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

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

October 9, 2012

MEMORANDUM

SUBJECT: Ethics Review of Completed AEATF II Study for Measurement of Potential Dermal and Inhalation Exposure during Manual Pouring of a Liquid Containing an Antimicrobial

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

TO: Nader Elkassabany, PhD, Chief
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REF: Rosenheck, L. (2012) A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of a Liquid Containing an Antimicrobial. Unpublished study sponsored by the Antimicrobial Exposure Assessment Task Force II (AEATF II), under Project No. AEA05. 1227 p. (MRID 48917401)

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 poured liquid antimicrobial products containing didecyl dimethyl ammonium chloride (DDAC) or tetradecyl dimethylbenzyl ammonium chloride (C14 ADBAC) from various sizes of containers, both with and without design features to reduce splash. 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).

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.

Background and Chronology:

The 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 2011. The protocol and EPA's review dated September 23, 2011, were discussed by the Human Studies Review Board (HSRB) on October 20, 2011. The HSRB review was generally favorable; the January 11, 2012, final report concluded, with respect to ethics, that "the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."

Following issuance of the HSRB's report, the protocol, informed consent form (English and Spanish), newspaper advertisements (English and Spanish), subject qualification worksheet (English and Spanish), and Scenario Design Document were revised to address EPA and HSRB comments and submitted to IIRB. IIRB granted approval on January 25, 2012.

Recruiting:

Recruiting was initiated on January 28, 2012, shortly after IIRB granted approval of the revised protocol and recruiting materials. Advertisements were placed in two major daily newspapers, The News-Herald of Northern Ohio and the Star Beacon, and in a regional weekly bilingual (English/Spanish) publication, La Prensa. The advertisement ran in the News Herald and the Star Beacon from January 28 to February 6, 2012. The advertisement ran in La Prensa, in both English and Spanish, from February 1 to 8, 2012.

The majority of the telephone calls came in response to the advertisement in the News-Herald. Because fewer than 22 qualified potential subjects were signed up by February 5th, the advertisement in the News-Herald was extended through February 13th. In addition to the printed advertisement, all three papers ran the advertisement in the online versions of their papers. The advertisement included a brief description of the study and provided a toll-free phone number to call for more information. The toll-free number connected English-speaking callers to the Study Director or Spanish-speaking callers to a bilingual researcher in order to obtain more information about the study.

Everyone who called in response to the advertisement were English speakers. Interested callers were interviewed by phone to determine whether they met the inclusion criteria and they were provided a short overview of the study. An IIRB-approved script was used during these phone calls. Callers were screened for janitorial or property management services experience by asking if they were currently employed as a janitor or maintenance worker, had previously worked as a janitor or maintenance worker, or currently own and operate a janitorial firm providing services to commercial buildings. Callers were asked if they were at least 18 years of age and were capable of lifting up to ten 5-gallon buckets weighing approximately 40 pounds each.

During the phone call, volunteers were given a brief overview of the purpose of the study and what it entailed. For those who met the inclusion criteria and were interested in participating, an Informed Consent Meeting was scheduled. Phone calls from interested participants responding to the recruitment advertisements were received from January 30 to February 10, 2012. On February 8th, a total of 23 interested potential subjects were signed up to attend consent meetings. Callers who responded after February 8th were put on a stand-by list in case someone did not show up for a consent meeting or dropped out after attending a consent meeting.

Informed Consent:

All informed consent meetings were held in a conference room at the Holiday Inn Express in Mentor, Ohio. Potential subjects were asked to bring a government-issued picture ID to the meeting. The consent meetings were held by the Study Director and the bilingual research associate on February 8, 9, 10, and 13, 2012. The number of people attending any one meeting ranged from one to five.

At each meeting, the Study Director provided an overview of the study and asked the potential subjects to read the Informed Consent Form. After the subjects were given time to read the form on their own, the Study Director read the consent form to the group and answered any questions. The study purpose and the inclusion and exclusion criteria were described in detail, and it was made clear that potential subjects could ask questions or request clarification during the meeting and at any point before, during, or after the study. The Study Director explained to potential subjects that they could withdraw from the study at any time without penalty. Potential subjects were offered the opportunity to take the forms and information home with them to discuss the study with family and friends, but none chose to do so.

If the eligible potential subjects met the inclusion criteria and were still interested in enrolling in the study, they were asked to remain in the conference room so that each could meet privately with either the Study Director or the bilingual research associate in another room. During the individual meetings, the potential subjects were asked again if they had any further questions; once those questions were answered, they were given a short standardized oral comprehension test to make sure they

understood what was being asked of them. When this was complete, they were asked to sign and date the Informed Consent Form and answer questions from and sign the Worker Qualification Worksheet. During this time, the government-issued, picture identification card was checked to verify identity and age. Once these forms were completed, the subject was considered officially enrolled in the study. Each volunteer was given a copy of the IIRB-approved Informed Consent Form to take home. All potential subjects who attended a consent meeting, including those who did not qualify or who changed their minds about participating, were paid $20 cash.

Enrolled subjects were informed that they would receive $100 for reporting to the study location on the scheduled day, regardless of whether they actually participated in the study or not. Subjects were informed that a total of 22 people were being enrolled for the study, four of whom would serve as alternates in case someone did not show up for their scheduled appointment. The alternates would be randomly selected and would be paid the $100 even if they were never called to be monitored.

Twenty-three people who responded to the recruitment advertisements and passed the initial telephone screening phase were signed up to attend the consent meetings. Twenty-two people attended the consent meetings held on February 8 through 10 (one person did not show up). Out of the 22 people who attended the consent meetings, one person decided that he did not want to participate in the study and one was deemed ineligible as he was the spouse of an employee of Ricerca Biosciences LLC, the facility where the research was conducted. As a result, the first two people from the stand-by list were contacted on February 10th. Those two individuals met with the Study Director on February 13th to go through the consent process. All test subjects were English speakers who either were working or had worked in the janitorial or property management industries.

An identification number was assigned to each of the 22 enrolled subjects and the numbers were randomized. The subjects assigned numbers 1-18 were selected to be monitored, and the remaining four enrolled subjects served as alternates. To determine which subjects were assigned to which container group for the monitoring events, two subject identification sequence numbers (SISN) between 01 and 18 were randomly selected (using the Research Randomizer tool at http://randomizer.org) and assigned to each subject identification code. This provided one ME number for the conventional pour and one for the reduced-splash sets of containers. The first sequential group of six SISNs (01 through 06) was assigned to the first container size group, the second sequential group of six numbers (07 through 12) was assigned the second group, and the third sequential group of six numbers (13 through 18) was assigned to the third group. The order in which the container types were poured (conventional pour first or reduced-splash first) was also randomly determined for each subject using the Research Randomization tool.

Subject Demographics:

Below is a summary of the demographics of the 22 enrolled subjects (summarized from p. 84 of 1227).

Table 1: AEATF II Liquid Pour Study Subject Characteristics			
	Enrolled Subjects (22)	**Monitored Subjects (18)**	**Alternate Subjects (4)**
Male	17	15	2
Female	5	3	2
Preferred to speak in English	22	18	4
Preferred to speak in Spanish	0	0	0
Range of number of years of experience	1-35	1-35	4-30
Mean number of years of experience	11.8	11.6	12.5
Age range (years)	19-65	19-65	36-60
Mean age (years)	48.7	48.5	49.8
Self-reported health as 'Good'	22	18	4
Self-reported health as 'Fair'	0	0	0

All 22 enrolled subjects' preferred language was English. Subjects' ages ranged from 19 to 65 years old. The subjects' years of experience working in the janitorial field ranged from 1 to 35 years. All subjects self-reported their health to be "good."

Preparation for monitoring:

Upon arriving at the study location, the subjects were reminded about the details of the study and that they could withdraw from the study at any time. Before being taken into the dressing room, the subjects were introduced to the medical professional who examined their hands and face for broken skin or open sores. Two medical professionals were hired to assist with the study; one was a Registered Nurse and the other was an EMT paramedic. The Registered Nurse was present on weekdays and the EMT worked on the weekend. In addition to examining the hands and face of the subjects before and after monitoring, the medical professional was available in case any skin reaction, heat stress, or other unanticipated adverse effects occurred during the conduct of the study.

In accordance with the protocol, the three female subjects self-administered a urine pregnancy test (using an over-the-counter pregnancy test kit). After the subject completed the pregnancy test, she was asked if she still wished to participate in the

study. All female subjects responded that they wanted to continue. The Study Director confirmed the negative results of the pregnancy tests and this was noted in the raw data.

Each subject was then taken into the changing room (restroom) by a same gender member of the research team and asked to wash his or her hands and face with Ivory soap and water. Subjects were then weighed and asked to verbally provide their height. After the hand/face wash, the subjects were asked to remove their street clothes down to their underwear and to put on the inner dosimeter followed by the outer dosimeter shirt and pants. The one set of dosimeters was worn through the two monitoring events by each test subject. Once the subjects were dressed in dosimeters, a low-volume SKC personal air-sampling pump attached to an OVS air sampling tube was placed on each subject. The OVS tube was clipped to the shirt collar in the subject's breathing zone and the pump was attached to the belt around the waist of the subject. The subjects were given safety glasses to wear during the pouring activity.

Monitoring:

To begin monitoring, subjects put on their safety glasses and the air sampling pump was turned on. The pump start time was recorded and served as the start time of monitoring for the first ME. Subjects were asked to begin pouring the way they normally would while working. A researcher observed each subject as they worked and recorded information necessary to characterize each monitoring event. Although subjects were instructed to take breaks at their discretion, no subjects chose to take a break during a monitoring event. There were no equipment malfunctions or other disruptions to cause subjects to suspend pouring.

When the subject was done pouring his/her first set of containers, the air sampling pump was turned off and the end time recorded. The subject took a short break between the first and second monitoring events while the researchers removed the used source containers and full receiving receptacles. During this time, the subject was allowed to sit on a chair covered with clean plastic. Subjects were not permitted to smoke or eat, but were offered either water or a sports drink. If they expressed a desire to drink, they were not permitted to touch the bottle, and had to sip from a straw while a researcher held the straw up to their mouth. Only a few subjects requested a drink.

Once the new source containers containing the second test substance and new, empty receiving containers were brought to the test room, the subject was instructed about what he/she needed to pour into which containers and whether to use a measuring cup or not. Once he/she was ready to start, the air-sampling pump was re-started and the start time of the second monitoring event recorded. Once the subject had poured all of the allocated containers, the air-sampling pump was turned off and the end time recorded. At this point, the subject was escorted out of the test room and to the changing room.

The activities of each subject were recorded by a designated observer. These observations covered all activities that occurred during the monitoring event. Any incidental occurrences that may have affected individual exposure were documented in the observation notes.

Photos and video of each subject were taken during the monitoring event. Photos were also taken of the hand wash and face/neck wipe procedures. Care was taken so that subjects' facial features were not distinguishable. If facial features were shown, the photos and video were either deleted or edited so that the facial features were obscured.

Subject monitoring was conducted without noteworthy incident, and there were no observed or reported adverse effects during the study. In addition, no subjects called after the monitoring was complete to report that they were experiencing a problem. The observation log describes general observations about how each subject performed the pouring task, and also describes actions that may have resulted in incidental exposure to the subject (for example, rubbing nose, scratching arm, wiping hands on pants). The behavior described in the logs all appears to be normal behavior that would be expected in normal working conditions. None of the behavior described in the observation logs was concerning in terms of possible risks, and nothing suggested that an adverse event occurred during the monitoring.

From my review of the report, it appears that the procedures provided for 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.

Protocol Amendments:

Subsequent to IIRB approval of the revised protocol on April 8, 2010, the protocol was amended six times. The first amendment involved removing Appendix B (the informed consent form) from the protocol; it was approved by IIRB on January 31, 2012. Details about the scope of the other five protocol amendments appears as Attachment 3 to this review. None of the amendments raised ethics issues.

Deviations:

Protocol and Analytical Deviations

Five reports of protocol deviations and two reports of laboratory deviations were submitted to IIRB, Inc. after initiation of the research. The protocol deviations are summarized in Attachment 3. None of the deviations affected subject safety, jeopardized the informed consent process, or otherwise raise ethical issues.

SOP Deviations

I did not note any SOP deviations.

Unreported Deviations:

I did not note any unreported deviations.

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 23, 2011, EPA concluded that the protocol met the applicable ethical requirements of 40 CFR part 26, subparts K and L. EPA recommended several revisions to the protocol and/or consent form. EPA's comments, and how the AEATF addressed those comments, is provided in Attachment 4.

HSRB Protocol Review Comments

In the January 11, 2012 report of its October 2011 review of the AEATF liquid pour 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.

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 January 2012.

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 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.

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

§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
AEATF II Liquid Pour Study: MRID 48917401

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. 118-149 pp. 1181-1199
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	pp. 757-9, 1000-1001, 1173
	§1115(a)(3): Records of continuing review activities.		Y	p. 1199
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	pp. 575-1227
	§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 pp. 118-140
	§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 (pp. 141-147)
	§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. 575-1227
	§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. 729-30 Revised p. 1002-3; Renewal p. 1199 Amdmt 1, 2: p. 1178; Amdmt 3: p. 1200; Amdmt 4, 5: p. 1206
(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. 118-140
(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 Liquid Pour Study

Based on pp. 78-79 from AEATF Submission

7 July 2011	Submission of AEA05 protocol, ICF (English and Spanish), newspaper advertisement (English and Spanish), Subject Qualification Worksheet (English and Spanish), Scenario Design Document, Submission Letter, Site Questionnaire, and study set-up form to IIRB
13 July 2011	IIRB approval letter for protocol and supporting materials
18 July 2011	Submission to IIRB of minor change – updated telephone number in consent form and newspaper advertisement
20 July 2011	IIRB approval of minor change in consent form (English and Spanish, version January 20, 2012) and newspaper advertisement
28 July 2011	Submission of IIRB-approved protocol and supporting documents to EPA for October HSRB meeting
23 Sept 2011	EPA Science & Ethics Review of AEA05 design document and protocol
19 Oct 2011	HSRB meeting and review of protocol
11 Jan 2012	Issuance of HSRB Final Report
20 Jan 2012	Submission to IIRB of updated AEA05 protocol (version January 20, 2012), ICF (English and Spanish, version January 24, 2012), newspaper advertisements (print proof, on-line banner ad proof, and on-line splash page proof, English and Spanish, version January 20, 2012), Subject Qualification Worksheet (English and Spanish, version January 20, 2012), and Scenario Design Document (version January 20, 2012)
25 Jan 2012	IIRB approval letter for January 20 2012 submissions
27 Jan 2012	Minor change submission to IIRB (remove ICF from protocol appendix)
28 Jan 2012	Newspaper recruiting advertisements first appeared in The News-Herald and The Star Beacon (in print and on-line); ads ran for one week
30 Jan 2012	First phone call received in response to recruiting advertisement
31 Jan 2012	IIRB approval of minor protocol change
1 Feb 2012	Newspaper recruiting advertisement first appeared in La Prensa (in print and on-line) and ran through Feb 8
2 Feb 2012	Study protocol signed by Study Director (study initiation date)

Chronological Listing of Events: AEATF Liquid Pour Study

Based on pp. 78-79 from AEATF Submission

7 Feb 2012	Newspaper recruiting advertisement extended for another week in The News-Herald
8 Feb 2012	Consent meetings held at Holiday Inn Express La Malfa Conference Center
9 Feb 2012	Consent meetings held at Holiday Inn Express La Malfa Conference Center
10 Feb 2012	Consent meetings held at Holiday Inn Express La Malfa Conference Center
13 Feb 2012	Last two volunteers signed consent forms
16-22 Feb 12	Test subjects monitored at Ricerca Biosciences LLC
21 Feb 2012	Submission of Protocol Amendments 1 and 2 and Protocol Deviations 1, 2, 3, 4 to IIRB
27 Feb 2012	Stamped acknowledgment of deviations 1 through 4 by IIRB
28 Feb 2012	IIRB approval of amendments 1 and 2
15 May 2012	All study samples analyzed at Ricerca Biosciences with the exception of one Dilution
25 June 12	Submission of annual progress report to IIRB
3 July 2012	IIRB approved progress report and research approval was extended one year
18 July 2012	Protocol amendment 3 submitted to IIRB
24 July 2012	IIRB approval of amendment 3
31 July 2012	Submission to IIRB of Protocol Amendments 4 and 5, Protocol Deviation 5, and two analytical deviations
3 Aug 2012	Stamped acknowledgment of Protocol Deviation 5 and 2 laboratory deviations
3 Aug 2012	Completion of analytical phase
7 Aug 2012	IIRB approval of Protocol Amendments 4 and 5
13 Aug 2012	Submission of study closeout report to IIRB
17 Aug 2012	IIRB acceptance of closeout report

Summary of Protocol Amendments and Deviations for
AEATF-II Liquid Pour Study Protocol

Amendment 1: dated 2/16/12 [p. 563]; approved 2/28/12 [p. 1178]

1. Section 10D of the protocol (Sample Collection) was changed to specify that test subjects' shoes would be removed upon entry to the dressing room and *prior to* (instead of after) removal of the air-sampling pump, hand-wash, and face-neck wipes. The reason for the change was to minimize potential contamination of the sample collection room floor by the test subjects' shoes.

Amendment 2: dated 2/16/12 [p. 564]; approved 2/28/12 [p. 1178]

1. Section 10B (Subject Preparation) will be changed to remove the requirement to calibrate the bathroom scale used to weigh the test subjects. The reason for the change was that certified weights bracketing the range of test subject weights were not available.

Amendment 3: dated 2/16/12 [p. 565]; approved 7/24/12 [p. 1200]

1. Section 10D.4 (Sample Collection) was changed to specify that the face/neck wipe samples would not be placed into glass jars after collection, but instead they should be wrapped in foil and placed into labeled plastic re-sealable bags. The use of foil rather than glass was selected because it saves costs and space. AEATF II SOP 8C.2 allows for the use of either glass jars or foil and re-sealable bags.

Amendment 4: dated 7-25-12 [p. 566]; approved 8-7-12 [p. 1206]

1. Section 19 (Reporting) on page 62 was changed to allow worker residues to be adjusted for field fortification recoveries in the analytical phase report.

Amendment 5: dated 7-25-12 [p. 567]; approved 8-7-12 [p. 1206]

1. Section 13B (Analytical Method) on page 55 was changed to indicate that acetonitrile was used to prepare the field fortification solutions instead of distilled or deionized water.
2. The extracting solution formulation listed on page 57 was changed to 70% acetonitrile/30% water/0.016% formic acid for inner and outer dosimeters, not 70% methanol/30% water/0.016% formic acid.
3. Samples that required dilution were diluted with acetonitrile, not acetonitrile and ammonium formate.

The reason for the changes are that the analytical method presented in the protocol was based on earlier versions of the analytical method and was not optimized for the samples being generated in this study. Due to the timing of the method write-up, modifications incorporated during method validation were not available when the protocol was generated.

Summary of Protocol Amendments and Deviations for
AEATF-II Liquid Pour Study Protocol

Protocol Deviation Report 1: dated 2/16/12 [p. 568]; stamped "received" 2/21/12 [p. 568]

Date of occurrence: 2/16/12

1. The bathroom scale used to weigh test subjects A and G was not calibrated according to GLP standards. The reason for the deviation was that no 200 lb certified weights were available for the calibration.

Protocol Deviation Report 2: dated 2/16/12 [p. 569]; stamped "received" 2/21/12 [p. 569]

1. The shoes of test subjects A and G were not removed after the removal of the air sampling pump, hand-wash, and face-neck wipe; instead, shoes were removed first. The reason for the deviation was concern that chemical residues on the bottoms of their shoes could be tracked into the sample handling area.

Protocol Deviation Report 3: dated 2/17/12 [p. 570]; stamped "received" 2/21/12 [p. 570]

1. Handwash sample number 184 and 369 (ME 13, conventional and ME07 reduced-splash) consisted of 400 ml instead of 500 ml. The reason for the deviation was that the rinse of the test subject's hands with 100 ml of hand wash solution was inadvertently omitted.

Protocol Deviation Report 4: dated 2/16/12 [p. 571]; stamped "received" 2/21/12 [p. 571]

1. Test Subject G (conventional pour ME 16 and Reduced-Splash ME 15) removed his own shoes in the dressing room after the monitoring events instead of letting a researcher do it. The reason for the deviation was that the subject acted quicker than anticipated.

Protocol Deviation Report 5: dated 2/19/12 [p. 572]; stamped 8/3/12 [p. 572]

1. Test Subject F (conventional pour ME 1 and Reduced-Splash ME 10) unbuttoned the first of two buttons of his shirt in the dressing room after the monitoring events instead of letting a researcher do it. The reason for the deviation was that the subject acted quicker than anticipated.

Two analytical method deviations were also reported to IIRB – see pp. 573-4.

Attachment 4

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

EPA Comment on Liquid Pour Protocol	Has comment been addressed?
Identify the newspapers in which the recruiting advertisements will be placed. The AEATF is advised to place the advertisements in several newspapers targeting different demographic groups, to further the goal of minimizing bias and achieving as much diversity as possible among respondents and subjects.	**Yes.** Advertisements were placed in two major daily newspapers, The News-Herald of Northern Ohio and the Star Beacon, and in a regional weekly bilingual (English/Spanish) publication, La Prensa.
Remove all generic references to "second alternate language" or "alternate language as appropriate to the area/population" and replace with "Spanish."	**Yes.**
Add a statement to the consent form that explains to subjects that if, within 24 hours of their participation in the study, they experience a skin or eye reaction or other symptom that they believe is related to their participation in the study, they should contact the Study Director. A telephone number should be provided.	**Yes.** See p. 980.
The AEATF should develop procedures for handling such a call and document those procedures in a new or existing SOP.	**Yes.** See revisions to SOP 11C.3 (pp. 995-7).
The AEATF should incorporate the forthcoming guidance from the HSRB about how to provide personal exposure results to subjects.	**N/A.** In light of the discussion and recommendations in the HSRB's report, the AEATF II did not return exposure results. At the October 2011 HSRB meeting in which this protocol was reviewed, the Board "determined that at this time there is neither a positive nor a negative duty to provide results to participants of this study as there is not a clear rationale or benefit to participants…Thus, the Board currently neither recommends nor discourages the return of individual study results. The Board remarked that it would not be objectionable should the study sponsors chose to return individual exposure results to study participants, nor would it be objectionable should they chose not to do so." (pp. 22-23 of Final HSRB Report dated 1/12/12)
HSRB Comment on Liquid Pour Protocol	**Has comment been addressed?**
The HSRB recommended several edits to improve the clarity of the Informed Consent Form.	**Yes.** All comments were addressed in the revised consent form that was approved by IIRB prior to initiation of the study. See pp. 974-983 to see the revisions in track-changes.