UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

September 29, 2016

MEMORANDUM

SUBJECT: Ethics Review of Completed AEATF II Study AEA07 on Dermal and Inhalation Exposure during Manual Pouring of Two Solid Formulations Containing an Antimicrobial

FROM: Maureen Lydon, Human Research Ethics Review Officer
Office of Pesticide Programs (OPP)

TO: Steven Knizner, Director
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Steven H. Weiss, Chief
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REF: Rosenheck, Leah. (2016) A Study for Measurement of Potential Dermal and Inhalation Exposure during Manual Pouring of Two Solid Formulations Containing an Antimicrobial. Study Number AEA07, 1100 p. April 21, 2016 (MRID 49905201)

I have reviewed the available information concerning the ethical conduct of the research reported by the Antimicrobial Exposure Assessment Task Force II (AEATF II) in "A Study for Measurement of Potential Dermal and Inhalation Exposure during Manual Pouring of Two Solid Formulations Containing an Antimicrobial," also referred to as study AEA07. The study was conducted to determine the potential dermal and inhalation exposure to occupational workers and consumers associated with the pouring and/or scooping of solid formulation antimicrobial products.

If study AEA07 is determined to be scientifically acceptable, I find no barrier in regulation to the EPA's reliance on it in actions under the Federal Insecticide, Fungicide or Rodenticide Act (FIFRA) or §408 of the Federal Food, Drug, and Cosmetic Act (FFDCA). I have recommended follow-up actions for the Antimicrobial Exposure Assessment Task Force II (hereafter referred to as AEATF) and AEATF has agreed to implement them as documented in this ethics review.

In addition, under 40 CFR 26.1604, the EPA is required to seek review by the Human Studies

Review Board (HSRB) for intentional exposure human studies covered by the EPA's human studies rule that are initiated after April 7, 2006. The EPA will share study AEA07, the associated support documents, and the EPA's science and ethics reviews of the study with the HSRB for their review. This memorandum and its attachments constitute the EPA's ethics review of AEA07.

Overview, Required Reviews of Protocol and Ethics-Related Chronology

Study AEA07 tested two solid formulations of antimicrobial products -- powders and granules. The objective was to generate four baseline dermal and inhalation unit exposures: one for pouring granules in occupational scenarios, one for pouring powders in occupational scenarios, one for pouring granules in residential scenarios, and one for pouring powders in residential scenarios. The data from this study will be used to assess consumer and occupational exposure and risks from the handling and pouring of solid formulation antimicrobials.

As summarized in the overview on page 15 of the study:

> "The study involved the open pouring and scooping from various sizes of containers into a swimming pool (consumers) or into a mix tank (occupational workers). Variability in exposure was captured by using eighteen different test subjects per demographic group (consumers and workers), a variety of source containers, pouring at different heights, direct pouring out of the container and the use of scoops, and a range in the amount of active ingredient handled. Monitoring of consumers was conducted outdoors where subjects poured into a swimming pool. Monitoring of occupational workers took place indoors where subjects poured into 180 gallon capacity rectangular mix tanks. Monitoring of the consumer pouring took place at Ricerca Biosciences LLC in Concord, Ohio between August 13 and 17, 2014. Monitoring of the occupational pouring took place at Ricerca Biosciences LLC in Concord, Ohio between March 26 and April 1, 2015. The surrogate test substance used in the study was cyanuric acid (1, 3,5-triazine-2,4,6-triol, CAS number 108-80-5) supplied as a granule and as a powder."

The AEA07 protocol, approved by the overseeing Institutional Review Board (IRB), and the EPA's science and ethics review, dated September 10, 2013, were discussed by the Human Studies Review Board (HSRB) at its April 8-9, 2014 meeting. With regard to ethics, as documented in the HSRB's June 25, 2014 final meeting report, the HSRB concluded that, "the protocol submitted for review, if modified in accordance with EPA (Leighton, Sherman & Cohen, 2013) and the following HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."

Following the HSRB April 2014 review and the issuance of the HSRB's final report on June 25, 2014, the protocol, consent form, recruitment and other support materials for AEA07 were revised to address the EPA and HSRB comments. Attachment 1 summarizes how AEATF addressed the EPA and HSRB comments. The revised protocol and support materials were submitted on July 14, 2014 to the overseeing IRB, which the study identifies as Schulman Associates Institutional Review Board (SAIRB). Schulman IRB approved the revised protocol and support materials in July 2014. Beginning on page 708, study AEA07 includes the protocol that was approved by the IRB on July 14, 2014 and signed by the Study Director on July 21, 2014. Between August 6,

2014 and April 12, 2016, Schulman IRB approved 16 protocol amendments and corresponding revisions to support materials as documented in AEATF's chronology of key study events in attachment 2. (The amendments are discussed in a separate section of this ethics review.)

Completeness of Submission

The EPA used the checklist in attachment 3 to verify that the requirements of 40 CFR §26.1303 were fulfilled. This completeness and ethics review considered the study material, AEATF's and the Study Director's responses to the EPA questions (which were integrated into the ethics review), and Schulman IRB correspondence including additional IRB meeting minutes not originally included and provided to the HSRB in a separate background file.

Recruiting

Recruitment of subjects was consistent overall with the protocol and amendments which were approved by SAIRB. (Amendments are reviewed in detail later in this ethics review.) As discussed on pages 25 – 26 of study AEA07:

> "Following review and approval of the protocol by the United States Environmental Protection Agency (EPA), the Human Studies Review Board (HSRB), and Schulman Associates Investigational Review Board Inc. (SAIRB), recruitment of test subjects for the consumer phase was started. Recruitment from the local community for people with experience treating their swimming pools with granular or powder chemicals was initiated on July 27, 2014. Advertisements were placed in two daily newspapers, The News-Herald of Northern Ohio and the Star Beacon, and in a regional weekly bilingual (English/Spanish) publication, La Prensa. Because of the initial low response rate, the newspaper ads were run for a second week and the protocol was amended on August 5, 2014 to include the use of recruitment radio ads. On August 6, 2014 another amendment was made to widen the inclusion criteria to include people who did not own a swimming pool and/or who had no prior experience with pool chemicals. The advertisements included a brief description of the study and provided a phone number to call for more information. The radio ads ran for just one day, August 8; the newspaper ads ran from July 27 through August 10, 2014."
>
> Recruitment for the occupational monitoring phase started on March 1, 2015 using both newspaper and radio ads. Advertisements were placed in two daily newspapers, The News-Herald of Northern Ohio and the Star Beacon, and in a regional weekly bilingual (English/Spanish) publication, La Prensa. Radio ads initially ran on one local station and then were expanded to run on two additional stations in the Cleveland area starting on March 10. Because of the initial low response rate, the protocol was amended on March 4, 2015, and approved by SAIRB on March 6, to include people who had occupational experience handling solid chemicals, but who were not necessarily currently employed in that position. Approved on March 9, 2015, the inclusion criteria were also expanded to allow employees of task force member companies participate in the study. Another amendment dated March 9, 2015 and approved by the SAIRB on March 12, 2015, increased the test subject reimbursement from $100 to $175. All of these amendments were done to

improve the chances of recruiting interested and qualified individuals. On March 11 the protocol was amended to add another newspaper with a greater distribution area (The Plain Dealer); however those ads were never run as 20 people had signed up for consent meetings before the next distribution date. Newspaper and radio recruiting advertisements ran from March 1 through March 15 and included a brief description of the study and provided a phone number to call for more information." – End of excerpt-

All individuals who responded to the recruitment advertisements were English speakers. Using the approved telephone screening scripts and taking into account the protocol amendments, interested callers were interviewed via telephone to determine if they met the inclusion criteria and to provide an overview of the study to potential subjects. The interviewer asked respondents who were both eligible for the study and interested in learning more to attend a consent meeting.

Informed Consent Process

For the consumer monitoring phase, as stated on page 27 of study AEA07:

"All but three of the Informed Consent Meetings were held in a conference room at the Marriott Residence Inn in Mentor, Ohio. These consent meetings were held by the Study Director and the bilingual research associate at various times on August 7, 8, and 9, 2014. One volunteer was met at a hotel in Painesville for his consent meeting on August 11, 2014, and two subjects who lived an hour away were consented at Ricerca on the day of their scheduled monitoring. Two of the 20 people who signed up for consent meetings did not show and were replaced by the next two people on the waiting list."

For the occupational monitoring phase, as stated on page 29:

"Informed Consent Meetings were held in a conference room at the Quail Hollow Resort in Painesville, Ohio. The consent meetings were held by the Study Director and the bilingual research associate at various times on March 19, 20, and 21, 2015. The number of people attending any one meeting ranged from one to three. One of the 20 people pre-qualified over the phone and scheduled a consent meeting did not show. One additional person was contacted from the waiting list on March 21, and a consent meeting was held with him on March 22 at a coffee shop in Mayfield, Ohio."

As explained on pages 27 and 29 in relationship to both phases of the study:

"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. Although potential subjects were allowed to take the forms and information home with them to discuss the study with family and friends, none of them did."

> "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 these 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 done 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 ID was checked to verify identity and age. Once these forms were fully filled out, the subject was considered officially enrolled in the study. Each volunteer was given a copy of the IIRB [sic] approved Informed Consent Form to take home along with $20 in cash." – End of excerpt -

The Study Director confirmed to the EPA that, "The Subject Qualification Worksheet was provided to each subject along with the Consent Form. The Subject Qualification Worksheet was filled out after the subject consented to be in the study. Each subject was provided a copy of the consent form to take home. Copies of the MSDS and labels were available at each consent meeting. During the consent meeting, subjects were asked whether they wanted to see the label and/or MSDS; no one requested to see these documents." The Study Director also indicated that, "The label safety statements were explained during the consenting process. To ensure that all required material was discussed and reviewed with the subjects again on the day of monitoring, the Study Director relied on a written checklist which she consulted just before each subject was monitored. The checklist included a reminder about the label safety requirements." Also, heat stress signs and symptoms were explained to subjects during the consenting process and again, right before monitoring.

The aforementioned is consistent with the "safety precautions" section of the protocol (on page 733 of the study) as it relates to a copy of the label and Safety Data Sheet being "available during the consenting process and provided upon request to the test subjects." However, when discussing consent meetings in a different section of the protocol (on page 752), the protocol states that "Potential volunteers will be provided with copies of the IRB approved Informed Consent Form, the Subject Qualification Worksheet, a copy of the Material Safety Data Sheet (MSDS), and copies of the product labels." The approved protocol is inconsistent with regard to providing the Safety Data Sheets and product labels to potential subjects, based on a comparison of pages 733 and 752. When reviewing protocols in the future, the study sponsor and the EPA should ensure that all sections of the protocol are consistent when discussing the same topic. In summary, the subjects were offered but declined the opportunity to see the Safety Data Sheets and product labels; however, the "label safety statements were explained during the consenting process" and "reviewed with the subjects again on the day of monitoring."

Consistent with the amended protocol, enrolled subjects were informed of the compensation they would receive for reporting to the study location on the scheduled day, whether or not they actually participated in the study, and that 20 individuals were being enrolled for the study, two of whom would serve as alternates in case a volunteer did not appear for their scheduled appointment. Subjects knew that alternates would be randomly selected and compensated the full amount even if they were never monitored as part of the study. After looking at the schedule of

the monitoring days and before leaving the consent meeting, enrolled subjects told the study staff which dates and times would be most convenient for them with regard to participating in the monitoring. The study staff provided enrolled subjects the address and building number for the test site, driving directions as necessary, and a heads-up that study staff would call them the day before their monitoring day to remind them of their appointment.

Regarding the occupational phase consent form, there is an error in the introduction to the form that refers to the study doctor, instead of the study director, in the following sentence: "Schulman Associates Institutional Review Board, Inc. (Schulman) has approved the information in this consent document and has given approval for the study doctor to do the study." The rest of the form refers to the Study Director where appropriate; this is a minor error but AEATF needs to be careful in the future to avoid giving subjects the impression that a physician is associated with implementing the study.

Subject Demographics

Consumer Monitoring

Twelve males and 8 females, for a total of 20 subjects, agreed to participate in the consumer monitoring phase of the study. Eighteen subjects, 11 males and 7 females, were monitored. Test subject 18 withdrew before the scheduled monitoring day due to a cut finger which disqualified her from participating. Subject 2 withdrew from the study for personal reasons prior to scheduled monitoring. As a result, both alternate subjects 19 and 20 were subsequently monitored. The language preference for all test subjects was English and all attested that they were in good health.

Participants in the study met the inclusion criteria of the amended approved protocol. Subjects were 19 to 75 years old and fifteen of the eighteen subjects had experience using powder and/or granular products to maintain their pools, while three subjects had no experience. The experience using powder and/or granular pool products ranged from 0 to 34 years. Eight of the subjects with experience had used both granular and powder products, five had experience with just granules, and two indicated experience with just powder products. Table 3 on pages 102-105 of the study summarizes test subject demographics and years of experience per type of product.

Occupational Monitoring

Nineteen males and 1 female, for a total of 20 subjects, agreed to participate in the occupational monitoring phase of the study. Eighteen subjects, 17 males and 1 female, were monitored. English was the language preference for all test subjects, who reported their health as good.

Participants in the study met the inclusion criteria of the amended approved protocol. Subjects were 22 to 62 years old and all had experience handling and pouring dry chemicals in an occupational setting. Of the eighteen subjects, ten were not working in a position where they handled dry chemicals at the time of the study. Experience working with powder and/or granular products ranged from 6 months to 30 years. Sixteen of the eighteen test subjects had experience with both granular and powder products. Table 4 on pages 106-109 of the study

summarizes test subject demographics, years of experience per type of product, whether the subject was in a job handling dry products at the time of the monitoring, and the type of industry in which each subject was employed at the time of the study.

Randomization Procedure

As discussed on page 30 of the study: "After signing the consent form, each subject was randomly assigned a unique subject identification code that determined who would be in the study and who would be alternates by asking him/her to pull a folded piece of paper containing a number out of a bowl. Subjects in the consumer monitoring phase were given subject identification numbers AEA07-01 through AEA07-20. Subjects in the occupational monitoring phase were given subject identification numbers AEA07-W21 through AEA07-W40. To determine which subject was assigned to which monitoring event, each subject was asked to pull a number out of two other bowls, one that would provide the granular ME number and one for the powder ME number. The subject ID code along with the corresponding ME numbers were recorded in the field trial notebook." This approach of assigning subjects to monitoring events is consistent with protocol section G on random selection and assignment of subjects to MEs, as described on pages 748 – 749 of the study.

Furthermore, as discussed on pages 35 and 36 of the study, in the consumer monitoring phase, the number and type of containers to use and whether any product was to be scooped were randomly determined and assigned to each monitoring event (ME) prior to the start of monitoring. In order to ensure that a range of product weight was handled, the MEs were divided into three groups; within groups one and two, two MEs were randomly selected to pre-dissolve product in a bucket before adding it to the swimming pool. With regard to occupational monitoring, the total amount of cyanuric acid to be transferred, which containers to use, and whether product was to be measured and weighed first or poured directly from the container were randomly determined and assigned to each ME prior to the start of monitoring. In order to ensure that a range of product weight was handled, the MEs were divided into three groups and within each group, three MEs were randomly selected to pour from a step while three stood on the ground while pouring.

Implementation of Monitoring Events and Procedures Compared to Amended Protocol

The consumer monitoring took place in August of 2014 while the monitoring of the occupational phase took place in March of 2015. Both field phases and the analytical phase of the study took place at Ricerca Biosciences, LLC in Concord, Ohio.

The implementation of the monitoring events under Study AEA07 is discussed in detail in different sections of the report including, but not limited to, the sections on: study design (pages 16-17), study conduct (pages 17-19), description of test site (pages 31-34), pouring parameters (pages 35-37), environmental monitoring (page 38), exposure monitoring procedures (page 39), role of researchers (pages 39-40), general procedures of the monitoring events (pages 42-43), consumer monitoring and occupational monitoring (pages 64-66), conduct of monitoring events (pages 66-67), environmental conditions (pages 68-69), and observations of subjects (pages 77-79). I compared the information in these sections of the final study to the protocol, as amended.

I determined that the monitoring events were conducted in substantial compliance with the protocol, as amended 16 times, with the exception of the reported and unreported deviations, described later in this ethics review.

With regard to breaks between a subject's monitoring events, when discussing occupational monitoring, the protocol (on page 743 of the study) states that "a minimum of 15 minutes will elapse between the two MEs conducted by one test subject." Page 33 of the study states that, "To allow for dust to settle after the first ME was done and the subject was in the dressing room, a period of at least 10 minutes was allowed to elapse before the subject could re-enter for the second ME **(actual time between end of granular ME and start of powder ME ranged from 16 to 21 minutes)**." The parenthetical statement from page 33 of the study indicates adherence to the protocol with regard to the break time between each subject's monitoring events during the occupational phase.

With regard to consumer pouring, the protocol states (on page 743) that: "Because the outdoor environment will help residues to dissipate quickly, **a minimum of 10 minutes** will elapse between the two MEs conducted by one test subject." Tables 9 and 10 in the study provide the start and stop times for each monitoring event; for the consumer monitoring phase, the time elapsed between the end of the granular ME and the start of the powder ME was 12 to 21 minutes, which complies with the protocol.

Safety Precautions and Personal Protective Equipment

Below, please section C of the protocol which focuses on safety precautions (and is excerpted from page 733 of the study).

> **Section C – Safety Precautions**
> "Copies of product labels and the Materials Safety Data Sheet (MSDS) for cyanuric acid are included in Appendices A and B respectively. They will be included in the study file and provided to the study research team. A copy of the label and MSDS (in English only) will be available during the consenting process and provided upon request to the test subjects. Label safety requirements will be explained to the subjects involved in the study before they are monitored.
>
> Directions on how many and which containers should be poured or scooped into the receiving receptacle will be explained to the subjects. The order in which the subject pours his/her containers (if they have multiple containers) will be up to the individual. Whether the subject is to pour from the container or use a scoop or pre-dissolve the product in a bucket of water and mix with a stick will also be explained before the subject starts working. Beyond that, there will be no instructions. The subjects will be allowed to handle the containers and pour product as they do so normally.
>
> Although not required for cyanuric acid, safety glasses and dust masks will be provided to all study participants to wear as a study safety precaution. This is being required as a safety precaution since some subjects may be handling up to 100 pounds of product. If a subject does not wear his/her required protective equipment or does not follow the directions within

reason, or does so in a manner that presents safety issues in the judgement of the study research personnel, the Study Director will be contacted and may terminate the subject's participation as per SOP AEATF II-11H. If the monitoring event is terminated, the Study Director will determine whether or not the samples will be collected and analyzed. Heat stress signs and symptoms will be explained to the subjects. A copy of the poster entitled "Controlling Heat Stress Made Simple" in English and Spanish will be posted in the dressing area.

A nurse will be hired for this study and will be present during the monitoring events. This individual will be responsible for examining hands and faces of the subjects before the study for open cuts or abrasions or certain skin conditions that would disqualify the individual from participating. The nurse will also be responsible for examining the subjects' hands and face for possible signs of dermal irritation following completion of the monitoring events. Section 11D includes additional details regarding stop criteria and medical management. Following completion of monitoring, each subject will be asked to wash their hands and face thoroughly with soap and water." – End of excerpt-

The Study Director confirmed that the safety precautions, described in the excerpt above, were implemented during the study. As described in Amendment 3, a nurse was not available, so the on-site medical professional was changed from a nurse to a certified first responder. The first responder implemented all of the activities that were assigned to the nurse as described above.

All subjects were given safety glasses and a dust mask to wear during the pouring activity. Subjects in the occupational monitoring were also given new chemical-resistant nitrile gloves to wear. As noted on page 20 of the study, "Dermal exposure was measured using inner whole body dosimeters (cotton long underwear), outer dosimeters (long sleeved shirt and long pants), hand washes, and face/neck wipes. Inhalation exposure was measured using IOM personal inhalable particulate samplers attached to personal air-sampling pumps."

The study also adhered to and/or implemented the other risk mitigation measures specifically referenced in the protocol (in the "risks to subjects" section). I am referring to the provisions of the protocol that discussed: a) the estimated range of duration of actual handling of containers during the day of participation; b) allowing a subject to take breaks based on the subject's need and as determined by each subject; and c) close observation of subjects by assigned observers. The Study Director confirmed that subjects were instructed to take breaks at their discretion. However, no subject chose to take a break. The Study Director noted that, "Additionally no subject requested to have a drink during his/her monitoring period. Drinks (bottled Gatorade and bottled water) were also available in an ice-chest outside the changing room. Several subjects did accept a drink after completing both monitoring events once all samples were collected and subjects had washed their hands and faces."

On page 249, the observations section for consumer monitoring for the powder formulation (monitoring event 14), includes the Study Director's following notes: "Subject 3 commented that before monitoring that he doesn't use powders and that the technique should be different due to the smaller particles and the tendency to drift. We did recommend that he not toss it out across the pool." This recommendation deviates from the language in the safety precautions section of the

protocol which reads, “The subjects will be allowed to handle the containers and pour product as they do so normally.” This deviation did not negatively impact the health and safety of subject 3.

Pregnancy Testing for Female Subjects

Consistent with the approved protocol, an over-the-counter pregnancy test was administered to the eight female subjects (seven in the consumer phase and one in the occupational phase). After each female subject took the pregnancy test in private, she was asked if she still wished to participate in the study. All female subjects responded that they wanted to continue. Consistent with the protocol, the Study Director confirmed the negative results of the pregnancy tests.

Confidentiality

The measures outlined in the protocol regarding confidentiality were implemented. For example, as discussed on page 52 of the study, each test subject had two monitoring event (ME) numbers assigned to him/her which were used in the study as opposed to the subject’s name.

The following section on confidentiality was included in the approved consent form and implemented: “We will give you an identification number for this study, and we will record and report all data under that number. We will keep only one record linking your name to this identification number, and we will store it away from other data, in a locked cabinet. We will not identify you by name or in any other way in study report. Any pictures of you in a report of this study will not show your face. We will restrict access to records of this study to only a few people. The companies who are paying for this research; the government agencies who will review the reports; and the independent ethical review board that looks out for your safety may all review the study records. Because of this we can’t guarantee complete confidentiality.”

Freedom to Withdraw

Subjects were informed of their freedom to withdraw from the study at any time, for any reason, as indicated in the informed consent form. Two subjects withdrew from the consumer monitoring phase of the study before their scheduled monitoring dates. Test subject 18 withdrew due to a cut finger which disqualified her from participating and subject 2 withdrew for personal reasons.

Compensation

The test subjects who participated in the consumer monitoring phase in August 2014 were compensated $100 each. As confirmed by AEATF, these were subjects AEA07-01 through AEA07-20 with the exception of subjects AEA07-2 and AEA07-18, both of whom withdrew from the study before coming out to the test site.

All 20 test subjects who participated in the occupational monitoring phase, conducted the following year during the spring of 2015, were compensated $175 each. According to the Study Director, these were subjects AEA07-W21 through AEA07-W40. Amendment 10 to the protocol increased the compensation for the occupational phase based on new information learned by the Study Director, as discussed in the amendment 10 section of this ethics review.

For both phases of the study, compensation was consistent with the amended protocol which indicated that subjects would be compensated the full amount for reporting to the study location on the scheduled day, whether or not they were actually monitored as part of the study.

Regarding the consent process, all subjects who attended the consent meetings were compensated $20 consistent with the approved protocol.

Protocol Amendments for AEA07

AEATF submitted 16 amendments to Schulman IRB, which approved all of them. Attachment 4 to this ethics memo lists the 16 amendments, 15 of which were implemented. Ten of the 16 amendments are discussed below because they are of ethical interest. The Study Director consulted with EPA's Office of Pesticide Programs (OPP) prior to implementing Amendments 4, 10 and 11. [The Study Director confirmed that, "The protocol amendments listed on pages 799 through 810 are exactly what were submitted to Schulman IRB with the following exceptions: Amendments 2, 10 and 11 were not signed by Has Shah (AEATF II Sponsor Representative) prior to them being submitted to Schulman IRB."]

The EPA found one component of Amendment 3 to be problematic from an ethics stand point. AEATF has already agreed to a follow-up action to address it for the future.

Amendment 3

On pages 801-802 of study AEA07, AEATF identified 6 components of Amendment 3 as excerpted verbatim below:

> "**Protocol Amendment 3**
>
> **Change/Addition:** Effective Date: 08/01/2014
>
> [Page 27] A first responder, not a nurse, will be present during the study to monitor test subject safety.
>
> Reason for Change/Addition:
> The nurse was not available; a first responder qualifies as a medical professional.
>
> **Change/Addition:** Effective Date: 08/08/2014
>
> The outer dosimeters [pants and long-sleeved shirt] need to be prewashed. This entails washing with a small amount of detergent followed by two rinses and then a second wash/double rinse cycle with no detergent.
>
> Reason for Change/Addition:
> An analytical interference peak that obscured the cyanuric acid peak was discovered during the method validation phase with the shirts and pants. Washing the clothing removed the

interference.

Change/Addition: Effective Date: 08/13/2014

(Page 52) A plastic bag was to be placed over the air-sampling pump to protect it from contact with residues. The design for the consumer monitoring portion was changed so that the pump is placed on the back pants pocket thus eliminating the need for the plastic bag in the consumer phase of the study.

Reason for Change/Addition:
Due to being outdoors, the potential for residue contamination of the pump is lower and placing it on the backside of the subjects reduces the potential for contact with direct or airborne residues.

Change/Addition: Effective Date: 08/13/2014
(Page 55 - Sample Collection) The sequence of sample collection requires the air sampling pump to be removed first, then hand wash performed, followed by the face/neck wipe. During sampling it was determined that the hand wash should be performed first since this is where the majority of the residues were located, the face/neck wipe performed next, and then the pump removed.

Reason for Change/Addition:
This was done to decrease the time period between the pouring activity and the hand wash, thus reducing the potential for loss of residue from the subjects' hands.

Change/Addition: Effective Date: 08/13/2014
Section 10.D. Product Transfer [page 33]: Only one scoop, not two, will be provided to the consumer test subjects to use to scoop product. A 16 oz red scoop was used to transfer granular product and a 32 oz yellow scoop was used for the powder product.

Reason for Change/Addition:
The second scoop purchased for the study was too large to fit into the pails. The two different size scoops were used, one for granules and one for powder, because the lower density of the powder necessitated a larger scoop in order to hold about one pound.

Change/Addition: Effective Date: 08/14/2014
(Page 18, 4th paragraph) Changes to the protocol currently require review and approval by the IRB prior to implementation. This is changed to: 'All other amendments must be reviewed and approved by the IRB.'"

Reason for Change/Addition:
Protocol amendments are normally signed by the Study Director before they are sent to the IRB and thus already implemented."

– End of excerpt on Amendment 3 -

Schulman IRB approved Amendment 3 on September 23, 2014. From an ethics standpoint, EPA has a problem with the last change proposed by Amendment 3 which substantively revised the language in section 7 (oversight of ethical conduct) of the EPA-approved and HSRB-reviewed protocol as highlighted in red below:

> "All protocol changes (amendments and deviations) shall be reported to the IRB in writing by letter, fax or email. Proposed changes (amendments) deemed necessary to eliminate apparent immediate hazards to the human subjects may be implemented without prior IRB approval. All other amendments must be reviewed and approved by the IRB ~~prior to implementation, or as specifically instructed by IRB policy in this regard~~."

As described in 40 CFR §26.1108, each Institutional Review Board (IRB) must follow written procedures for ensuring "prompt reporting to the IRB of proposed changes in research activity" and "ensuring that changes in approved research, during the period for which IRB approval has already been given, **may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects**." The approved research is based on the content of the approved protocol which, in this case, is the AEA07 research protocol.

The overseeing IRB for study AEA07 is Schulman Associates IRB, whose website includes the following policy on amendments: "Under normal conditions, you must submit to the Board all amendments, including administrative letters, or changes to the protocol for review and approval prior to the implementation. When submitting a revised protocol, provide a summary of changes between the revision and the previously reviewed version. Occasionally, safety concerns may require you to implement an amendment prior to Board approval. When changes to the protocol are implemented in order to eliminate an apparent immediate hazard to a research subject without prior Board approval, you must report changes to Schulman within 10 business days. Administrative changes to a protocol generally require Board approval. However, when you submit changes that are limited to typographical corrections or changes in contact information, Schulman will acknowledge receipt. Board approval is not required for these." With regard to submittal of amendments, study sponsors need to follow the overseeing IRB's policy, which in turn must be consistent with 40 CFR §26.1108.

Section 22, part A, of the protocol for study AEA07 that was approved by the EPA and reviewed by the HSRB states that, "Proposed changes (amendments) deemed necessary to eliminate apparent immediate hazards to the human subjects may be implemented without prior IRB approval. All other amendments must be reviewed and approved by the IRB prior to implementation or according to IRB standard procedures." The EPA approved the protocol based on this language and reasonably assumed that it would be retained given the importance of an independent ethics review prior to implementing protocol changes.

When study sponsors submit completed human research studies to the EPA, information pertaining to the ethical conduct of the completed research must be provided to the agency as described in 40 CFR §26.1303, which further references 40 CFR §26.1125 (a) through (f) and correspondence between the IRB and the investigators or sponsors. The ethical conduct of the completed research must be consistent with 40 CFR Part 26 and the EPA can only rely on

completed research which is scientifically sound and conducted in an ethical manner with one exception as noted in 40 CFR §26.1706. Compliance with the federal rule with regard to submittal of protocol amendments is considered when reviewing the ethical conduct of the study.

In summary, in order for AEATF and its study directors to implement current and future human research studies in conformance with 40 CFR Part 26, all amendments to the approved research protocol must be submitted to the IRB for review and approval prior to implementation, except for changes necessary to eliminate immediate hazards to human subjects, as described in 40 CFR §26.1108(a)(4), and as documented in the overseeing IRB's amendment policy. The Office of Pesticide Programs believes that the language in the protocol on the amendment process as reviewed and approved by the EPA should have been retained.

After reading the completed study, the EPA explained the above to AEATF in writing. With one exception, AEATF has already agreed to seek IRB approval of all protocol amendments prior to their implementation in current and future human research studies to be submitted to the EPA's Office of Pesticide Programs (OPP) consistent with the published policy of the overseeing IRB, which must comply with 40 CFR §26.1108; the only exception would be situations involving imminent hazard to human subjects.

Because Amendment 3 was approved by Schulman IRB on September 23, 2014, but its 6 components were implemented in August, 2014, the actions taken by the study sponsor under Amendment 3 were, in effect, deviations from the protocol at the time they were implemented in August 2014. They became formal amendments to the protocol only after the IRB approved them on September 23, 2014.

Timing of Implementation of Amendments

When the EPA posed questions to AEATF regarding the timing of implementation of their protocol amendments, the Task Force provided a chronology of their AEA07 protocol amendments (in Attachment 5 which lists the IRB approval date of each amendment and the researcher's implementation date) and accompanying documentation (in attachment 6) certifying that 6 of their amendments were implemented after IRB approval (either on the same day as the IRB approval or a subsequent day). AEATF certified that the following 6 amendments were implemented after IRB approval: Amendments 1, 2, 6, 9, 10 and 11. Each of these amendments, plus Amendment 5, is described below. Amendment 12 was never implemented. Eight amendments were implemented before the IRB had approved them but after the IRB had approved the component of Amendment 3 which stated "All other amendments must be reviewed and approved by the IRB"; these eight amendments (Amendments 3, 4, 7, 8, 13-16) were all reviewed and approved by Schulman IRB on the dates included in attachment 5.

Amendments 1 and 12

Amendment 1 allowed the use of radio advertisements to assist with subject recruitment. AEATF documented that it was implemented two days after the IRB approval date. The amendment resulted in broader outreach to potential subjects for recruitment purposes and was initiated due to

the low rate of response to the original recruitment plan; the amendment did not negatively impact the rights of prospective or participating subjects. Amendment 12 identified an additional newspaper in which AEATF intended to place a recruitment advertisement. AEATF did not need to implement amendment 12 because a sufficient number of subjects volunteered.

Amendment 2

Amendment 2 modified the inclusion criteria for consumer monitoring to allow participation by people who did not own a swimming pool and did not have experience with adding granules or powder products to a pool. Page 800 of the completed study provides the following rationale:

> "Because of the difficulty in recruiting homeowners with swimming pools in Northeastern Ohio, the target of 20 qualified test subjects could not be reached. By removing the constraint of pool ownership, a larger number of potential subjects can be obtained. By not having experience pouring pool chemical products, these subjects would be representative of first-time pool owners."

AEATF documented that the amendment was implemented two days after the IRB approval date. As stated on page 21 of the study, "Cyanuric acid (CYA) is a swimming pool stabilizer widely marketed to consumers and pool care companies." Including subjects who did not have experience adding granules or powder products to a pool did not negatively impact the health and safety of participating subjects.

Amendment 4

Amendment 4 removed the use of 25 pound buckets of powder from the consumer monitoring program and specified other smaller containers to be used by the three affected subjects/monitoring events (MEs). This amendment did not negatively impact the health and safety or rights of participating subjects; in fact, switching to smaller containers reduced the amount of powder and dust to which subjects would be exposed after implementing this amendment. AEATF documented that the study director signed the amendment on September 19, 2014, the SAIRB approved it on September 23, 2014, and it was implemented on August 15, 2014.

Table 9 in the protocol (which is included on page 748 of the completed study) lists the amount of powder product and container sizes to be handled by each monitoring event via pouring and/or scooping during the consumer portion of the study. Page 804 of the completed study provides the following specifics on amendment 4:

> "Change/Addition: Effective Date: 08/15/2014
> (Table 9, page 41) Consumer powder MEs 13, 17, and 18 will not pour from the 25 pound pails and ME 17 will not scoop from a 25 pound pail. Instead the amount that will be poured and container size will be as follows:

ME	Total Amount Poured	Container Size
13	1 lb	1 lb can

17	0.5 lb	0.5 lb plastic bag
18	0.5 Ib	0.5 Ib plastic bag

Powder ME 16 will not scoop from a 25 pound pail; instead he will pour from two 4.5 pound jugs.

Reason for Change/Addition:
Biocides formulated as powders are not generally sold in large containers to the general public. The use of a 25 pound pail in the consumer pouring phase does not represent a container size that is normally marketed and sold to consumers. Using the smaller containers is more representative of actual products that might be used by the average consumer. Switching to smaller containers was discussed with EPA on August 15, 2014, prior to implementation."
- *End of excerpt* -

By way of background, AEATF's September 26, 2014 summary of communications with EPA on this topic is provided in attachment 7 and references conversations prior to implementation.

Pages 66-67 of the completed study provide the following information on this topic:

"Initially, five MEs were assigned to pour the contents of 25-pound buckets of powder; however, after observing the first two subjects (MEs 14 and 15) pouring powder from the buckets, the Study Director questioned whether this represented a typical consumer scenario. After discussions with the manufacturers of cyanuric acid, the study sponsor, and EPA, the protocol was amended (Amendment 4) to remove the remaining 25-pound buckets of powder from the consumer phase. Biocides formulated as powders are normally not sold to consumers in large containers because of poor pouring characteristics of powder and dust that is generated when handling large volumes of powder, as was observed during MEs 14 and 15. Powder is normally used for shocking pools and is sold in small plastic pouches typically weighing one pound or less. Therefore, although the exposure data from MEs 14 and 15 are not reflective of typical consumer use patterns, they were included in the data set. The three other subjects (MEs 13, 17, and 18) who had been assigned 25 pound buckets of powder were switched to smaller containers. Amendment 4 did not impact the granules which are commercially available in 25 pound or larger buckets." – End of excerpt -

Timing of Amendment 4: As noted previously, in response to EPA questions posed while reviewing the completed study, in June 2016 the Task Force provided a chronology of their AEA07 protocol amendments; this is provided in attachment 5 and lists the IRB approval date of each amendment and the researcher's implementation date. In attachment 5, AEATF noted that Amendment 4 was implemented on August 15, 2014, about a month prior to IRB approval, "upon the determination that there was a potential and immediate hazard that needed to be eliminated."

The aforementioned rationale and characterization were not referenced in the correspondence with SAIRB. Under the IRB's published reporting policy, "When changes to the protocol are implemented in order to eliminate an apparent immediate hazard to a research subject without prior Board approval, you must report changes to Schulman within 10 business days."

Amendment 4 was submitted to the SAIRB on September 22, 2014, 38 calendar days after implementation so this reporting timeframe was not met. The EPA does not agree that this situation falls within the category of eliminating an apparent "immediate" hazard to a research subject because at the time of implementation, there were other options available to the study sponsor, such as waiting for IRB approval of Amendment 4 before continuing to monitor subjects in the consumer pouring phrase. The EPA agrees that switching to smaller containers reduced exposure to dusts and power generated when handling the 25 pound pail during the consumer pouring phase of the study. In the future, if AEATF implements changes to the protocol to eliminate an apparent immediate hazard to a research subject without prior Board approval, AEATF has agreed to report changes to the overseeing IRB within the reporting timeframe dictated by the IRB's policy.

Amendment 5

Amendment 5 included three different components as follows: 1) corrected the protocol header so it identified the appropriate study number; 2) clarified that the total amounts of product to be handled, poured, and/or scooped as listed in protocol Tables 6-9 are target amounts; and 3) for consumer monitoring event 8, removed the requirement to scoop from a 25 pound bucket in addition to pouring from two 4.5 pound jugs of powder. Page 805 of the study describes the reasons for the amendment. This amendment did not negatively impact the rights or health and safety of participating subjects.

AEATF documented that SAIRB approved Amendment 5 on October 1, 2014 and the three different components of Amendment 5 were implemented on July 21, 2014, August 13, 2014 and August 16, 2014, respectively. By the time the IRB had received Amendment 5, the SAIRB had already approved Amendment 3 on September 23, 2014 (and Amendment 3 revised the language impacting the timing of amendment implementation). From my perspective, because the different components of Amendment 5 were implemented in July 2014 and August 2014 prior to the SAIRB approval of both Amendments 3 and 5, the actions which the researcher implemented under Amendment 5 were, in effect, protocol deviations at the time they were taken in July and August 2014. They became formal amendments to the protocol only after the IRB approved them on October 1, 2014.

Amendment 6

AEATF documented that Amendment 6 was implemented on February 3, 2015, the same day that the IRB approval was issued. There were 6 components to Amendment 6. As summarized on page 93 of study AEA07, "Amendment No. 6 added the 30-gallon fiber drum with a plastic liner as a source container to the occupational monitoring program; revised the product transfer procedure for the occupational monitoring program to include weighing product before adding it to the tank; added a second identical mix tank to be used in the occupational monitoring program to reduce down-time between MEs; provided an updated Safety Data Sheet for cyanuric acid; changed the inclusion criteria from being able to lift and pour up to two 40 lb buckets to being able to lift and pour up to four 25 lb buckets; changed field fortification from occurring every day of monitoring to every other day, starting on the first day of monitoring with a minimum of 3 sets to be collected." By way of background regarding one element of amendment 6, the weights and

types of the containers to be used in the occupational monitoring portion of the study had been changed so there was no longer a 40 pound bucket being used.

Pages 807-810 of study AEA07 explain the details of each change and accompanying rationales. The different components of Amendment 6 did not negatively impact the health and safety and/or the rights of subjects.

Amendment 9

Amendment 9 expanded the inclusion criteria for the occupational phase to allow people with occupational experience handling and pouring solid formulations of chemicals, but not necessarily currently working in that position. This allowed more flexibility in enrolling subjects for the study, but still maintained the required occupational experience of handling and pouring solid formulations.

AEATF documented that the amendment was implemented on the same day that the IRB approval was issued. Amendment 9 did not negatively impact the health and safety and/or the rights of subjects.

Amendment 10

Amendment 10 increased the test subject compensation from $100 to $175 for the occupational monitoring phase which was conducted in the spring of 2015. Each subject who participated in occupational monitoring was compensated the same amount of $175 for participating in the study. AEATF highlighted that the occupational monitoring phase required potential subjects to have unique work skills in order to qualify for the study. AEATF consulted with the EPA prior to implementing this amendment and documented that the amendment was implemented on the same day that SAIRB issued their approval.[1] AEATF's rationale for the increase is described on page 829 of the study as follows:

> "The test subject compensation is being increased to reflect a more accurate remuneration for the time and effort needed from potential test subjects in this study. The skill set being recruited is very specific [experience handling and pouring solid chemicals in a manufacturing or industrial capacity] which further limits the pool of qualified individuals. Subjects will be committing up to 6 hours, approximately 4 hours for the study in addition to driving one to two hours or more round trip. Since the study is taking place in a rural area of Ohio (approximately 30 miles east of Cleveland) where there is no densely populated central area from which the volunteers are being recruited, many of the volunteers will need to drive a considerable distance to participate in a one day research study. That combined with the fact that there is no other tangible benefit for people to

[1] For Amendments 4, 10 and 11, AEATF consulted with OPP's former Human Research Ethics Review Officer who worked in that role at the time of these amendments. Regarding Amendment 10, prior to responding to AEATF, OPP's former ethics reviewer consulted with the former Director of EPA's Program in Human Research Ethics and Oversight.

participate in this study warranted an increase in the remuneration."[2]

Amendment 10 provided a reasonable increase in proposed compensation in light of the new information learned by the Study Director and provided above. Because all subjects in the occupational phase received the same compensation, this amendment did not negatively impact the rights of subjects

Amendment 11

Amendment 11 expanded the inclusion criteria for the occupational phase to allow employees or spouses of employees of companies represented in the Antimicrobial Exposure Assessment Task Force to participate in the study with specific enrollment safeguards as required by SAIRB. AEATF discussed this amendment with the EPA's former Human Research Ethics Review Officer in March 2015 to ensure the Agency's support prior to submitting it to SAIRB. AEATF documented that the amendment was implemented three days after the IRB approval date.

The amendment affected the last exclusion criterion on page 20 of the protocol (which is page 727 of the completed study). The original language read: "*Is an employee or a spouse of an employee of any company represented by the AEATF, the contract research organizations conducting the study, or the American Chemistry Council.*" The amended version reads, "*Is an employee or a spouse of an employee of the contract research organizations conducting the study or the American Chemistry Council.*"

As explained by AEATF II on page 830 of the study, this amendment allowed more flexibility in enrolling test subjects for the study. Manufacturing and research and development plants of at least two "chemical companies who are members of AEATF are located in the Painesville-Concord, Ohio area and could potentially provide qualified individuals who would like to participate in the study. As required by SAIRB, a statement has been added to the informed consent form. Additionally, the Study Director will conform to the following safeguards as it relates to employee enrollment:

- recruiting would not take place in the workplace;
- no managers would be present during recruiting, consent process, or testing;
- employers/managers will not be notified of employees who respond to the ads or participate in the study;
- employees in the study would be treated the same as other study participants;
- no study participants including employees will be identified by name or any other way in the study report;
- employment affiliation or company name will not be recorded in the study raw data."

– End of excerpt from page 830-

AEATF confirmed that the additional safeguards were implemented as identified above and in follow-up to conversations with the EPA prior to implementing the Amendment.

In response to a question from the EPA, the Study Director further explained that: "The two subjects in the occupational phase who worked for companies which are members of the task

[2] EPA recognizes that compensation for participating in a human research study is not a "benefit."

force are W33 and W40. As described in the amendment, the facilities located in the local area of Ohio where the study took place were regional manufacturing and/or R&D facilities and for this reason neither subject was aware of or had any knowledge of their company's participation on the AEATF. The decision to amend the protocol to expand the inclusion criteria to employees or spouses of employees of member companies was discussed with and agreed upon with the EPA prior to its implementation. No spouses of employees of member companies were recruited for or participated in the study.

- W33 conducted monitoring events 4-Granular and 10-Powder.
- W40 was randomly assigned to be an alternate and was never monitored.
- Each of these subjects worked for a different member company
- No spouses of employees of AEATF companies participated."

As required by SAIRB and recommended by the EPA, the following additional language was added to the consent form and approved by SAIRB:

Introduction of Consent Form Expanded for Two Affected Subjects and Approved by SAIRB

"For subjects who are employees of or a relative of an employee of BASF or Lubrizol or other AEATF II member companies:

BASF and Lubrizol are members of the task force that is funding this research. As an employee or relative of an employee of BASF or Lubrizol or any other company that is a member of the Antimicrobial Exposure Assessment Task Force II, you are under no obligation to participate in this study. Your employer will not be contacted about this study.

You/your family member may decide not to participate in this study and there will be no penalty. You/your family member may withdraw from the study at any time and for any reason without penalty.

There will be no study record linking your name to your employer and we will not let your employer know if you participate or decide to participate in the study. In order to maintain your confidentiality. We will not identify you by name or in any other way in the study report or record the identity of your employer."

Introduction of Consent Form Revised for Two Affected Subjects and Approved by SAIRB

"You will not be allowed to participate in this research if you are an employee of or married to an employee of ~~Occidental Chemical Company or any one of the chemical companies who make up the Antimicrobial Exposure Task Force or~~ the American Chemistry Council or Ricerca Biosciences."

Expanded Breach of Confidentiality Section for Two Affected Subjects and Approved by

SAIRB

"Breach of Confidentiality: There is potential for a breach of confidentiality because photographs and video will be taken while you are participating in the study. However, efforts will be taken to conceal your identity by not including your face or editing so that your facial features are not recognizable. There will be no study record linking your name to your employer and we will not let your employer know if you participate or decline to participate in the study. In order to maintain your confidentiality, we will not identify you by name or in any other way in the study report and we will not record the identity of your employer."

In light of the safeguards put in place and associated revisions to the consent form, this amendment did not negatively impact the rights or health and safety of affected subjects.

Remaining Amendments

Amendments 7-8 and 13 – 16 addressed the topics below which did not raise ethical concerns in terms of the substance of the amendments themselves. These amendments were implemented before the IRB had approved them but after SAIRB had approved the last component of Amendment 3 which stated "All other amendments must be reviewed and approved by the IRB" without indicating when they must be approved; AEATF identified the implementation dates for these amendments in attachment 5. The substance of these amendments did not negatively impact the participants' rights, health or safety.

- Amendment 7: Changed field fortification levels and added a mid-level spike to all matrices except the glass fiber filter during the occupational phase.
- Amendment 8: Changed the analytical principal investigator from Dan Keenan to Jim Formanik.
- Amendment 13: Increased the LOQ for the face/neck wipes from 0.05 µg per sample to 1 µg per sample;
- Amendment 14: Increased the LOQ for the face/neck wipes again, from 1 µg per sample to 10 µg per sample;
- Amendment 15: Clarified that the extraction time for sample analysis was 4 hours, not one hour as stated in the analytical method and updated the contact information for the Study Director. With regard to the timing of this amendment, it should be noted that, on April 12, 2016, the overseeing Operations Coordinator for SAIRB emailed the Study Director regarding Amendment 15 and requested that a non-compliance acknowledgement be submitted to SAIRB because the IRB "noted that these changes took place in 2014 and should have been submitted to the IRB for review and approval prior to implementing the changes." This is documented on pages 1082 – 1084 of the completed study.
- Amendment 16: Corrected the report format requirements from Pesticide Registration (PR) Notice 86-5 to the newer PR 2011-3.

Effective Dates Listed on Proposed Amendments

The EPA noticed that all of the amendments submitted to the SAIRB for review and approval already had effective dates listed on them at the time of submittal to the IRB. In the future, if the study sponsor must include an effective date on the protocol amendment form when applying for IRB approval, unless the change addresses an imminent hazard, the EPA recommends and requests that the study sponsor insert "IRB approval date" as the effective date. AEATF has already agreed to this for current and future studies. Unless there is an immediate hazard to a research subject, protocol amendments should not be implemented prior to approval by the IRB. This same recommendation was discussed at the last HSRB meeting in July 2016 in relationship to a different study submitted by a different study sponsor.

Reported Protocol Deviations

Attachment 8 provides the list of reported protocol and SOP deviations from pages 94-95 of study AEA07. From the EPA's perspective, the reported deviations did not negatively impact the health and safety and/or rights of subjects.

Unreported Protocol Deviations with Ethical Implications

This section on unreported protocol deviations addresses: 1) environmental monitoring; 2) late submittal of proposed amendments to the IRB; 3) a deviation resulting from a discrepancy in the protocol; 4) comment in observations section; and 5) AEATF's proposed follow-up documentation.

Environmental Monitoring of air temperature, humidity, wind speed, and direction

Page 31 of the study states that: "A portable data-recording weather station was set up on the deck. During the conduct of the study, air temperature, relative humidity, wind speed and direction were recorded at **15 minute intervals**."

Page 38 of the study states: "During the **consumer monitoring** the air temperature, the relative humidity, wind speed and directions were collected during each monitoring event using GLP-compliant hand-held instruments. In addition, a GLP-compliant weather station with a data logger was set up on the deck approximately 7 feet above the pool to collect environmental conditions every 10 seconds. **The output from the data logger was summarized in 15 minute intervals.** Air temperature, percent relative humidity, wind speed and direction as well as wind gusts were measured and recorded.

Environmental measurements during the **indoor occupational monitoring** were collected using a GLP-compliant HOBO® Pro V2 data logger. **Hourly air temperature and relative humidity were collected and recorded.** In addition, temperature and relative humidity were recorded at the start of each monitoring event using GLP-compliant hand-held instruments."
– End of excerpt –

However, the protocol (on page 766 of the completed study) states that: "Air temperature and relative humidity of the work area for the duration of exposure monitoring will be documented with automated instrumentation logging and recording at **5 minute intervals** for the duration of

the work period per SOP AEATF II-10C. In addition, wind speed and direction will be recorded for the consumer monitoring that will take place outdoors. If sustained wind speeds reach 10 mph or more or it starts to rain, the monitoring will stop. Environmental monitoring equipment will be calibrated or standardized according to field facility SOPs. A facilities maintenance engineer with HVAC training or an industrial hygienist will document the HVAC system (if there is one) in the warehouse and measure the air intake and exhaust flow as well as the direction of air flow around the receiving tank. The dimensions of the warehouse will be documented in study field notes. It will be noted whether the HVAC system is operating during each ME."

During the study, recording occurred at 15 minute intervals as opposed to the 5 minute intervals stipulated by the protocol. This appears to be an unreported deviation. There is no evidence that this deviation negatively impacted subjects' health or well-being. However, in future AEATF studies, it's important to follow the protocol with regard to the recording intervals for air temperature, relative humidity, wind speed and direction.

Deviations Resulting from Late Submittal of Proposed Amendments

As previously discussed, because Amendment 3 was approved by SAIRB on September 23, 2014, but its 6 components were implemented in August, 2014, the actions taken by the study sponsor under Amendment 3 were, in effect, deviations from the protocol at the time they were implemented in August 2014. They became formal amendments to the protocol only after the IRB approved them on September 23, 2014. Amendment 4 was submitted to the SAIRB on September 22, 2014, 38 calendar days after implementation so the required reporting timeframe was not met. The actions which the researcher implemented under Amendment 5 were, in effect, protocol deviations at the time they were taken in July and August 2014. They became formal amendments to the protocol only after the IRB approved them on October 1, 2014. As discussed previously, AEATF has already agreed to a follow-up action to avoid such issues for any current and future studies.

Deviation Resulting from Discrepancy in Protocol

The approved protocol provides inconsistent guidance with regard to providing Safety Data Sheets and product labels to potential subjects, based on a comparison of pages 733 and 752 of the completed study. The "safety precautions" section of the protocol (on page 733 of the study) states that a copy of the label and Safety Data Sheet should be "available during the consenting process and provided upon request to the test subjects." However, when discussing consent meetings in a different section of the protocol (on page 752), the protocol states that "Potential volunteers will be provided with copies of the IRB approved Informed Consent Form, the Subject Qualification Worksheet, a copy of the Material Safety Data Sheet (MSDS), and copies of the product labels." The subjects were offered but declined the opportunity to review the Safety Data Sheets and product labels; however, the "label safety statements were explained during the consenting process" and "reviewed with the subjects again on the day of monitoring." The subjects were not provided copies of the Safety Data Sheets and copies of the product labels during the consent meetings; this is a deviation from the protocol. When reviewing protocols in the future, the study sponsor and the EPA should ensure that all sections of the protocol are consistent when discussing the same topic.

Comment in Observation Records

As noted earlier, on page 249, the observations section for consumer monitoring for the powder formulation (monitoring event 14), includes the Study Director's following notes: "Subject 3 commented that [sic] before monitoring that he doesn't use powders and that the technique should be different due to the smaller particles and the tendency to drift. We did recommend that he not toss it out across the pool." This recommendation deviates from the language in the safety precautions section of the protocol which reads, "The subjects will be allowed to handle the containers and pour product as they do so normally." This deviation did not negatively impact the health and safety of subject 3.

AEATF Proposed Documentation of Unreported Deviations

AEATF took the initiative to recommend to EPA that it prepare and submit to the EPA an addendum to the study report that incorporates the unreported deviations following HSRB review of completed study AEA07. The EPA agrees that it would be appropriate for AEATF to document all unreported deviations listed in this ethics review memo as part of the formal documentation for AEA07.

Report of Dermal Irritation by Two Subjects (W30 and W35) during Occupational Monitoring

As discussed on page 65 of the study, during the occupational monitoring, "Two of the 18 test subjects (W30 and W35) reported some dermal irritation on their faces at the end of their powder monitoring events (ME 11 and ME 16). Both subjects stated that they felt fine after their faces were washed. Slight skin irritation is a known adverse effect listed on the Safety Data Sheet for cyanuric acid and washing the affected area with soap and water is recommended."

The "stop criteria and medical management" section of the protocol (on page 755 of the study) states that: "If a subject reports an eye irritation (or other adverse effect) during the work period, they will be asked to immediately stop working. Research staff will then move the subject to a clean area and assist the subject in gently washing the eye with clean water. The nurse will determine whether medical treatment is necessary."

The protocol was followed in responding to the dermal irritation reported by subjects W30 and W35. Under protocol Amendment 3, the on-site medical professional was a first responder. In response to the EPA's questions, the Study Director confirmed the following: "The emergency responder was the observer who watched the test subjects and determined whether medical treatment was necessary. Since slight skin irritation is a known potential adverse effect (listed on the MSDS), the first aid instructions on the label were followed. For skin irritation, the instructions are to wash the contaminated area with soap and water. The emergency responder instructed the subjects to first have their faces wiped by the researcher and then wash with soap and water. Once this was completed, she checked with the individuals to see if the skin was still irritated. In both cases, the washing with soap and water alleviated the irritation; thus she determined that no medical treatment was necessary."

Guidance in Protocol Relevant to Subject W24 Incident

Pages 65-66 of study AEA07 state that: "One test subject (W24, granule ME 6 and powder ME 18 on March 30, 2015) contacted the Study Director the morning after monitoring complaining of stomach pain, vomiting, and sweating. Although these symptoms were not indicative of cyanuric acid exposure, the Study Director accompanied him to the emergency room. No diagnosis was made and the subject was later released from the emergency room. Follow-up phone calls to the subject were made on April 1 and 2 to monitor his status. On April 2 the subject was feeling better and had returned to work; no further follow-up was done."

This section provides only the facts associated with the guidance in the protocol, AEATF SOPs specifically cited in the applicable protocol sections, and the portions of the consent form which are relevant to this incident. The Office of Pesticide Programs' (OPP) interpretation of the study sponsor's compliance with the guidance is provided later in this ethics review.

The "stop criteria and medical management" section of the protocol (on page 756 of the completed study) includes the following relevant information:

> "The medical management procedures set forth in SOP AEATF II-11C will be implemented for any instance where the subject's work is halted for medical reasons (other than solely because of a heat stress index above 95), and **for any post-study reports of illness, eye or respiratory reactions or other unanticipated adverse effects**."
>
> "**The Study Director will maintain a record of adverse health observations and reports, and follow the Study Sponsor, IRB, and EPA policies for medical event reporting as described in SOP 11F.** Sufficient personnel will be present at the study site to maintain an appropriate level of technical support, scientific supervision, and observations relevant to the safety of test subjects."

Section 2.9 of AEATF SOP 11C (referenced above) states that:

> "2.9 If a test subject contacts the Study Director within 24 hours of participating in a study with complaints about a skin or eye reaction of other adverse effects that he/she believes are related to his/her participation in the study, the Study Director will instruct him/her to call 911 or seek medical treatment and to call the toll-free number on the product label. The Study Director will not make any medical recommendations. A follow-up phone call to the individual will be made by the Study Director or designee (who had the required ethics training) within 24 hours of a volunteer subject's phone call. The purpose of the call will be to inquire about the health of the individual and to close the case. If the Study Director or designee is unable to speak to the test subject, he/she will leave a message. Only one attempt will be made to reach the individual in recognition of the subject's privacy. Based on the Study Director or designee contact with the subject, incident reporting as described in Section 7.0 will be followed."

AEATF SOP 11F (also referenced above) states that:

2.2 "The Study Director and/or their designees , are required to report adverse events that meet both of the following criteria:

a. Event is UNANTICIPATED (An unanticipated event is any adverse experience where the nature, severity or frequency is not identified in the Informed Consent Form or described in the protocol. Events which are already cited in the protocol are not unanticipated and do not have to be reported to an IRB).

AND

b. Event is POSSIBLY RELATED to the study design, procedures or drug/device. If the adverse event is clearly not related to the study drug, device, procedures, or washout process, it would not represent a risk to other subjects in the research and, therefore, does not have to be reported to an IRB.

2.3 If these criteria are not met then the event does not have to be reported to an IRB." – End of excerpt -

The approved consent form states the following regarding payment for medical treatment for study-related illness or injuries:

> **"Research-Related Injuries**
> If you get hurt or sick while you are participating in this study, a nearby medical facility will provide care. If necessary, we will take you there. The AEATF II will pay for reasonable and appropriate medical treatment **for a study-related injury or illness** that is not paid for by your own insurance or insurance provided by your employer. **The Study Director in consultation with the on-site medical professional will decide if you have an illness or injury that is due to your participation in the study.**
>
> If you experience a skin reaction, respiratory irritation, eye reaction, or other physical injury that you believe is related to your participation in the study you should seek medical treatment and call the Study Director immediately at 1-877-298-7008. Medical records will not be part of the study."

Also, there is language in the risk section of the approved consent form that states, "If you have [sic] are sensitive to chemicals or cyanuric acid, be sure to tell us as this will mean that you cannot participate in the study." Similarly, the approved qualification worksheet for the occupational use scenario asks, "Do you have any known sensitivities or allergies to CYA, soaps, or chemicals?"

Finally, beyond the language included in the protocol itself, a primary point of reference for safety information in the protocol is the Safety Data Sheet (SDS) in Appendix B to the protocol (on pages 785-792 of the study and dated July 25, 2011). The SDS was updated as part of protocol amendment 6; the updated SDS is included on pages 814-826 of the completed study and dated

7/18/14. The product labels are also referenced in the protocol and included on pages 783-784 of the completed study. [By way of reminder, as discussed in the protocol on page 727 of the completed study, "Since cyanuric acid (CYA) is not classified as a biocide, it is not a registered active ingredient with EPA. It is registered as an adjuvant (a product that is an efficacy enhancer) in the state of California." Because the product used in the study does not include a registered active ingredient, the product label was not reviewed by EPA.] Below is the first paragraph from the safety precautions section of the approved protocol (from page 733 of the study):

> "Copies of product labels and the Materials Safety Data Sheet (MSDS) for cyanuric acid are included in Appendices A and B respectively. They will be included in the study file and provided to the study research team. A copy of the label and MSDS (in English only) will be available during the consenting process and provided upon request to the test subjects. Label safety requirements will be explained to the subjects involved in the study before they are monitored." – End of excerpt –

The next section provides details of the incident, other relevant information and follow-up actions.

Hospital Visit by Subject W24 after Occupational Monitoring

This section focuses on subject W24, specifically his role in the study, an incident involving subject W24, the Study Director's discussion with SAIRB and OPP/EPA in April 2015, other publically available information related to cyanuric acid, coverage of the subject's medical examination and treatment costs, EPA's conclusion regarding study sponsor adherence to the protocol and SOPs associated with follow-up, and follow-up actions.

Role of W24:

As part of the occupational monitoring portion of the study, as noted on page 37, some subjects were required to stand on a step while pouring cyanuric acid to allow for variability in pouring height. The steel-constructed stand consisted of two steps, the first 7 inches from the ground and the second 13 inches from the ground. As described in the observations on page 262, subject W24 poured a 25 pound bucket of the granular formulation of cyanuric acid into a tank while standing on the top step. As described in the observations on page 295 of the study, this same subject poured three 25 pound buckets of the powder formulation into a tank while standing on the top step.

Personal Protective Equipment and Clothing Worn by W24:

During the exposure monitoring, W24 wore the personal protective equipment required for occupational monitoring and new clothing consistent with the approved protocol including: two layers of clothing (long underwear under a long sleeved work shirt and long work pants), respiratory protection (N95 dust mask), 15 mil chemical-resistant nitrile gloves, and safety glasses.

Incident involving W24:

Pages 65-66 of study AEA07 summarize the incident, along with the Study Director's follow-up discussions with SAIRB and EPA as follows:

> "One test subject (W24, granule ME 6 and powder ME 18 on March 30, 2015) contacted the Study Director the morning after monitoring complaining of stomach pain, vomiting, and sweating. Although these symptoms were not indicative of cyanuric acid exposure, the Study Director accompanied him to the emergency room. No diagnosis was made and the subject was later released from the emergency room. Follow-up phone calls to the subject were made on April 1 and 2 to monitor his status. On April 2 the subject was feeling better and had returned to work; no further follow-up was done. Since this event did not qualify as a serious adverse event (SAE), the SAIRB was contacted to determine how it should be reported. SAIRB confirmed that they do not have a reporting requirement for an incident that was unrelated to participation in the study. As such, no report was made to the SAIRB. EPA was informed of this incident and concurred with the Sponsor's decision not to file a subject safety report with the IRB. The incident and the follow-up actions were extensively documented in the raw data; a copy of the documentation is located in Appendix H."

Appendix H (pages 699-706 of the study) is identified as "Subject W24 Incident Report" and provides extensive details on what transpired from the time that the Study Director received the initial message from test subject W24 until his release from the hospital and the Study Director's subsequent conversations with the subject. Appendix H is included as Attachment 9 to this ethics review. The HSRB should read Appendix H as part of its review.

As stated in Appendix H, subject W24 "is a 22 year old male. He works at a chemical production plant and worked on Monday before coming to Ricera after work. As a materials handler, he did indicate that he worked with a number of chemicals during the day." The Safety Data Sheet (SDS) for cyanuric acid is included on pages 814-825 of the study. As summarized on page 3 in Appendix H and page 702 of the completed study:

> "The only health hazard listed on the SDS for 'cyanuric acid, dry' is slight eye and skin irritation. There is no GHS signal word as CYA is classified by OSHA as nonhazardous (29 CRF 1910.1200). First Aid Measures (section 4) of the SDS indicates that inhaling powder or particles may cause respiratory track irritation or cough; exposure of skin may result in slight skin redness or irritation; eye exposure may cause mild irritation of the eye lids and conjunctiva; and there are no known effects from ingestion. Under 'note to physician' – 'This material causes mild irritation to the skin and eyes. Removing the material via irrigation is usually sufficient. There is no antidote. Cyanuric acid is readily removed from the body via the renal system and is not bioaccumulated. Treatment is supportive care.'"

Page 4 of Appendix H and page 703 of the completed study provides the following discussion:

> "Cyanuric acid is a common swimming pool maintenance chemical sold to consumers and pool maintenance professionals. Due to the low mammalian toxicity of CYA which is classified by OSHA as non-hazardous, there are no label required protective equipment. As a study precaution, all subjects in this phase of the study wore a dust mask, chemical-resistant gloves, and safety glasses in addition to the two layers of clothing. Anticipated

adverse events/problems with exposure to dry cyanuric acid are slight eye, skin, or respiratory irritation. The subject's symptoms of nausea/vomiting, diarrhea, abdominal cramps/pain, muscle aches, and sweating were not consistent with the information known about exposure to cyanuric acid."

Discussion with IRB and OPP/EPA on Reporting of Incident:

After the incident, the Study Director consulted with Mr. Jeff Atlas, the SAIRB's Operations Coordinator, regarding potential reporting categories for the incident. As documented by the Study Director in Appendix H to the study: "Mr. Atlas went through the five subject safety reporting categories listed on the SAIRB website. There are:

1. Unanticipated problems involving risks to human subjects or others
2. Unanticipated adverse device effects
3. Serious adverse event (SAE)
4. Safety report
5. Non-compliance or protocol variance/deviation."

"Mr. Atlas confirmed that since the SAIRB does not require an event that has been determined to be unrelated to participation in the study to be submitted, there is no appropriate category to file it under. He indicated that if we choose to submit it for acknowledgment, we would need to submit it as a serious adverse event (SAE). According to Mr. Atlas, this would be the only category that would fit our situation. After conducting a search on the internet to better understand the definition of these terms, I called Mr. Atlas back. During this second conversation I informed him that based on my understanding of an SAE the incident with worker W24 does not meet the criteria of an SAE [an adverse event or suspected adverse reaction is considered 'serious' if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization (24 hours or more) or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect]. He agreed that this is also the SAIRB's interpretation of an SAE, but this was our only option for getting an acknowledgment."

The nature of the incident, analyzed at the time it occurred, did not fit any of the SAIRB's reporting categories. The Study Director documented in Appendix H that, "Based on the flowchart, the reporting of this event to Schulman Associates is not necessary. I confirmed this in a telephone conversation with Mr. Atlas on April 7, 2015."

In April 2015, the Study Director consulted with the Office of Pesticide Programs' former Human Research Ethics Review Officer (who conducted ethics reviews at that time). OPP agreed with the Study Director's decision not to file the incident as an SAE with SAIRB after learning the definition of an SAE. However, OPP recommended that the event, the Study Director's conversation with the SAIRB, information about the reporting risk categories, and the conclusion that the incident did not meet the definition of an SAE be included in the final AEA07 study. The information and details were included in the study as recommended by EPA.

Additional Publically Available Information:

After reading Appendix H, in the interest of due diligence, I checked the Internet for public information on effects of cyanuric acid. Information was available from the TOXicology Data NETwork (TOXNET)[3], the National Institute for Occupational Safety and Health (NIOSH), and the Pesticide Action Network (PAN) Pesticide Database. In addition to the information already provided in the Safety Data Sheet for cyanuric acid, the NIOSH International Chemical Safety Cards identified ingestion as a hazard/exposure with abdominal pain and sore throat as symptoms. The PAN Pesticide Database similarly identified abdominal pain as a symptom of ingestion and TOXNET stated "The substance irritates the respiratory tract and the eyes." Subject W24 experienced abdominal pain. Subject W24 wore a dust mask throughout the exposure period which eliminates or significantly reduces the likelihood of ingestion during the study; also, an observer was assigned to subject W24 and did not observe and/or document subject W24 ingesting cyanuric acid.

Subject W24's Employment:

It's also important to highlight that subject W24 worked in a chemical production plant with a number of chemicals during the day before participating in the study. From my perspective, this factor potentially impacts and complicates the determination as to whether or not this incident occurred as a result of the subject's participation in the study. The EPA does not have any information on the identity and/or nature of the chemicals with which the subject worked. Appendix H (page 704 of the study), written by the Study Director, concludes that, "Based on the SDS and discussion with the manufacturer of cyanuric acid combined with the very short duration of exposure (5 minutes) and the fact that the subject was wearing protective equipment, the Study Director does not believe that this event was associated with participation in the exposure monitoring study." According to the language in the approved consent form, the Study Director was the decision-maker on this point after consulting with the "on-site medical professional." (This language assumes that an adverse effect is being reported during the test day after consultation with the medical professional at the test site.) However, reporting of this incident occurred during the early morning hours after the test day when the subject was at home. The nurse and doctor who examined the subject did not share information with the Study Director regarding their diagnosis due to HIPAA laws. Based on the available information as noted above, the Study Director did "not believe that this event was associated with participation in the exposure monitoring study."

Language in Consent Form regarding Sensitivity to Chemicals or Cyanuric Acid:

It should be noted that there is language in the risk section of the approved consent form that states, "If you have [sic] are sensitive to chemicals or cyanuric acid, be sure to tell us as this will mean that you cannot participate in the study." Similarly, the approved qualification worksheet for the occupational use scenario asks, "Do you have any known sensitivities or allergies to CYA,

[3] ToxNET is a group of databases covering chemicals and drugs, diseases and the environment, environmental health, occupational safety and health, poisoning, risk assessment and regulations, and toxicology and is managed by the National Library of Medicine.

soaps, or chemicals?" Subject W24 did not indicate any known sensitivities or allergies to cyanuric acid, soaps, or chemicals.

Coverage of Medical Costs:

There was no information in Appendix H regarding whether or not the study sponsor covered the medical costs associated with the subject's visit to the emergency room. When EPA asked about payment of medical costs, the Study Director explained that, "I do not know who paid for the subject's treatment – it was not the AEATF. It is AEATF policy to pay for research-related injuries or illnesses not covered by a subject's or his employer's insurance. However, in this case, the symptoms that appeared the following day were not reflective of exposure to cyanuric acid. For this reason, the task force did not offer to pay for the medical expenses, and the subject did not request that we pay the bill. W24 was not an employee of one of AEATF member companies."

The approved consent form states the following regarding payment for medical treatment for study-related illness or injuries:

> **"Research-Related Injuries**
> If you get hurt or sick while you are participating in this study, a nearby medical facility will provide care. If necessary, we will take you there. The AEATF II will pay for reasonable and appropriate medical treatment **for a study-related injury or illness** that is not paid for by your own insurance or insurance provided by your employer. **The Study Director in consultation with the on-site medical professional will decide if you have an illness or injury that is due to your participation in the study.**
>
> If you experience a skin reaction, respiratory irritation, eye reaction, or other physical injury that you believe is related to your participation in the study you should seek medical treatment and call the Study Director immediately at 1-877-298-7008. Medical records will not be part of the study."

Regarding the reference to the "on-site medical professional" in the paragraph above, given the context of the paragraph, it's unclear if the "on-site medical professional" refers to the certified first responder who was on-site at the study site while study AEA07 was underway or if it refers to the on-site medical professional at the "nearby medical facility" mentioned in the same paragraph. In future protocols, the EPA should ensure that the meaning of such references is clear. The Study Director clarified that: "The 'on-site medical professional' referenced in the consent form was the medical professional who was hired to be present during the study. Accordingly, during this study, the 'on-site medical professional' was the certified first responder who was also a member of the study team."

In the future, when a consent form includes language similar to "*The Study Director in consultation with the on-site medical professional will decide if you have an illness or injury that is due to your participation in the study*," the EPA should request that a provision be included in the protocol that the on-site medical professional cannot be a member of the study team. It's difficult to predict all circumstances when reviewing a draft protocol. However, in such

circumstances, it's preferable to have a medical professional who is not funded by the research team consulting with the Study Director when determining whether or not an illness or injury resulted from the subject's participation. This avoids even the appearance of impropriety.

Based on available information, the Study Director concluded that the incident was not the result of the subject's participation in the study. As a result, the study sponsor was not required to pay for the medical costs associated with the subject's visit to the emergency room that were not covered by his insurance or his employer's insurance.

As documented in Appendix H, the Study Director called the subject back after their initial conversation and offered to take the subject to the emergency room to be examined; OPP believes this was an appropriate action on the part of the Study Director in light of the language in AEATF SOP 11C on emergency procedures that the "Study Director will instruct him/her to call 911 **or seek medical treatment**…". On this point, the study team went beyond the requirements of the protocol and SOP by taking the subject to the hospital emergency room (ER), waiting there until the subject was released, and taking the subject home.

As a result of the Study Director offering to take the subject to the ER, he might have assumed, given his state of distress and illness, that the study sponsor would pay for the costs of his visit that were not covered by his or his employer's insurance. The consent form states that "If you experience a skin reaction, respiratory irritation, eye reaction, or other physical injury **that you believe is related to your participation in the study, you should** seek medical treatment and **call the Study Director immediately at 1-877-298-7008**." The subject calling the Study Director implies that the subject believed his reaction could have been related to his participation in the study. According to Appendix H, the Study Director questioned the nurse and doctor who examined the subject at the emergency room about the results of their tests and diagnosis, "but they said they couldn't tell me anything due to the HIPAA laws." The Study Director documented in Appendix H that, "To my knowledge they also did not provide W24 with any information about the tests that they had run or a diagnosis. They suggested that he see a local doctor the next day if the symptoms persisted and provided a prescription for anti-nausea."

Given the facts as presented in Appendix H of the study, the language in the signed consent form, protocol and AEATF's SOP 11C on emergency procedures (which is explicitly referenced in the protocol), AEATF was not <u>required</u> to pay for the subject's medical and treatment costs that the subject's own insurance or his employer's insurance did not cover. While acknowledging this, EPA's Office of Pesticide Programs believes it would have been preferable for the study sponsor to do so out of an abundance of caution. The doctor and nurse were prohibited under HIPAA laws from sharing a diagnosis and, as a result, the Study Director's consultation with them did not yield any information that she could factor into her decision as to whether or not the illness was due to participation in the study. The factors which were taken into account in deciding that the incident did not result from the subject's participation in the study were reflected in the following statement in Appendix H, on page 704 of the study: "Based on the SDS and discussion with the manufacturer of cyanuric acid combined with the very short duration of exposure (5 minutes) and the fact that the subject was wearing protective equipment, the Study Director does not believe that this event was associated with participation in the exposure monitoring study."

SOP 11C Instruction to Call Toll-Free Number on Product Label:

As noted previously, section 2.9 of AEATF SOP 11C states, in part, that:

> "2.9 If a test subject contacts the Study Director within 24 hours of participating in a study with complaints about a skin or eye reaction of other adverse effects that he/she believes are related to his/her participation in the study, the Study Director will instruct him/her to call 911 or seek medical treatment and to call the toll-free number on the product label. The Study Director will not make any medical recommendations. A follow-up phone call to the individual will be made by the Study Director or designee (who had the required ethics training) within 24 hours of a volunteer subject's phone call. The purpose of the call will be to inquire about the health of the individual and to close the case."

As discussed in detail previously, the study team went beyond the requirements of the protocol and SOP when they drove the subject to the hospital emergency room (ER), waited there until the subject was released, and took the subject home. Two follow-up phone calls were also made to the subject to inquire as to his health status. As noted on pages 65-66 of the study, "Follow-up phone calls to the subject were made on April 1 and 2 to monitor his status. On April 2 the subject was feeling better and had returned to work; no further follow-up was done."

The only applicable portion of section 2.9 of AEATF SOP 11C that was not carried out was instructing the subject to call the toll-free number on the product label. As such, this is a protocol deviation. As the Study Director explained to EPA:

> "The subject was in considerable distress when he contacted the Study Director. Based on the subject's condition, the Study Director decided not ask him to call the toll-free number; instead the study team took him to the ER and waited there until he was released and took him home. This went beyond the requirements of the SOP. The Study Director did contact and inform the chemical supplier company of this incident from the ER. The company did not provide any additional direction or information for her or the ER staff to follow."

At the EPA's request, the Study Director asked the chemical supplier company what the company does with the information it receives from such calls. The Study Director clarified that, "According to the chemical company, the information would be reviewed internally to determine whether there were any reporting requirements under TSCA." [The Toxic Substances Control Act (TSCA) Section 8(e) states that U.S. chemical manufacturers (including importers), processors, and distributors must notify the EPA within 30 days of obtaining information that reasonably supports the conclusion that their chemical products present a *substantial risk of injury to the health or environment*.]

It's reasonable that the Study Director did not ask the subject to call the toll-free number on the label at the time that he was ill and had to be driven to the hospital emergency room. However, in hindsight, near the conclusion of the Study Director's second follow-up call with the subject, it would have been preferable for the Study Director to provide the subject with the toll-free number and suggest that he call it to report his illness; during the second phone call, the subject said that he was feeling better and had returned to work so it would have been an appropriate time to recommend this to the subject. Consistent with standard operating procedure 11C, which is

referenced in the protocol, EPA believes the Study Director should have provided the toll-free number to the subject and instructed the subject to call the chemical company to report what had occurred.

EPA Conclusion Regarding Study Sponsor Adherence to Protocol in Handling W24 Incident:

As it relates to this incident, the Study Director complied with the requirements of the protocol and relevant SOPs with the exception of instructing the subject to call the toll-free number on the product label, as discussed above. The fact that AEATF did not instruct the subject to call the toll-free number on the product label is a protocol deviation.

As a result of considering the incident involving subject W24 and reviewing applicable language in the protocol, SOPs and the consent form, the Office of Pesticide Programs identified the following lessons learned and follow-up actions:

- In future screening of potential subjects for human research studies, study sponsors could ask a standard question, "What specific chemicals, if any, do you currently work with as part of your job?" If the study sponsor and/or EPA recognize that the specific chemicals with which the subject works could potentially present a problem in terms of the subject's involvement in the study, the subject could be excluded from participation. The related exclusion criterion could be, "Works with chemicals which are potentially problematic in terms of subject's participation in study." EPA should consider this option, as appropriate, when reviewing future protocols.
- As discussed previously, in the future, when a consent form includes language similar to "*The Study Director in consultation with the on-site medical professional will decide if you have an illness or injury that is due to your participation in the study*," EPA should request that a provision be included in the protocol that the on-site medical professional cannot be a member of the study team. In such circumstances, it's preferable to have a medical professional who is not employed as a member of the research team consulting with the Study Director when determining if an illness or injury resulted from the subject's participation. This avoids even the appearance of impropriety.
- In future studies, if an incident occurs, AEATF needs to follow all applicable aspects of AEATF SOP 11C if this SOP is referenced in the protocol, including the Study Director instructing the subject to call the toll-free number on the product label and ensuring the subject has the product label, consistent with the protocol.

Subject ME 9 in Consumer Monitoring and Inclusion in Dataset

Pages 83-84 of the study states the following with regard to subject 9:

> "The subject (AEA07-09) who performed ME 9 had no pool maintenance experience and no experience pouring solid pool products; his extremely messy work practice, including splashing solution onto the deck, inserting his fingers into the mix solution, choosing the small 2-gallon bucket to use, and pouring the entire container of product (4.5 lb) into the bucket at once, reflected his inexperience. Based on his inexperience and the fact that he was selected to do the more complex task of pre-dissolving product in a bucket, it was

> decided that ME 9 was not representative of the population being monitored for that particular task and should be removed from the dataset."

Page 87 of the study adds that: "The highest unit exposure (17.8 µg/lb ai) during the pouring of granules was seen with ME 9. This ME was removed from the granular pouring dermal dataset due to the complexity of the task and the unfamiliarity of the subject with the procedure of pre-dissolving pool chemicals and was also removed from the inhalation dataset. Table 48 contains the inhalation data for consumer pouring of granules without ME 9. Without ME 9, the inhalation unit exposure arithmetic mean is 2.00 µg/lb ai and the standard deviation is reduced by a factor of two."

From an ethics standpoint, there is no reason to exclude the data associated with ME 9 and the EPA does not intend to do so. Protocol amendment 2 modified the inclusion criteria for consumer monitoring to allow participation by people who did not own a swimming pool and did not have experience with adding granules or powder products to a pool. Page 800 of the completed study provides the amendment rationale, which states in part, "By not having experience pouring pool chemical products, these subjects would be representative of first-time pool owners." Given that the protocol was specifically amended to allow participation by subjects who did not have experience adding granules or powder products to a pool, it would be unreasonable for the EPA to exclude data from such a subject from the agency's assessment, unless other reasons made the data unreliable. If data were determined to be scientifically unreliable, it would not be ethical to rely on it, but that is not the case here based on available information (and as discussed in the EPA's science review of study AEA07). The EPA intends to include the data associated with ME 9 in its assessment.

Findings

Responsiveness to EPA and HSRB reviews

The EPA's and HSRB's comments on the protocol for AEA07 were addressed as described in attachment 1.

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

40 CFR §26.1703 prohibits research involving intentional exposure of pregnant or nursing women or of children under 18. All subjects who participated in study AEA07 were at least 18 years old. All female subjects in the study self-administered over-the-counter pregnancy tests on the day of the monitoring consistent with the approved protocol; all such tests were negative. Therefore, 40 CFR §26.1703 does not prohibit reliance on this research.

Substantial compliance with 40 CFR 26 subparts A through L

40 CFR §26.1705 requires that EPA have "adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." Within this range, only subparts K and L are directly applicable to the conduct of third-party research such as this. The AEA07 study was conducted in substantial compliance with subparts K and L. AEATF

also agreed to implement follow-up actions identified in this ethics review.

Compliance with 40 CFR §26 subpart M

As documented in attachment 3 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.

Summary of Recommended and Agreed-Upon Follow-up Actions

In this ethics review, the Office of Pesticide Programs recommends that AEATF take the following actions:

1. With one exception, AEATF has already agreed to seek IRB approval of all protocol amendments prior to their implementation in current and future human research studies to be submitted to EPA's Office of Pesticide Programs (OPP) consistent with the published policy of the overseeing IRB, which must comply with 40 CFR §26.1108; the only exception would be situations involving imminent hazard to human subjects.
2. In the future, if AEATF implements changes to the protocol to eliminate an apparent immediate hazard to a research subject without prior Board approval, AEATF agrees to report changes to the overseeing IRB within the reporting timeframe dictated by the IRB's policy.
3. In future studies, if an incident occurs, AEATF needs to follow all applicable aspects of AEATF SOP 11C if this SOP is referenced in the protocol, including the Study Director instructing the subject to call the toll-free number on the product label and ensuring the subject has the product label, consistent with the protocol.
4. When implementing future AEATF studies, it's important to follow the protocol with regard to the recording intervals for air temperature, relative humidity, wind speed and direction.

As noted previously, AEATF took the initiative to recommend to the EPA that it prepare and submit to the EPA an addendum to the study report that incorporates the unreported deviations following the HSRB's review of completed study AEA07. The EPA agrees that it would be appropriate for AEATF to document all unreported deviations listed in this ethics review memo as part of the formal documentation for AEA07.

This ethics review recommends the following actions for the EPA and study sponsors in general:

1. When reviewing protocols in the future, the study sponsor and the EPA should ensure that all sections of the protocol are consistent when discussing the same topic.
2. In future screening of potential subjects for human research studies, study sponsors could ask a standard question, "What specific chemicals, if any, do you currently work with as part of your job?" If the study sponsor and/or the EPA recognize that the specific chemicals with which the subject works could potentially present a problem in terms of the subject's involvement in the study, the subject could be excluded from participation. The related

exclusion criterion could be, "Works with chemicals which are potentially problematic in terms of subject's participation in study." The EPA should consider this option, as appropriate, when reviewing future protocols.

3. As discussed previously, in the future, when a consent form includes language similar to "*The Study Director in consultation with the on-site medical professional will decide if you have an illness or injury that is due to your participation in the study,*" the EPA should request that a provision be included in the protocol that the on-site medical professional cannot also be a member of the study team. In such circumstances, it's preferable to have a medical professional who is not employed as a member of the research team consulting with the Study Director when determining if an illness or injury resulted from the subject's participation in the study. This avoids even the appearance of impropriety.

Conclusion

This study reports research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L. In its conduct, study AEA07 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. The EPA recommends follow-up actions in this ethics review to which AEATF has agreed; AEATF will implement these follow-up actions in human research studies underway or to be conducted in the future for submittal to the EPA's Office of Pesticide Programs. From the EPA's perspective, if this study is determined to be scientifically valid and relevant, there is no regulatory barrier to the EPA's reliance on it in actions under FIFRA or §408 of FFDCA. This research will also undergo review by the Human Studies Review Board.

cc: Richard Keigwin
Tim Leighton
Jennifer McClain
Michelle Arling

Attachments

1: Ethics Comments from April 2014 HSRB Meeting and AEATF II Actions
2: AEATF II's Chronology of Key Study Events
3: Checklist for Completeness of Reports of Human Research
4: List of AEATF II Protocol Amendments
5: AEATF II Chronology of Protocol Amendments – Dates of IRB Approval and Implementation
6: AEATF II Documentation for Amendment Implementation Dates
7: AEATF II Communications with EPA on Amendment 4
8: AEATF II Reported Deviations
9: Appendix H of Study

Attachment 1

Ethics Comments from April 2014 HSRB Meeting & AEATF II Actions

EPA Comments on AEA07 Protocol	AEATF II Actions to Address Comments
Add skin conditions of the ***face/neck*** to the exclusion criteria listed in the protocol	Comment was incorporated.
Revise section 9D of the protocol to specify that if two or more subjects develop eye irritation or respiratory irritation after they leave the study site, all subjects will be contacted by the Study Director to determine whether further medical management is appropriate. [See the last sentence of the 7th paragraph in section 9D; this section currently only lists "adverse skin reaction" as a triggering event.]	The AEATF explained that the Task Force "had agreed to make this change to Section 9D of the protocol, but it was inadvertently missed when making other changes." The referenced paragraph in the current stop criteria and medical management section of the protocol (page 756 of the completed study) reads as follows: "Study personnel will be instructed to inform the Study Director and nurse immediately of any eye irritation, respiratory irritation, heat stress, or other unanticipated adverse effects observed or reported during conduct of the study. The medical management procedures set forth in SOP AEATF II-11C will be implemented for any instance where the subject's work is halted for medical reasons (other than solely because of a heat stress index above 95), and for any post-study reports of illness, eye or respiratory reactions or other unanticipated adverse effects. If two or more subjects withdraw or are withdrawn from the study for the same medical reasons, the study will be suspended until the cause of the withdrawal is fully investigated and determined. If two or more subjects develop an adverse skin reaction after they leave the study site, all subjects will be contacted by the Study Director to determine whether further medical management is appropriate."
Revise the Residential Monitoring consent form to explain that subjects will need to wear a particulate dust mask as a safety precaution.	Comment was incorporated.
Revise the "Research-Related Injuries" section in both the Residential Monitoring and Occupational Monitoring consent forms by adding skin reactions and respiratory irritation as reactions for which	Comment was incorporated.

EPA Comments on AEA07 Protocol	AEATF II Actions to Address Comments
subjects should seek medical treatment and call the study director. Please revise as follows: *"If you experience an eye reaction, **skin reaction, respiratory irritation** or other adverse effect that you believe is related to your participation in the study, you should seek medical treatment and call the Study Director immediately at 1-877-298-7008."*	
Revise the newspaper advertisement for the Occupational Scenario to specify that only candidates who are currently employed for a company where they use powder or granule chemicals as part of their job. The protocol and screening questions indicate that current employment in a manufacturing or industrial company is a requirement, but the newspaper advertisement does not make that clear.	Comment was incorporated.
The AEATF should incorporate the forthcoming guidance from the HSRB about how to provide personal exposure results to subjects.	The HSRB did not finalize the report from the HSRB's working group.
HSRB Comments on AEA07 Protocol	**AEATF II Actions to Address Comments**
The Board respectfully disagrees with the Agency's suggestion that the "Research-Related Injuries" section of the informed consent forms be revised to read as follows: "*If you experience an eye reaction, **skin reaction, respiratory irritation** or other adverse effect that you believe is related to your participation in the study, you should seek medical*	EPA's comment on this topic was addressed in the revised consent form, the applicable section of which reads: **"Research-Related Injuries** If you get hurt or sick while you are participating in this study, a nearby medical facility will provide care. If necessary, we will take you there. The AEATF II will pay for reasonable and appropriate medical treatment for a study-related injury or illness that is not paid for by your own insurance or insurance provided by your employer. The Study Director in consultation with the

EPA Comments on AEA07 Protocol	AEATF II Actions to Address Comments
treatment and call the Study Director immediately at 1-877-298-7008" (Leighton, Sherman & Cohen, 2013, p. 18). In fact, this revision does not go far enough. Study participants should be instructed to seek treatment and inform the Study Director of any eye reaction, skin reaction, respiratory irritation or other physical injury that occurs during or after participating in the study, regardless of whether or not the volunteer believes that it is related to the study.	on-site nurse will decide if you have an illness or injury that is due to your participation in the study. If you experience a skin reaction, respiratory irritation, eye reaction or other physical injury that you believe is related to your participation in the study you should seek medical treatment and call the Study Director immediately at 1-877-298-7008. Medical records will not be part of the study. If you have any questions regarding your rights as a research participant, please contact Schulman Associates IRB toll free at 1-(877) 888-4472 from 9:00 am – 5:00 pm (Eastern Time), Monday-Friday. You can also contact Schulman Associates IRB if you would like to report problems in a research study, express concerns, ask questions, request information, or provide input. Schulman Associates IRB is a committee established for the purpose of protecting the rights of participants in a research study. For more information about your rights and role as a research participant you can visit the Subjects section of the Schulman Associates IRB website at www.sairb.com. **You do not waive (give up) any of your legal rights** or release the Sponsor, the study staff, or study site from liability for mistakes or intentional misconduct **by signing this form."** – End of excerpt - In response to this comment, AEATF II explained the following: "The AEATF agreed with the EPA's recommendation and added "***skin reaction"*** and ***"respiratory irritation"*** to the consent form. The AEATF considered the Board's recommendation and agreed to add ***"physical injury"*** to the consent form. However, the AEATF disagreed that it should incorporate "***regardless of whether or not the volunteer believes that it is related to the study***". The AEATF believed that it was necessary that the subject believe his or her injury was related to the study. If a volunteer did not believe his or her symptom(s) were related to the study, it was not appropriate, in the Task Force's opinion, for the AEATF to instruct the volunteer seek medical help and contact the Study Director. Following the release of the HSRB draft meeting report, the AEATF decision not to fully incorporate HSRB's recommendation was communicated to the EPA via email on June 12, 2014."

EPA Comments on AEA07 Protocol	AEATF II Actions to Address Comments
It is not necessary or appropriate to state that cyanuric acid "does not require gloves or any other protective equipment to use" (Shah, 2013b, p. 31) on the occupational monitoring informed consent form. This may be confusing to participants, as they will be required to wear PPE during the study and will be given a copy of the MSDS to read, if requested. The study investigators should also consider how to handle the possibility that a participant in the consumer-monitoring phase of the study may ask to wear gloves.	The language in the original consent form was revised and clarified. The occupational monitoring consent form (dated 3/12/15) now reads: "We will give you safety glasses, a dust mask, and chemical-resistant gloves to wear while you are pouring. You must wear the safety equipment while handling and pouring the containers. Cyanuric acid does not require that this safety equipment is worn; however, this is required as a safety precaution for this study."
Since study participants must self-report being in "good health," it should be clear what that term means. For example, since participants will be required to move 25-90 lbs. of product, some mention of those physical requirements should be made in reference to the health-related inclusion criterion.	On this point, the occupational monitoring phase consent form (dated 8/6/14) states that you will not be allowed to participate if you are not able to lift and pour up to four 25 pound buckets. The residential monitoring phase consent form references being able to lift and pour two 25 pound containers. The referenced inclusion criteria was expanded to read: • "Self-identified as being in good health as defined as able to lift and pour up to two 25 pound buckets of product (consumer monitoring) or up to two 40 pound buckets of product (occupational monitoring) and wear a dust mask for the duration of the study."
With respect to the balance of risks and benefits, the submitted documents state that the risks of this study are "far lower than the risks of not being able to use effective antimicrobials for lack of information on the potential exposure to users" (Shah, 2013b, p. 26). This language includes assumptions about downstream consequences of decisions about conducting or not conducting specific research studies. The	AEATF revised the language to take into account the HSRB's comment. The sentence in question now reads: "The very slight incremental risks from participation in this study are reasonable in relation to the importance of understanding exposure patterns for consumers and occupational users of antimicrobials."

EPA Comments on AEA07 Protocol	AEATF II Actions to Address Comments
Board thus recommended that the study sponsor change this wording to read that "risks are reasonable in relation to the importance of understanding exposure patterns for consumers and occupational users of antimicrobials."	
Participants in the study are allowed to take a short break if requested, either to use the bathroom or to have a cold drink. If the former, the researchers will conduct a hand wash to remove any product. Is the same true of the latter case, when a participant asks for a cold drink? Hand washes should also occur before any beverage consumption to reduce a participant's risk of accidental ingestion.	In response to this comment, the protocol (on page 761 of the completed study) was revised to state: "If the subject requests a drink, the researcher will insert a straw into a bottle of water or Gatorade and hold it while the subject drinks. The subject will remove his own dust mask. The subject will not touch the bottle or straw with his hands."
The study protocol should define the qualifications of the medical personnel needed and clarify this in the appropriate sections of the protocol.	The language in the original protocol referenced an on-site medical professional. In the revised protocol, this was changed to "nurse." However, when a nurse was unavailable for the monitoring days, SAIRB approved an amendment (#3) which allowed a first responder to be the on-site medical professional.
The Board recommended that researchers complete a course in human subjects protections within three years of study initiation and completion. Depending on when the study occurs, some investigators may exceed this recommended time limit.	Comment was addressed. Researchers completed training on human subjects protection within three years of study initiation.

Attachment 2

Note: AEATF provided the following summary in completed study AEA07.

Table 1 Chronological Listing of Key Events

4/19/2013 Submission of AEA07 protocol, IGF (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 SAIRB

4/25/2013 SAIRB conditional approval letter for protocol and supporting materials

4/26/2013 Protocol revised and submitted to SAIRB

4/29/2013 SAIRB approval of revised protocol, consumer ICF, and occupational ICF

5/22/2013 SAIRB approval of translated test subject and recruiting documents

6/6/2013 Submission of SAIRB-approved protocol and supporting documents to EPA for October 2013 HSRB meeting (meeting subsequently canceled and rescheduled for 2014)

9/10/2013 EPA Science & Ethics Review of AEA07 design document and protocol

3/28/2014 Submission of Continuing Review form to SAIRB

4/8/2014 HSRB meeting and review of protocol

4/10/2014 SAIRB Continuing Review approval letter received

6/25/2014 HSRB Final Report of April public meeting

7/14/2014 Submission of updated AEA07 protocol (version, 7/14/14), ICF (English and Spanish, version 7/17/14), newspaper advertisements (print proof, on-line banner ad proof, and on-line splash page proof, English and Spanish), and Subject Qualification Worksheet (English and Spanish)

7/17/2014 SAIRB approval letter for updated protocol and ICFs

7/18/2014 SAIRB approval of English phone script, qualification worksheet, and print ad

7/21/2015 Study protocol signed by Study Director (study initiation date)

7/28/2014 SAIRB approval of Spanish translated ICFs and recruitment documents

7/27/2014 Newspaper recruiting advertisements started for consumer phase

8/4/2014 Test substance for the consumer phase arrived at Ricerca

8/6/2014 SAIRB approval of revised consumer ICF (version 8/6/2014), Protocol Amendments 1 and 2, radio ads and revised print ad

8/8/2014 Ran radio ad for one day; revised newspaper recruiting advertisement in News Herald through August 10

8/7/2014 Consent meetings held at Residence Inn, Mentor Ohio through August 9

8/11/2014 Consent meeting held at Quail Hollow Resort Hotel in Painesville, Ohio

8/13-17/2014 Consumer phase subject monitoring at Ricerca Biosciences LLC in Concord, Ohio

9/9/2014 Analysis of study samples initiated at Ricerca

9/19/2014 Submission of protocol deviations 1 and 2 and amendment 3 to SAIRB

9/22/2014 Submission of protocol amendment 4 to SAIRB

9/25/2014 SAIRB approval of amendments 3 and 4

9/30/2014 Submission of protocol amendment 5 to SAIRB

10/1/2014 SAIRB approval of amendment 5

10/30/2014 Submission of deviations 1 and 2 through SAIRB portal and acknowledgment

1/28/2015 Submission of amendment 6, revised occupational ICF (version 1/27/2015), revised test subject recruitment materials (dated 1/27/2015) to SAIRB

2/3/2015 SAIRB approval of amendment 6 and revised occupational ICF (version 2/3/2015)

2/4/2015 SAIRB approval of revised test subject recruitment materials,

2/6/2015 SAIRB approved Spanish translated ICF

2/6/2015 Submission of revised print ad (version 2/3/2015) to SAIRB

2/9/2015 SAIRB approval of revised print ad

2/12/2015 Submission of revised Spanish script and print ad (version 2/3/2015) and questionnaire to SAIRB

2/16/2015 SAIRB approval of revised Spanish telephone script, ad, and questionnaire

2/24/2015 Submission of radio scripts and audio files and on-line banner and splash page to SAIRB

2/24/2015 SAIRB approval of radio and internet ads

3/1/2015 Recruitment for occupational monitoring initiated

3/5/2015 Submission of amendments 7, 8, and 9, revised occupational ICF (version 3/5/2015), and additional radio scripts and audio files and revised print ad (dated 3/5/2015) to SAIRB

3/6/2015 SAIRB approval of amendments 7, 8, and 9; revised occupational ICF (version 3/6/2015); radio ad and revised print ad

3/9/2015 Submission of revised compensation form and change justification; revised Spanish print ad (dated 3/6/2015); amendments 10 and 11; and revised occupational ICF to SAIRB

3/9/2015 Periodic review reminder from SAIRB

3/11/2015 Submission of Continuing Review Report to SAIRB

3/12/2015 SAIRB approval of Spanish print ad; approval of amendments 10 (compensation adjustment) and 11, and revised occupational ICF (version 3/12/2015)

3/12/2015 Test substance for occupational monitoring arrived at Ricerca

3/13/2015 Submission of revised qualification worksheet (dated 3/13/2015) to SAIRB

3/13/2015 SAIRB approval of revised qualification worksheet

3/19/2015 SAIRB Continuing Review approval letter received

3/26/2015 Start of occupational phase test subject monitoring at Ricerca Biosciences LLC in Concord, Ohio (March 26 through April 1, 2015)

4/15/2015 Submission of deviation 3-6 and amendment 12 to SAIRB

4/16/2015 SAIRB approval of amendment 12

6/18/2015 Submission of amendments 13 and 14 to SAIRB

6/19/2015 SAIIB approval of amendments 13 and 14

7/28/2015 Analytical experimental completion date

2/15/2016 Periodic review reminder from SAIRB

2/15/2016 Submission of Continuing Review Report to SAIRB

2/16/2016 Additional information provided to SAIRB regarding Continuing Review

3/15/2016 SAIRB Re-approval letter received

4/11/2016 Submission of deviation 7 through 9 and amendments 15 and 16 to SAIRB

4/12/2016 Submission of noncompliance issue/deviation to SAIRB

4/12/2016 SAIRB approval of amendments 15 and 16

Attachment 3
§ 26.1303 Checklist for Completeness of Reports of Human Research Submitted for EPA Review

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

	Requirement		Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y N Y Y	Protocol and study submissions included these documents. Study included W24 incident report.
	§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	EPA received and passed onto HSRB minutes from IRB meeting 4/4/16 which were missing from original submission. EPA and HSRB also received rest of IRB correspondence.
	§1115(a)(3): Records of continuing review activities.		Y	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	Please see note above.
	§1115(a)(5): • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution		Y	EPA previously obtained this.
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		Y	See note above.
	§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)-(d)	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	
		(2) The measures proposed to minimize risks to the human subjects;	Y	
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	
		(5) The balance of risks and benefits of the proposed research.	Y	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	

Requirement		Y/N	Comments/Page References
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.	Y	
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research		Y	
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.		N/A	

Attachment 4 – List of Protocol Amendments

Excerpt from Study AEA07

13.1 Protocol Amendments

A total of 16 protocol amendments were generated for this study.

1. Amendment No. 1 allowed the use of radio ads to help with subject recruitment.

2. Amendment No. 2 modified the inclusion criteria for the consumer monitoring to allow people who did not own a swimming pool and who did not have experience with adding granules or powder products to a pool.

3. Amendment No. 3 changed the on-site medical professional from a nurse to a first responder; specified that the outer dosimeters needed to be prewashed before use in the study to remove interfering chemicals; specified that covering the air-sampling pump with a plastic bag to protect the pump from cyanuric acid residues was not necessary in the consumer monitoring phase; the order of sample collection was changed to hand wash, face/neck wipe, and then removal of the air-sampling pump; only one scoop, not two, were provided for the consumers to use; clarified that protocol amendments are reviewed by the IRB after they have been signed.

4. Amendment No. 4 removed the use of 25 pound buckets of powder from the consumer monitoring program and specified other containers to be used by the three affected MEs.

5. Amendment No. 5 clarified that the total amount of product to be handled, poured, and/or scooped listed in protocol Tables 6-9 are target amounts; removed the requirement to scoop from a 25 pound bucket in addition to pouring from two 4.5 pound jugs for residential ME 8 powder.

6. Amendment No. 6 added the 30 gallon fiber drum with a plastic liner as a source container to the occupational monitoring program; revised the product transfer procedure for the occupational monitoring program to include weighing product before adding it to the tank; added a second identical mix tank to be used in the occupational monitoring program to reduce down-time between MEs; provided an updated Safety Data Sheet for cyanuric acid; changed the inclusion criteria from being able to lift and pour up to two 40 lb buckets to being able to lift and pour up to four 25 lb buckets; changed field fortification from occurring every day of monitoring to every other day, starting on the first day of monitoring with a minimum of 3 sets to be collected.

7. Amendment No. 7 changed field fortification levels and added a mid-level spike to all matrices except the glass fiber filter during the occupational phase.

8. Amendment No. 8 changed the analytical principal investigator from Dan Keenan to Jim Formanik.

9. Amendment No. 9 expanded the inclusion criteria for the occupational phase to allow people

with occupational experience with dry chemicals, but not necessarily currently working in that position.

10. Amendment No. 10 increased the test subject compensation from $100 to $175.

11. Amendment No. 11 expanded the inclusion criteria for the occupational phase to allow employees or spouses of employees of companies represented in the Antimicrobial Exposure Assessment Task Force to participate in the study with specific enrollment safeguards as required by SAIRB.

12. Amendment No. 12 added another newspaper to use for recruitment ads.

13. Amendment No. 13 increased the LOQ for the face/neck wipes from 0.05 µg/sample to 1 µg/sample.

14. Amendment No. 14 increased the LOQ for the face/neck wipes again, from 1 µg/sample to 10 µg/sample.

15. Amendment No. 15 clarified that the extraction time for sample analysis was 4 hours, not one hour as stated in the analytical method; updated the contact information for the Study Director.

16. Amendment No. 16 corrected the report format requirements from PR 86-5 to the newer PR2011-3.

Attachment 5 – AEATF Chronology of Protocol Amendments

Note to HSRB: Please see separate PDF file provided for Attachment 5.

Attachment 6 – AEATF Documentation for Amendment Implementation Dates

Note to HSRB: Please see separate PDF file provided for Attachment 6.

Attachment 7

AEATF Communications with EPA on Amendment 4

Note: Signatures on last page were impacted by conversion from PDF to WORD versions.

September 26, 2014

Dear Tim and Kelly,

This is a follow up to the two emails sent from Tim Leighton on August 25 and 27 and an email from Kelly Sherman dated August 29, 2014. As discussed with Tim Leighton by phone on August 15, the scope of the pour solid study (AEA07) for consumer monitoring of powder products was changed to include only small and medium container sizes. The original study protocol prescribed four container types/sizes to be used for both the granular and powder formulations. These were based on commercially available containers of granular pool maintenance products and included a small (1 lb) plastic pouch, a small (1.75 lb) can, a medium (6 lb) handled jug, and a 6 gallon bucket containing 25 pounds. We made the assumption that powder biocides would also be sold in similar size containers. During the study the 25 lb buckets of powder were removed from the testing program. This decision was made following the observation of dust generated by two test subjects pouring powder from the 25 lb buckets, concern that none of the subjects had experience pouring large quantities of powder, and realization that powder packaged in 25 pound pails is not reflective of what is typically on the market for consumers. Switching to smaller containers was discussed with Tim Leighton on August 15, 2014, prior to implementation of protocol amendment 4. The three other subjects scheduled to pour from the 25 lb buckets were reassigned small containers to pour from and no further scooping from the 25 lb buckets was done.

All the available information supports the conclusion that antimicrobial products formulated as a powder are quite rare in the consumer market and those that do exist are in small packaging sizes. After extensive searching on the internet, the powder formulations found on-line are pool shock products packaged in up to one pound single-use plastic pouches. Of the member companies who responded to the AEATF 2012 survey on pour solid products, there were only two who reported selling consumer powder products (all were pool products) and these were packaged in small containers (2 oz packets and one pound pouches). One company sells a professional product to sanitize beer brewing equipment that could be used by beer brewing hobbyists; this is packaged in a 1.6 pound (25 oz) container.

The 25 pound container of pool chemical sold by Leslie's Poolmart Inc. that Tim Leighton provided a link to (http://www.lesliespool.com/leslies-power-powder-plus-25lbs-chlorine-shock-bucket/14183.htm) is actually a granular product, not a powder product. The Safety Data Sheet for Leslie's Power Powder Plus (manufactured by Axiall LLC) indicates in sections 1 and 9 that this product consists of granules, not powder (see attached). This was confirmed by the Leslie's corporate regulator manager in Phoenix, and we were told that the pail contains a scoop as the entire contents would not be used at once. No powder products packaged in 25 lb containers for consumer use have been located.

The scarcity of commercially available powder formulations for consumer use was noticed during protocol development and the monitoring of consumer pouring of powders was originally not included in the study design. After being requested by the Agency to include consumer powders, we made a

conservative assumption that the container sizes and types commercially available for granules would be the same as those for powders. After additional research we found that commercially available consumer powder biocides are limited to small container sizes. Protocol amendment 4 rectified this by removing the 25 pound pails. The product container sizes of powder monitored in the study were 0.5 lb plastic pouches, 1 lb cans, and 4.5 lb jugs. Subjects were randomly assigned between one and three containers to pour and two subjects scooped product in addition to pouring.

Even without the 25 pound containers in the consumer monitoring study, the remaining 16 test subjects handled between 0.5 pounds and 16 pounds, providing a range of active ingredient handled. This will allow us to estimate exposure over a range of use rates for a consumer product. The protocol included a third group of six MEs where the total amount of product handled ranged from 20 to 50 pounds. The purpose of this was to ensure detectable residues and to extend the range of chemical handled to test proportionality. This third group was effectively eliminated for the powder formulation by Amendment 4 which switched two subjects to handling one 0.5 lb pouch each, one subject to pouring a 1 lb can, and removed scooping from one subject who poured from two 4.5 lb jugs.

Until the sample analysis is complete, we cannot say whether the two individuals who poured from the 25 pound pails had higher than anticipated exposures or not. This will be accomplished by comparing these individual's exposure to that predicted using the dermal and inhalation unit exposures from the open pour mixer/loader wettable powder scenario in PHED. One subject (ME 15) poured the entire contents of two 25-pound pails while the other (ME 14) poured the contents of one 25 lb pail and then scooped approximately 15 lb from a second 25 pound pail.

Neither of the two subjects who poured from the 25 lb pails complained of irritation or any other adverse effect during or after their monitored task. ME 15 who poured two buckets was monitored on August 14; his activity took 2 minutes. ME 14 who poured one bucket and scooped from another was monitored on August 15; his activity took 5 minutes. Following their activity, each subject was walked back into the building with the study director and observer to the sample collection room where their hands and face were washed and samples collected. After they were dressed in their own clothes, the subjects spoke to the first responder who examined their hands and face for signs of irritation or redness before they left. No irritation, redness or other problem was noted for any test subject. At the start of his or her monitoring event, each test subject was instructed to call the toll-free number in the consent form if they experienced any problems after the study; in addition they were given the cell phone number of the Study Director so they could contact her immediately if there was an issue. No follow-up phone calls from any of the test subjects were received.

Protocol amendment 4 to remove the 25 pound containers of powder from the study and replace them with one pound containers was discussed with Schulman Associates IRB on September 22, 2014. According to the SAIRB there is no requirement to report higher than expected exposure/residues with the SAIRB since the anticipated exposures/residues are not stated in the protocol. It was confirmed that neither of the two test subjects who poured from the 25 lb pails complained of irritation or other adverse effects during or after pouring. Since this change involves reducing the amount of product

handled by the subjects, the SAIRB views this as making the study safer, which is considered a positive modification. The amendment was reviewed by SAIRB and has now been approved.

In conclusion, the AEATF believes that the study design was improved by removing the 25 lb buckets of powder from the study as they do not reflect a combination of container size and product form available to consumers. Reducing the amount of product handled by the test subjects also reduces the potential for exposure, thus improving the safety of the study. The range of product handled in this study covers the range of anticipated product that could be poured in a day by a consumer. The AEATF is cognizant that the data from this study cannot be used to support risk assessments for consumers pouring powder from 25 pound containers. Based on the information that the AEATF has regarding container sizes for powder biocides, this is not anticipated to be a problem.

Sincerely,

HS

Has Shah
Manager AEATF II

Leah Rosenheck
Study Director for Study AEA07

Attachment 8 – AEATF II Reported Deviations

Excerpt from AEA07 Study: Section 13.2 Protocol Deviations

The following deviations occurred during the conduct of this study:

1. No travel spikes for the inner dosimeters were done during set 1, consumer phase, as no solutions had been prepared.

2. The outer pant leg of ME 4 granular (consumer phase) on the left leg was cut too short and exposed approximately 4 inches of the inner dosimeter.

3. ME 3 granular (occupational phase) poured 8 kg of product, not 8 lb.

4. The temperature of the test substance storage was not monitored between receipt at Ricerca on 3/12/15 through 3/18/15; occupational monitoring ME 9 granular and ME 17 powder transferred product into the mix tanks using a scoop rather than pouring as that represented his typical work practice; the face/neck wipe sample for ME 15 powder (occupational phase) was collected before the hand wash to remove some product that had got onto his face.

5. No one-pound marks were made on the scoops used in the consumer phase as the scoops did not hold one pound; travel spikes during the occupational phase were done at the mid-level, not the high level, for the foam plugs.

6. Analytical phase method deviation – aliquots of the face/neck wipe extracts were not evaporated to dryness and reconstituted as directed by the method; instead aliquots were diluted with the internal standard solution and analyzed.

7. Analytical phase deviation – fortification aliquots were larger than the specified 1 ml for the high level hand wash and inner dosimeter field fortifications in the occupational monitoring phase due to the much higher concentration levels.

8. Analytical phase deviation – rather than analyzing the first set of field fortifications last, analysis of the field fortified samples was purposefully spread out to coincide with the analysis of the worker samples from the occupational monitoring.

9. Analytical method deviation – during the analysis of the occupational phase samples the face/neck wipe extracts were not evaporated to dryness and reconstituted as described in the method; instead the extracts were diluted with the internal standard and analyzed.

10. ME 9 occupational powder scooped from a 90-lb instead a 50-lb drum as stated in Amendment 6.

The deviations from the protocol had no impact on the integrity of the study.

13.3 SOP Deviations

The following deviations occurred during the conduct of this study:

1. (Ricerca SOP 00-C008) Calibration of the two balances used to weigh the empty (or partially empty) test substance containers was not done at the beginning of Day 2 (8/14/14) of consumer monitoring.

2. (SOP AEATF-II-8B.4) (a) The researcher did not always push up the sleeves of the subject's inner and outer dosimeters or change gloves between pushing up the cuffs of the outer dosimeter and the inner dosimeters prior to taking the hand wash sample. (SOP AEATF-II-8A.2) (b) The researcher did not changes gloves between sectioning the inner and outer dosimeters; (c) sample labels were placed on the plastic sample bag rather than on the aluminum foil containing the dosimeter section; (d) buttons were not removed from the inner and outer dosimeters since the extraction solution was water instead of a solvent.

The deviations from the SOPs had no impact on the integrity of the study.

Attachment 9 – Appendix H

Note to HSRB: Please see separate PDF file provided for Attachment 9.