



Ethics Assessment: AEATF II Solid Pour Study AEA07

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Recruitment

- Subjects were recruited through newspaper advertisements in 2 daily newspapers in Northern Ohio and 1 regional weekly English/Spanish publication
- Because of initial low response rate, newspaper ads were run for a second week and radio ads were also used based on an IRB-approved amendment
- For 2014 recruitment for the consumer phase, in order to increase the response rate, people who did not own a pool and/or had no prior experience with pool chemicals were allowed to participate, based on another IRB-approved amendment



Recruitment 2

- For 2015 recruitment for the occupational phase, in order to increase the response rate, people who had occupational experience handling solid chemicals but were not necessarily currently employed in that position were allowed to participate, based on an IRB-approved amendment
- A second amendment expanded the inclusion criteria to allow employees of task force (AEATF II) member companies to participate in the study
- Another amendment increased compensation for participating in the occupational phase to \$175



Recruitment 3

- Using the approved telephone screening scripts and taking into account IRB-approved protocol amendments, interested callers were interviewed by phone to determine if they met the inclusion criteria
- If subjects were interested and eligible, they were scheduled for an informed consent meeting
- Recruitment was consistent with the amended protocol
- Recruitment process was free of coercion or undue influence



Informed Consent Process

- Initial consent meetings were held with 1 to 3 potential subjects:
 - Study Director provided overview of study and asked subjects to read the consent form
 - After subjects read the consent form, Study Director read the consent form to group and answered questions
 - Study purpose, inclusion/exclusion criteria, and freedom to withdraw at any time were described in detail and subjects were encouraged to ask questions at any time
 - Label safety statements were explained and subjects were asked if they wanted to see the labels and/or Safety Data Sheets but they declined



Informed Consent Process 2

- If a potential subject met the inclusion/exclusion criteria and was still interested in enrolling, he/she met one-on-one with the study director or bilingual research associate
- ID was checked to verify identity and age
- During individual meetings, potential subjects were asked again if they had further questions; after answering questions, Study Director gave a short standardized oral comprehension test to ensure each subject understood what was being asked of them
- Subjects signed and dated the consent form, and completed and signed the Worker Qualification Worksheet



Informed Consent Process 3

- Each volunteer was given a copy of the consent form to take home and \$20 for attending the consent meeting
- The fact that the Study Director asked subjects, during the consent process, if they wanted to see the labels and/or safety data sheets was consistent with the safety precautions section of the protocol
- However, a different section of the protocol, page 752, states that potential volunteers will be given copies of the **safety data sheets and product labels**, in addition to the consent form and subject qualification worksheet



Informed Consent Process 4

- The protocol for study AEA07 provides inconsistent guidance on providing safety data sheets and labels to subjects
- **In the future, when reviewing protocols, the study sponsor and EPA should ensure that different 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”



Subject Demographics – Consumer Monitoring

- 20 subjects volunteered to participate
- 18 subjects (11 males, 7 females) were monitored and all met inclusion criteria
- 2 other subjects withdrew prior to their scheduled monitoring
- All subjects preferred to speak in English
- Subjects ranged in age from 19 to 75
- 15 of 18 subjects had 1-34 years experience using powder or granular products to maintain pools



Subject Demographics – Occupational Monitoring

- 20 subjects volunteered to participate
- 18 subjects (17 males, 1 female) were monitored
- All met inclusion criteria
- All subjects preferred to speak in English
- Subjects ranged in age from 22 to 62
- Experience working with powder and/or granular products ranged from 6 months to 30 years



Implementation of Monitoring Events Compared to Amended Protocol

- Implementation of monitoring events is discussed in different sections of study including:
 - Study design
 - Description of test site
 - Environmental monitoring
 - Role of researchers
 - Consumer monitoring
 - Conduct of monitoring events
 - Observations of subjects
 - Study conduct
 - Pouring parameters
 - Exposure monitoring
 - Procedures of MEs
 - Occupational monitoring
 - Environmental conditions



Implementation of Monitoring Events Compared to Amended Protocol 2

- EPA compared the aforementioned sections of the study to the amended protocol
- The monitoring events were conducted in substantial compliance with the amended protocol, with the exception of the reported and unreported deviations discussed later



Safety Precautions and Personal Protective Equipment (PPE)

- Study Director confirmed that safety precautions described in the study were implemented
- As described in Amendment 3, a nurse was not available, so the on-site medical professional was a certified first responder
- First responder implemented all activities assigned to the nurse, including examining hands and faces before the study for cuts, abrasions, skin conditions and checking for signs of dermal irritation after monitoring events



Safety Precautions and PPE 2

- Subjects were given safety glasses and dust masks to wear during pouring
- Subjects in occupational monitoring were also given new chemical-resistant nitrile gloves
- Dermal exposure was measured using inner whole body dosimeters (long underwear), outer dosimeters (long sleeved shirt/pants), hand washes, face/neck wipes
- Inhalation exposure was measured with personal inhalable particulate samplers attached to air-sampling pumps



Safety Precautions and PPE 3

- Study adhered to other risk mitigation measures referenced in protocol (in “risks to subjects” section) including:
 - Adhering to the estimated range of duration for subjects to handle containers during monitoring events (MEs)
 - Telling subjects to take breaks at their discretion, although none chose to do so
 - Closely observing subjects during MEs



Safety Precautions and PPE 4

- The observations section for consumer monitoring for the powder formulation and ME 14 notes that:
Subject 3 commented, before monitoring, that he doesn't use powders and the handling technique should be different due to smaller particles
- Study Director recommended to subject 3 that he not toss the powder across the pool. This deviates from protocol which states subjects will be allowed to handle containers as they normally do
- This deviation did not negatively impact the health and safety of the subject



Compensation

- The 18 test subjects who participated in the consumer monitoring phase in August 2014 were compensated \$100 each. Two subjects withdrew before their scheduled monitoring day
- All 20 test subjects who participated in the occupational monitoring phase, conducted during the spring of 2015, were compensated \$175 each
- Amendment 10 increased compensation for the occupational phase based on new information learned by the Study Director
- Each subject who attended a consent meeting was compensated \$20



Protocol Amendments

- AEATF II submitted 16 amendments to the overseeing IRB, Schulman IRB, which approved all of them
- Ten of the 16 amendments are discussed in OPP's ethics review because they are of ethical interest
- **Of these 10, OPP found one component of Amendment 3 to be problematic from an ethics standpoint**
- AEATF II has already agreed to a follow-up action to address it for the future



Protocol Amendments 2

- Part of Amendment 3 submitted to IRB states that:
“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.’”
- The stated reason for the change submitted to the IRB was:
“Protocol amendments are normally signed by the Study Director before they are sent to the IRB and thus already implemented.”



Protocol Amendments 3

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



Protocol Amendments 4

- “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.~~”
- The intent of the proposed revision was to eliminate the need for Schulman IRB to approve future amendments (which did not involve imminent hazard) prior to implementation.



Protocol Amendments 5

- 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.**



Protocol Amendments 6

- The overseeing IRB for study AEA07 is Schulman 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....”



Protocol Amendments 7

- Schulman IRB policy on amendments (on website) continued:

"...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.**



Protocol Amendments 8

- 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."
- **OPP 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.**



Protocol Amendments 9

- When study sponsors submit completed human research studies to the OPP, information pertaining to the ethical conduct of the research must be provided to EPA 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 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 OPP reviews the ethical conduct of the study.



Protocol Amendments 10

- In summary, in order for AEATF II 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 (OPP) believes that the language in the protocol on the amendment process as reviewed and approved by OPP and as reviewed by the HSRB should have been retained.



Protocol Amendments 11

- After reading the completed study, OPP explained its position to AEATF II in writing.
- With one exception, AEATF II 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 **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.



Protocol Amendments 12

- 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 OPP posed questions to AEATF II regarding the timing of implementing their protocol amendments, the Task Force provided a chronology of their AEA07 protocol amendments.
- This was provided to HSRB in Attachment 5 of EPA's ethics review and lists the IRB approval date of each amendment and the researcher's implementation date.



Timing of Implementation of Amendments 2

- Attachment 6 to the ethics review provides AEATF II's accompanying documentation 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 II 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 in EPA's ethics review. Amendment 12 was never implemented.



Timing of Implementation of Amendments 3

- 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" without stating when they must be reviewed.
- 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 to EPA's ethics review.



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).
- The rationale submitted to the IRB was that, “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.”
- However, when justifying the timing of amendment 4 to EPA in 2016, AEATF II stated 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.”



Amendment 4

- EPA does not agree that this situation falls within the category of eliminating an apparent “immediate” hazard to a research subject. 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 phase.
- The EPA agrees that switching to smaller containers reduced exposure to dusts and powder generated when handling the 25 pound pail during the consumer pouring phase.



Amendment 4

- Amendment 4 was submitted to the IRB on September 22, 2014, 38 calendar days after implementation so the IRB reporting timeframe was not met.
- 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 policy, which in this case was 10 days.



Amendment 11

- Due to recruitment challenges, 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 Reviewer in March 2015 to ensure OPP's support prior to submitting it to SAIRB.



Amendment 11

- 2 employees of AEATF member companies (W33 and W40) participated in the occupational monitoring phase. The facilities located in the monitoring area were regional manufacturing and/or R&D facilities, so the subjects did not even know the parent companies participated in AEATF II.
- As recommended by EPA and required by Schulman IRB, the following safeguards were implemented:
 1. Language was added to the consent form;
 2. Recruiting did not take place in the workplace;
 3. No managers were present during recruiting, the consent process or testing;
 4. Employers/managers were not notified of employees who responded to the ads or participated in the study;



Amendment 11

- As recommended by EPA and required by Schulman IRB, the following safeguards were implemented:
 5. Employees in the study were treated the same as other study participants;
 6. No study participants including employees were identified by name or any other way in the study report;
 7. Employment affiliation or company name was not recorded in the study raw data."
- This amendment did not negatively impact the rights or health and safety of participating subjects.



Amendment 15

- 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. The substance did not raise ethical issues.
- However, on April 12, 2016, Schulman IRB requested that the Study Director submit a non-compliance acknowledgement 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.”



Reported Deviations

- The reported deviations are included on pages 94-95 of study AEA07
- The reported deviations did not negatively impact the health and safety and/or rights of subjects



Unreported Deviations

- EPA identified 4 unreported deviations:
- During the conduct of the study, air temperature, relative humidity, wind speed and direction were recorded at 15 minute intervals, although the protocol states that air temperature and humidity will be documented at 5 minute intervals
- The Safety Precautions section of the protocol states that a copy of the label and Safety Data Sheet (SDS) will be made available to subjects upon request during the consent process. A different section of the protocol states the subjects will be provided with copies of the label and SDS.



Unreported Deviations 2

- 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.” Because the subjects were not provided copies of the Safety Data Sheets and product labels, this is a deviation.
- As noted earlier, the study observer assigned to subject 3 recommended that he not toss the powder across the pool; given that study staff are not supposed to influence how subjects use the product, this is a deviation
- Finally, the implementation of certain protocol amendments prior to IRB approval could be considered deviations at the time they were implemented



Reports of Dermal Irritation

- During occupational monitoring, as stated on page 65 of study AEA07:

“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.”



Reports of Dermal Irritation 2

- 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.”
- Under protocol Amendment 3, the on-site medical professional was a first responder. The amended protocol was followed in responding to the dermal irritation reported by subjects W30 and W35.



Reports of Dermal Irritation 3

- The Study Director confirmed: "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."
- The amended protocol was followed.



Summary of Subject W24 Incident

- Pages 65-66 of study AEA07 summarize subject W24's phone call and hospital visit after participating in **occupational** monitoring: "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." **Appendix H to the study provides the details.**



Guidance Relevant to Subject W24 Incident

- A section of EPA's ethics review discusses the guidance relevant to this incident which includes:
 - The "stop criteria and medical management" section of the protocol (on page 756 of the completed study);
 - Section 2.9 of AEATF SOP 11C, as well as AEATF SOP 11F;
 - The approved consent form, specifically the sections on risk and medical treatment for study-related illness or injuries; and
 - A primary point of reference for safety information in the protocol is the Safety Data Sheet (SDS) in Appendix B to the protocol, and the product labels referenced in the protocol and included on pages 783-784 of the completed study.
- OPP reviewed the aforementioned guidance and compared follow-up actions to the guidance. Before we present the results, let's review the role of subject W24.



Subject W24's Role in Occupational Monitoring

- Over a 2 minute period, Subject W24 poured a 25 pound bucket of the granular formulation of cyanuric acid (CYA) into a tank, and, over a 3 minute period, he poured three 25 pound buckets of the powder formulation into a tank, both while standing on the top step of a 13-inch stand.



PPE & Clothing worn During Occupational Monitoring

- During the occupational exposure monitoring phase of the study, as a study precaution and consistent with the protocol, all subjects wore:
- Two layers of clothing (long underwear under a long sleeved work shirt and long work pants), and
- Respiratory protection (N95 dust mask), 15 mil chemical-resistant nitrile gloves, and safety glasses.



Hospital Visit by Subject W24

- Appendix H states that, 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.”
- After Subject W24 spoke with the Study Director the morning after his participation in the study and told the SD that he was ill, the Study Director offered to take the subject to the ER and the subject accepted this offer. The Study Director and 2 members of the SD’s research team drove the subject to the ER, stayed with the subject until he was released, and drove him home.
- The Study Director shared the product’s Safety Data Sheet with the physicians in the ER and explained the subject’s involvement in the study.



Hospital Visit by Subject W24 - 2

- **The Safety Data Sheet, updated in 2014 and discussed in the approved protocol, was the Study Director's point of reference for symptoms.**
- The Safety Data Sheet (SDS) for cyanuric acid is on pages 814-825 of the study. As summarized in Appendix H: "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 CFR 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." (cont.)



Hospital Visit by Subject W24 -3

- The Safety Data Sheet states: "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.'"
- In Appendix H, the Study Director wrote, "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."
- The Study Director told EPA: "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."



Hospital Visit by Subject W24 - 4

- 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...**".



Hospital Visit by Subject W24 - 5

- 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.



Hospital Visit by Subject W24 - 6

- 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.”



Hospital Visit by Subject W24 - 7

- 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 required 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.



Hospital Visit by Subject W24 - 8

- 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."



Hospital Visit by Subject W24 - 9

- 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 or 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.”



Hospital Visit by Subject W24 - 10

- 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."



Hospital Visit by Subject W24 - 11

- **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 to 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.”



Hospital Visit by Subject W24 - 12

- 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.*]



Hospital Visit by Subject W24 - 13

- 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.



Hospital Visit by Subject W24 - 14

- 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 discussed in the ethics review, after consulting with Schulman IRB, the Study Director determined that the Subject W24 incident did not fit any of the IRB's reporting categories and as a result did not require formal reporting to the IRB.
- 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:



Hospital Visit by Subject W24 - 15

- 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.



Hospital Visit by Subject W24 - 16

- 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 as was the case here. 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.



Hospital Visit by Subject W24 - 17

- 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; this includes 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.



ME 9 Inclusion in Data Set

- Pages 83-84 of the study states, in part, the following with regard to ME 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...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.”



ME 9 Inclusion in Data Set 2

- Page 87 of the study adds that:

“The highest unit exposure... 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. ”

- **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.**



ME 9 Inclusion in Data Set 3

- 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 to be more 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 solely because of inexperience.**
- EPA does not intend to exclude the ME 9 data.



Responsiveness to EPA & HSRB Protocol Reviews

- Attachment 1 to EPA's ethics review provides AEATF II responses to EPA and HSRB comments on the protocol.
- **AEATF II was responsive to 10 of the 12 applicable comments from EPA and the HSRB on the protocol.** I'll briefly touch on the 2 comments that weren't addressed.
- EPA asked that the research-related injuries section of the consent form be revised to add skin reactions and respiratory reactions to the list of reactions for which subjects should seek medical attention and call the Study Director if they thought the symptoms were due to the study. This comment was addressed. The HSRB thought that the subjects should call the Study Director if they were experiencing symptoms regardless of whether or not the subject thought they were related to the study. AEATF did not think it was appropriate to advise subjects to seek medical treatment for symptoms unrelated to the study.



Responsiveness to EPA & HSRB Protocol Reviews 2

- Secondly, the protocol states that if two or more subjects develop an adverse skin reaction after leaving the test site, all subjects will be contacted by the Study Director to determine whether further medical management is appropriate. EPA asked that this sentence be expanded to include eye or respiratory irritation. The Task Force had agreed to address this comment but AEATF stated they inadvertently missed this change when making the other requested changes.
- The other 10 changes requested by the HSRB and EPA were incorporated into the revised materials. These changes are summarized on the next two slides.



Responsiveness to EPA & HSRB Protocol Reviews 3

Here's a summary list of the EPA and HSRB comments addressed in the revised protocol and support materials:

- ☑ Add skin conditions of the ***face/neck*** to the exclusion criteria listed in the protocol
- ☑ Revise residential monitoring consent form to reflect that subjects will wear a dust mask as a precaution
- ☑ Revise research-related injuries section of consent form to add skin reactions and respiratory reactions to the list of reactions for which subjects should seek medical attention and call the Study Director. Note: This section focuses solely on symptoms or injuries that the subject thought were related to the study
- ☑ Clarify inclusion criteria related to work experience/employment in advertisement



Responsiveness to EPA & HSRB Protocol Reviews 4

- ☑ Clarify the consent form language regarding PPE requirement
- ☑ Clarify what it means for subjects to be in “good health”
- ☑ In the risks and benefits section, revise the wording regarding risks from participating in the study
- ☑ Clarify whether hand washes will occur before subject drinks a beverage, if the subject requests one
- ☑ Clarify what’s intended by the on-site medical professional
- ☑ Researchers should complete a course in human subjects protection within 3 years of study initiation



Completeness of Documentation

- Schulman IRB submitted additional documentation at EPA's request
- With that additional information, the IRB correspondence records are complete
- Requirements of §26.1303 are satisfied



Substantive Acceptance Standards

- 40 CFR §26.1703
 - Prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children

- 40 CFR §26.1705
 - Prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 CFR 26

- FIFRA §12(a)(2)(P)
 - Makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent



EPA Recommended Follow-up Actions

- In EPA's ethics review, the Office of Pesticide Programs recommends that AEATF II take the following actions:
- With one exception, AEATF II 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.
- In the future, if AEATF II 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 IRB policy.



EPA Recommended Follow-up Actions 2

- In future studies, if an incident occurs, AEATF II 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.
- When implementing future AEATF II studies, it's important to follow the protocol with regard to the recording intervals for air temperature, relative humidity, wind speed and direction.



EPA Recommended Follow-up Actions 3

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



EPA Recommended Follow-up Actions 4

- 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.
- 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.



Findings

- All subjects were at least 18; pregnant or nursing women were excluded; all female subjects were tested for pregnancy
- Subjects were free to withdraw, as demonstrated by two subjects who withdrew prior to their monitoring day
- Protocol was amended when needed and implemented according to the amended protocol, with the exception of the reported and unreported deviations; these deviations as implemented did not compromise the safety or consent of subjects. EPA recommended follow-up actions.
- Subjects were informed and their consent was voluntary, without coercion or undue influence



Conclusion

- AEATF II agreed to implement the follow-up actions recommended by EPA
- Available information indicates that the AEATF II Solid Pour Study AEA07 was conducted in substantial compliance with subparts K and L of 40 CFR part 26



Charge Questions

Science

Did the research in study AEA07 generate scientifically reliable data, useful for assessing the exposure of occupational workers and consumers who manually pour or scoop solid formulation antimicrobial products?

Ethics

Does available information support a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26?