol Deviations:

Two reports of protocol deviations were made to the IIRB, Inc. after completion of the research; they are also summarized in Attachment 3. Two points raised in Deviation Report 1 (V1: 1731-1736) 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. In my judgment neither of these deviations affected either data quality or subject safety.

The demographic data shows what may have been another, unacknowledged deviation, in that two enrolled subjects (#8, who was monitored in cluster 2, and #5, an alternate) reported their general health as only "fair". The protocol (§9.3.1, V1:384) specifies that to be included subjects must be "in good health." The consent form (V1:419) states that participants "must be healthy adults." The "Subject Self-Reporting Demographic Form," Appendix D to the protocol (V1:430) 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.

Recruiting:

The initial design of the recruiting process relied on flyers, posted in the workplaces of janitorial services providers who agreed to do so after discussing the

research with the investigators. This process was attempted, but proved unproductive. Very few service providers were willing to post flyers, and very few candidates responded to the few that were posted by calling the investigators for more information. A few candidates did respond, but the protocol did not provide for enrolling them until after the full complement had been recruited and randomized; the investigators were concerned that they would lose contact with these candidates. After discussion with EPA, the investigators put forward Amendment 3, which permitted them to inform, consent, and enroll subjects as they came forward, and randomly assign them to monitoring sites and slots (M1-M6 at each site) after recruiting was completed. EPA endorsed this revision to the original plans for recruiting and randomization.

Response to the recruiting flyers continued slow, and after further discussion with EPA, the investigators put forward Amendment 4, to allow recruiting through newspaper advertisements. This change—and newspaper advertisements in English and Spanish—was approved by the IIRB, Inc. in mid July, and recruiting was completed on July 24.

No demographic information was provided about the subjects in the primary study report or supplement. In response to an EPA request, a spreadsheet was provided on 30 September 2010 reporting subject characteristics. The full spreadsheet appears as Attachment 5 to this review; its content is summarized in Table 1 below.

Table 1: AEATF II Mop Study Subject Characteristics

	All Enrolled Subjects	Monitored Subjects	Alternate Subjects
Male	15	10	5
Female	17	8	9
English	20	11	9
Spanish	12	7	5
Range of Experience	3 mos – 40 yrs†	3 mos – 40 yrs	1 – 20 yrs
Mean Years Experience	8.8 yrs	11.1 yrs	5.8 yrs
Age Range	18 - 53	18 - 53	18 - 50
Mean Age	36.8 yrs	38.1 yrs	35.3 yrs
Health 'Excellent'	18	10	8
Health 'Good'	12	7	5
Health 'Fair'	2	1	1
Requested Results	25 (78%)	15 (83%)	10 (71%)

† Experience was not reported for subject #30 (alternate; dropped because she moved away)

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

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 of 10 March 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 26 February 2009, all references in protocol and consent form to translators were replaced by references to researchers fluent in Spanish, to whom the recruiting and consenting responsibilities of the PI would be delegated when candidates preferred to interact in Spanish. The Consent Form and California Experimental Subject's Bill of Rights were revised to show hours for calling in Pacific (local) time.

HSRB Protocol Review Comments

In its 25 June 2008 report of its April 2008 discussion 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. Most were addressed responsively by the investigators, some less responsively, and some were not addressed.

One HSRB comment observed that "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 agrees that it might be possible to design studies using tracers, but disagrees that it would be appropriate for AEATF II protocols to discuss this possibility. EPA has accepted the approach defined in the AEATF II Governing Document, which relies on exposure monitoring with registered antimicrobial products used in approved use patterns. EPA believes that tracer studies would be likely to raise more new issues, including issues of safety, than studies with registered antimicrobials.

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 16 March 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.

Notwithstanding initially poor documentation of the interaction of the investigators and the overseeing IRB, and the failure of the investigators to address all the points raised by the HSRB in its review of the proposal, 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.

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

Compliance with 40 CFR §26 subpart M

As is documented in Attachment 1 to this review, taking into account both the primary study report (MRID 48210201) and the supplement (MRID 48231201), the central requirements of 40 CFR §26 subpart M, §26.1303 to document the ethical conduct of the research were addressed. The failure to provide minutes of IIRB, Inc., meetings, the IIRB roster and IIRB procedures did not compromise this review. Taking the two submissions together, along with the separately submitted roster and procedures of the IIRB, Inc., the requirements of 40 CFR §26.1303 were satisfactorily 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. Initially deficient reporting was promptly corrected, and all requirements for documentation of ethical conduct of the research were 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 Mop Scenario Report
Attachment 2: Chronology of AEATF Mop Study
Attachment 3: Summary of Amendments and Deviations to AEATF Mop Study
Attachment 4: Responsiveness of AEATF to HSRB Comments on Mop Study
Attachment 5: GPL Spreadsheet: "Subject Info All 32"

§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
AEATF II Mop Scenario Report: MRIDs 48210201, 48231201, and 48231901

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; Amend. 1 (S1:525-527) Amend. 2 (S1:528-532) Amend. 3 (S1:601-602) Amend. 4 (S1:604-607) Amend. 5 (S1:633-636) Amend. 6 (S1:771-772) Amend. 7 (S1:642-643) Approved English CFs: 3/16/09 (S1:382-392) 5/5/09 (S1:573-583) 8/21/09 (S1:691-701) Approved Spanish CFs: 3/16/09 (S1:442-454) 5/5/09 (S1:584-596) 8/21/09 (S1:722-732) Progress Rpt (S1:173-177)
	§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	S1:171, 735, 796
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	S1:163-796; V1:584-1760
	§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	Already available to EPA
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		N	Already available to EPA
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		n/a	
(b) Copies of all of the records relevant to the information	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	Addressed in protocol; slightly revised S1:17
		(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

§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
AEATF II Mop Scenario Report: MRIDs 48210201, 48231201, and 48231901

Requirement		Y/N	Comments/Page References
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Provided CFs S1:245-256; 325-336; 365-375; 419-431; 484-495; 504-514; 658-668; 705-717 Approved Engl CFs S1:382-392; 573-583; 691-701 Approved Span. CFs S1:442-454; 584-596; 722-732
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	Initially satisfied in protocol. Flyers & Ads in Engl & Span
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.	Y	Initially satisfied in protocol; see also amendments 3 and 4
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	See §1115(a)(4) above
	§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 Renewal S1:183 3/16/09 S1:381; 394-395; 438 5/5/09 S1:559; 566; 572 Amend 3 6/25/09 S1:610 Amend 4 7/10/09 S1:616 Amend 5 7/27/09 S1:637 8/21/09 S1:690 Amend 6 5/25/10 S1:774 Final CDPR approval S1:1145-46
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research		Y	S1:739-760
(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 (V1:100) and Supplemental Chronology (S1:161-162)

14 Jan 08	GPL submission of undated protocol and supporting materials to IIRB for review
16 Jan 08	Submission of ICF to CDPR
18 Jan 08	GPL resubmission of protocol with (erroneous) version date of 16 Jan 07 and undated 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 review calling for revisions in protocol and ICF submitted on 16 Jan 08
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
27 Jan 09	GPL submission of responses to CDPR review of 11 Apr 08
19 Feb 09	CDPR provisional approval of study
23 Feb 09	Start of search for test site selection
26 Feb 09	GPL submission of undated revised protocol and supporting materials to IIRB, with extensive changes from version of Jan 08 not characterized or tracked
3 Mar 09	GPL resubmission of 22 Jan 08 IIRB-approved CF with tracked changes
16 Mar 09	GPL resubmission of protocol with revised title page incorporating version date of 26 Feb 09 and revised total page count
16 Mar 09	IIRB approval of revised protocol, CF, and other materials.
8 Apr 09	Study Initiation (V1:6) *[Date on which SD /s/ protocol]*
17 Apr 09	CDPR final approval of study
24 Apr 09	Start of subject recruitment
4 May 09	GPL submission of protocol Amendments 1 and 2
5 May 09	IIRB approval of revised protocol, protocol Amendments 1 and 2, and CF, recruiting flyer, and recruiting scripts in English and Spanish
24 Jun 09	GPL submission of Amendment 3 to IIRB.
25 Jun 09	IIRB approval of Amendment 3
1 Jul 09	Start of subject enrollment
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
24 Jul 09	End of subject enrollment
27 Jul 09	GPL submission of Amendment 5 to IIRB
27 Jul 09	IIRB approval of Amendments 5

Chronological Listing of Events: AEATF Mop Study

Based on Table 1 (V1:100) and Supplemental Chronology (S1:161-162)

27 Jul 09	Start of analytical work: preparation of analytical standards and laboratory fortification solutions
27 Jul 09	Secured Cluster 1 test site at former IRS office building
29-30 Jul 09	Preparation of field fortification solutions
10-15 Aug 09	Cluster 1 exposure monitoring at IRS office building
10 Aug 09	First subject ME M5 enrolled/monitored; “Experimental Start” (V1:6)
11 Aug 09	ME M6; field fortifications
11 Aug 09	Analyses started for subject and field fortification samples
12 Aug 09	ME M2
13 Aug 09	ME M3; field fortifications
14 Aug 09	ME M4
15 Aug 09	ME M1; field fortifications
17 Aug 09	Secured Cluster 2 test site at vacant Rite Aid retail 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	Cluster 2 exposure monitoring at Rite Aid retail building
24 Aug 09	ME M6
25 Aug 09	ME M5; field fortifications
26 Aug 09	ME M4
27 Aug 09	ME M3; field fortifications
28 Aug 09	ME M2
29 Aug 09	ME M1; field fortifications
8 Sep 09	Secured Cluster 3 test site at Retired Teacher’s Education Center
28 Sep-3 Oct 09	Cluster 3 exposure monitoring at Retired Teacher’s Education Center
28 Sep 09	ME M6
29 Sep 09	ME M5; field fortifications
30 Sep 09	ME M4
1 Oct 09	ME M3; field fortifications
2 Oct 09	ME M2
3 Oct 09	ME M1; field fortifications; last subject monitored
13 Nov 09	Analyses completed for subject and field fortification samples (p. 100)
15 Jan 10	GPL submission of closeout report to IIRB
29 Jan 10	IIRB acceptance of closeout report
2 Mar 10	“Experimental Termination” (V1:6) “Last day of data collection” (V1:100)
20 May 10	GPL submission of Amendment 6 to IIRB

Chronological Listing of Events: AEATF Mop Study

Based on Table 1 (V1:100) and Supplemental Chronology (S1:161-162)

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
28 Jul 10	GPL submission of Deviation Report 2 to IIRB
28 Jul 10	IIRB acceptance of Deviation Report 2
28 Jul 10	“Study Completion” (V1:6)
2 Aug 10	Informal Submission of “Final Report” to EPA
31 Aug 10	Formal Submission of “Final Report” to EPA
20 Sep 10	Formal Submission of Supplement 1 to EPA
21 Sep 10	Formal Submission of Supplement 2 to EPA

Summary of Amendments and Deviations
AEATF-II Mop Study GPL Protocol # 070265

Amendment 1: (May 2009; S1:525-527)

- Incorporated minimum size of 10K sq ft in definition of acceptable sites
- Permitted use of "non-vacant" meeting spaces for hire
- Adds provision to send copy of flyer to employers before decision about posting

Amendment 2: (May 2009; S1:528-532)

- Clarified that CF would be available in either English or Spanish
- Added commitment to make MSDS available in both English and Spanish
- Clarified when SD would notify local sewer authority of intended flushing of waste
- Clarified that at least 7 days would elapse between monitoring at different clusters
- Clarified that all recruiting materials and communication with subjects would be available in either English or Spanish
- Clarified availability of 24-hr toll-free answering service in both English and Spanish
- Committed to provide each subject with a copy of the label and MSDS
- Harmonized descriptions of recruiting procedures in sections 9.1.2 and 9.3
- Reflected name change of Grayson Research in exclusion criteria
- Changed study procedures:
    - To permit discussion with subjects either individually or in a group
    - To specify removal of shoes before removal of pants
- Clarified procedure for weighing buckets of mop solution
- Clarified collection of sock dosimeters before WBDs
- Revised reference to SOP
- Clarified reporting of weights of buckets and mop solution
- Deleted unnecessary reference to QAU statements
- Reflected name change of Grayson Research throughout protocol

Amendment 3: (June 24, 2009; S1:601-602)

- Revised procedures in recruitment phase

Amendment 4: (July 9, 2009; S1:604-607)

- Added newspaper advertisements (English and Spanish) to recruiting process

Amendment 5: (July 27, 2009; S1:633-636)

- Revised method for assigning subjects to ME slots
- Corrected reference to SOP
- Revised §10.4 Re: Field Recovery Evaluation to be consistent with revised SOP

Summary of Amendments and Deviations
AEATF-II Mop Study GPL Protocol # 070265

Amendment 6: (August 4, 2009; S1:771-772)

- Further revised §10.4 Re: Field Recovery Evaluation
- Revised §12.2 Re: Analytical Method

Amendment 7: (August 21, 2009; S1:642-643)

- Changed Field Study Coordinator and Field Study Associate

Deviation Report 1: (May 25, 2010; V1:1731-1736)

- Subjects washed hands with 50% IPA and water as well as with soap before monitoring
- Light readings were not taken at monitoring sites as called for in the protocol
- Subjects declined to take breaks at 30-minute intervals or took less than 10 minute breaks
- Subject face/neck wipe samples at sites 2 and 3 not collected as specified
- Environmental measurements made less frequently than specified at site 1
- One environmental data logging device failed to record humidity
- Field fortification samples of hand wash at site 1 not collected at all prescribed times
- Air pump flows improperly recorded for subjects M5 and M6 at site 1
- Air pump calibration data for 11 Aug 09 lost
- Two subjects mopped a few minutes over or under allotted time
- Air pumps malfunctioned in two instances
- Two sites had less floor area than specified in protocol
- On one day, photographs included faces of subjects
- Temperature of walk-in cold locker in which samples were stored was not confirmed at site 2
- One subject mopped the same area twice during the same ME, after mopping all available floors
- Air pump ID not recorded for one ME; could not be linked to calibration data
- OVS tubes fortified at field site vice lab at site 2
- Background air samples at site 3 collected at 3 ft vice 5 ft above floor

Deviation Report 2: (July 13, 2010; V1:1754-1755)

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

Responsiveness to HSRB Comments
AEATF-II Mop Study GPL Protocol # 070265

	HSRB Comment	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 anti-microbials 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" (S1:31)
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." (V1:38)
	[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."	"same-sex member of the research team" unchanged. Two other references to a "researcher of your own sex" changed to "researcher of your own gender."
	Explain any known risks to subjects, such as eye irritation.	"Permanently" changed to "forever" in CF discussion of risk of eye irritation
	Correct garbled sentence in IIRB-approved CF concerning risks to the unborn; Explain origin of garble not initiated by investigators.	Garble not present in post-HSRB CFs. Source of earlier garble not explained.

Responsiveness to HSRB Comments
AEATF-II Mop Study GPL Protocol # 070265

	HSRB Comment	Response
Recruiting Flyer	Explain in flyer that research will measure inhalation as well as dermal exposure	Not changed (S1:82)
	Correct garbled eligibility criterion in Flyer	Corrected (S1:82)
	Correct mischaracterization of how EPA will use the resulting data	Corrected (S1:82)
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 (S1: 19) and in Appendix H (S1:87). Intention was to engage unions through pre-recruiting employer meetings, none of which took place.
	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." (S1:29)

GPL Spreadsheet: Subject Info All 32

Attachment 5

Cluster	Monitoring Event Conducted	SUBJECT NUMBER	AGE	SEX	WEIGHT	HEIGHT	YEARS OF EXPERIENCE	HEALTH	English/Spanish Speaking	REQUESTED RESULTS	Notes
Cluster 1 Subjects											
Cluster 1	M6	6	38	F	145	5'3"	5 Years	Excellent	English	YES	
Cluster 1	M5	13	24	M	175	5'8"	3 Years	Good	Spanish	YES	
Cluster 1	M4	15	50	F	127	5'0"	25 Years	Excellent	English	YES	
Cluster 1	M3	28	29	M	NA	NA	5 Years	Excellent	English	YES	
Cluster 1	M2	12	53	F	128	5'	20 Years	Excellent	Spanish	YES	
Cluster 1	M1	27	48	M	204	5"7"	10 Years	Excellent	English	YES	
Cluster 2 Subjects											
Cluster 2	M6	8	46	M	203	5' 9"	8 Years	Fair	Spanish	YES	
Cluster 2	M5	24	21	M	215	5' 7"	3 Years	Excellent	English	YES	
Cluster 2	M4	2	46	M	186	5' 7"	23 Years	Excellent	Spanish	YES	
Cluster 2	M3	4	38	M	190	5' 7"	10 Years	Good	English	YES	
Cluster 2	M2	10	38	F	110	5' 5"	6 Years	Good	Spanish	YES	
Cluster 2	M1	21	47	F	132	5' 1"	40 Years	Good	English	YES	
Cluster 3 Subjects											
Cluster 3	M6	7	50	F	147	5' 6"	20 years	Excellent	English	No	
Cluster 3	M5	18	26	M	160	5'6"	3 Years	Excellent	English	No	
Cluster 3	M4	26	18	M	240	5' 11"	3 Months	Good	English	No	
Cluster 3	M3	14	46	F	160	5'	4 Years	Good	Spanish	YES	
Cluster 3	M2	20	46	M	170	5'7"	2 Years	Good	English	YES	
Cluster 3	M1	1	50	F	152	5' 2"	12 Years	Excellent	Spanish	YES	
Enrolled Alternate Subjects											
		3	42	M	260	5"11"	10 Years	Excellent	English	YES	
		5	33	M	215	5' 11"	2 years	Fair	English	No	
		9	50	F	155	5'2"	20 Years	Good	Spanish	No	
		11	21	M	210	5' 11"	5 Years	Excellent	English	YES	
		16	43	F	150	5'3"	1 Years	Excellent	Spanish	YES	
		17	18	F	105	5'1"	2 Years	Excellent	Spanish	YES	
		19	48	F	135	5' 1"	20 years	Excellent	English	YES	
		22	23	M	145	5'8"	1 Years	Good	Spanish	YES	
		23	20	F	124	5' 1"	2 Years	Excellent	Spanish	YES	
		25	42	F	195	5'0"	1 years	Good	English	NO	
		29	42	M	190	5' 6"	4 Years	Excellent	English	YES	
Enrolled Subjects that were Dropped											
Dropped		30	42	F	220	NA		Good	English	No	Moved to San Diego
Dropped			49	F	210	5'8"	4 Years	Good	English	YES	Withdrew due to alcohol sesitivity
Dropped			21	F	138	5'3"	5 Years	Excellent	English	YES	Withdrew due to alcohol sesitivity