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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

*September 10, 2013*

**MEMORANDUM**

**SUBJECT:** Science and Ethics Review of AEATF II Solid Pour Scenario Design and Protocol for Exposure Monitoring

**FROM:** Timothy Leighton, Senior Scientist
Antimicrobials Division
Office of Pesticide Programs

Kelly Sherman, Human Research Ethics Review Officer
Office of the Director
Office of Pesticide Programs

Jonathan Cohen, Ph.D.
Statistician
ICF International (EPA Contractor)

**TO:** Steven Weiss, Chief
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division
Office of Pesticide Programs

We have reviewed the referenced proposal from both scientific and ethics perspectives. Scientific aspects of the proposed research are assessed in terms of the recommendations of the EPA Guidelines Series 875 and of the EPA Human Studies Review Board. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board. Below is a summary of the conclusions reached in our science and ethics reviews.

Science Review

- The protocol addresses the technical aspects of applicable exposure monitoring guidelines and is likely to produce scientifically valid and useful data.

- The following elements in the protocol require revision before the research goes forward:

    - The number of scoops and pours from the containers are not provided; only the range of the total amount of active ingredient handled (AaiH) in each subgrouping is specified in the protocol. Therefore, individual MEs have not yet been assigned AaiH. The AEATF II will need to assign specific AaiH, scoop sizes, and containers before proceeding with the research.

    - The protocol should be revised to specify that subjects in the consumer portion of the study are required to wear particulate dust masks to provide additional respiratory protection. The protocol currently states that subjects in the occupational portion will be required to wear dust masks but that subjects in the consumer portion will be "given the option" to wear one.

    - The AEATF-II should provide additional details about how the airflow in the indoor environment is oriented between the pouring of the solids and the test subject (e.g., is the airflow blowing powder in the direction of the test subject as they pour?).

- The AEATF-II will need to provide hand wash removal efficiency information, possibly a hand wash removal efficiency study, to allow EPA to correct for incomplete residue removal from the hand sampling.

- In future protocols, the AEATF-II is advised to provide detailed calculations about the anticipated risks from exposure to the test substance and the likelihood of occurrence of these risks. EPA performed these calculations in its review, but the AEATF-II should provide this type of information in future protocols.

<u>Ethics Review</u>

- The protocol meets the applicable ethical requirements of 40 CFR part 26, subparts K and L.

- Before the research is initiated, the documents should be revised as follows and resubmitted for review by the approving IRB:

    - Add skin conditions of the ***face/neck*** to the exclusion criteria listed in the protocol.

    - 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 7$^{th}$ paragraph in section 9D; this section currently only lists "adverse skin reaction" as a triggering event.]

- Revise the Residential Monitoring consent form to explain that subjects will need to wear a particulate dust mask as a safety precaution.

- 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 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.

- The AEATF should incorporate the forthcoming guidance from the HSRB about how to provide personal exposure results to subjects.

## A. Responsiveness to Previous EPA and HSRB Comments

| Applicable EPA and/or HSRB Comments from the October 2011 HSRB Meetings | Has the comment been addressed in this protocol? |
|---|---|
| 1. Identify the newspapers in which the recruiting advertisements will be placed. The AEATF is advised to place the advertisements in several newspapers targeting different demographic groups, to further the goal of minimizing bias and achieving as much diversity as possible among respondents and subjects | **Yes** |
| 2. Remove all generic references to "second alternate language" or "alternate language as appropriate to the area/population" and replace with "Spanish." | **Yes** |
| 3. Add a statement to the consent form that explains to subjects that if, within 24 hours of their participation in the study, they experience a skin or eye reaction or other symptom that they believe is related to their participation in the study, they should contact the Study Director. A telephone number should be provided. | **Yes** |
| 4. The AEATF should develop procedures for handling such a call and document those procedures in a new or existing SOP. | **Yes**. See section 2.9 in AEATF-II SOP-11.C.3 |

## B. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 6. All elements of required documentation are provided in the submitted protocol package.

Volume 1 of the submitted package includes the following supporting documents—all considered in this review:

- Transmittal Letter (p. 2)
- 40 CFR 26.1125 Checklist (pp. 7-8)
- Pour Solid Scenario: Study Design and Rationale (pp. 10-32)

Volume 2 of the submitted package includes the following documents:

- IIRB-approved protocol dated 4/26/13 (approved 4/29/13) (pp. 4-100)
- IIRB Approval Letter dated 4/29/13 and Supporting Documents (pp. 101-183)
    - English Language Occupational Monitoring Consent Form (approved 4/29/13) (p. 102)
    - English Language Residential Monitoring Consent Form (approved 4/29/13) (p. 113)
    - Spanish Language Occupational Monitoring Consent Form (approved 4/29/13) (p. 126)
    - Spanish Language Residential Monitoring Consent Form (approved 4/29/13) (p. 138)
    - English Language Recruitment Material (approved 5/1/13) (p. 152)
    - Spanish Language Recruitment Material (approved 5/1/13) (p. 163)
    - IRB approval letters (p. 176)

Volume 3 of the submitted package includes documentation of communications with IIRB, Inc. concerning the protocol.

Volume 4 of the submitted package includes the following documents:

- CVs and Ethics Training Records for Field Investigators (p. 3-24)
- AEATF II Standard Operating Procedures (SOPs) referenced in the AEA07 solid pour protocol.

## C. Summary Assessment of the Scenario Design

Supporting details are in Attachment 1.

1. **Scenario Design:** The EPA assesses potential occupational and consumer exposure from various antimicrobial products that are applied by a multitude of application techniques many of which require the pouring of a solid formulated product. AEATF II defines this solid open pour scenario as *"…the manual transfer by pouring or scooping of a solid formulation product from a source container into a receiving container. Solid formulations within this scenario are defined as formulations that can be poured, rather*

*than placed. Examples of a pourable solid formulation are powders, granules, small pellets, crystals, and flakes. They do not include larger solid formulations that are placed rather than poured, such as tablets, rods, sticks, gel discs, large pellets, and water-soluble packets."* (V1:13)[1] The size of the containers is not limited to those that can be manually lifted because the scenario includes not only physical pouring, but also the use of a scoop in larger (e.g., 100 pound) containers. The Super Sack containers (e.g., greater than 1000 pounds) are outside the scope of this proposal. The solid pour is subdivided into two separate solid formulations: pouring (or scooping) powders and pouring (scooping) granulars. Each of these formulations is further subdivided into subjects recruited from occupational (who will wear chemical resistant gloves) and residential populations (who will not wear gloves). In total, four distinct "scenarios" are proposed with 18 monitoring events (MEs) per scenario:

(1) Occupational pouring of granules (18 MEs with gloves)
(2) Occupational pouring of powders (18 MEs with gloves)
(3) Residential pouring of granules (18 MEs without gloves)
(4) Residential pouring of powders (18 MEs without gloves)

*"Each ME will consist of measuring potential dermal exposure (through use of inner and outer dosimeters and hand washes) and breathing zone air concentrations for a single subject working within a specified set of conditions. These conditions will characterize a pouring scenario with either a granular product or a powder product, and each ME is designed to represent potential exposures from a characteristic pouring task."* (V1:22)

EPA intends to use the data developed by the AEATF II for the solid pour scenario to describe a typical occupational and residential handler's daily exposure to solid antimicrobial formulated products while pouring or scooping. The data must be generic enough to be useful for estimating exposures using various size source (product) containers and types of receiving containers. EPA plans to use the data generated from the proposed solid pour study generically to estimate dermal and inhalation exposures, and ultimately risks, for other non volatile antimicrobial ingredients that are manually poured/scooped. When appropriate, EPA will combine the results from this proposed scenario with the results from different application scenarios (e.g., applying a disinfectant by mopping if the solution was prepared using a solid formulation) in order to assess the exposure from the overall use of these products. Typically solid formulations are poured into a system (e.g., pool/spa, material preservative in manufacturing, etc) rather then a solution to be subsequently applied.

Antimicrobial products have been grouped by EPA into the 12 Use Categories listed below as presented in the 158W data requirements. Although solid pouring of antimicrobial products may occur in many of the Use Categories noted below, most of

[1] This pagination convention is used throughout this review. "V1" refers Volume 1 (Study Design Document) of the AEATF-II submission; and "V2" (protocol) refers to Volume 2. Entries after the colon are page references; many page images bear more than one page number. In Volume 1, the cited page number is from the expression "Page n of 32" found at the bottom right-hand corner. Volume 2 page references are from the expression "Page n of 183" found at the bottom right-hand corner.

the solid formulations are expected to occur in Use Categories IV (pools & spas), VII, VIII, and XI.

| | |
|---|---|
| I | Agricultural premises and equipment |
| II | Food handling/storage establishments/premises and equipment |
| III | Commercial/institutional/industrial premises and equipment |
| IV | Residential and public access premises |
| V | Medical premises and equipment |
| VI | Human drinking water systems |
| VII | Material preservatives |
| VIII | Industrial processes |
| IX | Antifouling coatings |
| X | Wood preservatives |
| XI | Swimming pools |
| XII | Aquatic areas |

EPA believes that the AEATF II solid pour scenario is well defined (except scoop sizes and assignment of specific MEs to specific AaiH as discussed below), and we expect that the resulting data will meet the needs of EPA and other regulatory agencies. The diversity of daily exposures under the solid pour scenario as defined in this proposal will adequately describe a typical occupational and residential handler's daily exposure to the antimicrobial application. This exposure can then be extrapolated to the likely exposure expected from future pouring events of antimicrobial products.

2. **Sampling Design:** The AEATF II has described in detail their sampling design for the two solid pour scenarios and has incorporated random elements where feasible. The AEATF II proposes to monitor dermal and inhalation exposures using passive dosimetry techniques to measure exposure of human subjects during the manual pouring of solid formulations. The proposed sample size for each of the four scenarios is 18 monitoring events (MEs). The plan is to use 18 individual test subjects for the two occupational scenarios and 18 different test subjects for the two residential scenarios (i.e., the same 18 test subjects will be used in the occupational powder and granular scenarios, likewise for the residential scenarios). Each of the four scenarios will segregated into three groups delineated by the amount of active ingredient handled (AaiH). The sampling size is believed adequate to provide data to meet EPA's 3-fold relative accuracy goal as per the AEATF II Governing Document (2011). As discussed below, once the planned studies by the AEATF II have been completed, the sampling size of completed studies will be revisited.

   The solid pour test subjects for the occupational portion of the study will be recruited from professional applicators with no restriction as to a specific industry or years of experience. The solid pour test subjects for the residential portion of the study will be recruited from the general public that have lived in a home with a swimming pool (or lived in a home with a pool in the past 5 years) and have experience treating their pool with solid formulations. The study participants will pour or scoop the chemical from the product containers into receiving containers. The product containers will vary in size, ranging from 1 up to approximately 100 pounds (V1:17) as well as type (e.g., bags, cans,

pails, and drums (V2:36)). Note: V1:17 suggests up to 90 pound containers as opposed to approximately 100 pound containers (minor inconsistency). The subjects will be instructed to *"…pour the way they would normally pour"* (V1:23). The physical aspects of pouring and scooping include holding the product container, removing cap/lid and then manually pouring or scooping the contents into a receiving container.

Table 1 below summarizes range of AaiH for the 3 groupings within each of the four scenarios. The same study participants selected for the occupational granular scenario will be used a second time for the occupational powder scenario. Likewise, the same study participants selected for the residential granular will be used for the residential powder scenario.

Table 1. Range of AaiH Handled for Each Group within each of the 4 Scenarios.

| Group Number | Occupational (Gloves) (25, 50, 90 lb containers) | | | Residential (No Gloves) (1, 2, 6, 25 lb containers) | | |
|---|---|---|---|---|---|---|
| | Method | Scenarios | | Method | Scenarios | |
| | | Granules | Powders | | Granules | Powders |
| Group 1 | Scoop (n=6) | 5 to 20 lbs AI | 5 to 20 lbs AI | Pour (n=6) | 1 to 10 lbs AI | 1 to 10 lbs AI |
| Group 2 | Scoop (n=3) Pour & Scoop (n=3) | 20 to 50 lbs AI | 20 to 50 lbs AI | Pour (n=3) Pour & Scoop (n=3) | 10 to 30 lbs AI | 10 to 30 lbs AI |
| Group 3 | Scoop (n=3) Pour & Scoop (n=3) | 50 to 100 lbs AI | 50 to 100 lbs AI | Pour (n=3) Pour & Scoop (n=3) | 30 to 50 lbs AI | 30 to 50 lbs AI |
| Individual Scenarios | Combined | 5 to 100 lbs AI (n=18) | 5 to 100 lbs AI (n=18) | Combined | 1 to 50 lbs AI (n=18) | 1 to 50 lbs AI (n=18) |

Sources: V1:24 and V2:39

The AEATF II solid pour study is designed to be representative of the use of antimicrobials in the marketplace. There is a wide variety of uses of antimicrobial solid formulation products in the marketplace making this a difficult endeavor. Therefore, the study is designed to capture characteristics that will lead to the high end of potential exposure. The characteristics included in the design to monitor the high end of exposure include (V1:25-27):

- **Source container type and size** – an array of source container sizes were identified by the AEATF II during their 2012 survey of their membership and by what is available in the market place. The actual results of the survey are not reported in the protocol but the size source containers selected are reasonable. The size of the containers are 25, 50, 90 pounds for the occupational participants and 1, 2, 6, 25 pounds for the residential participants. The container types include bags, cans, pails, and drums (V2:37).
- **Receiving container type, size, and contents** – The receiving containers for the occupational portion of the study *"…will consist of a 100 to 200 gallon capacity cylindrical plastic tank … approximately 30 inches in diameter and 36 inches*

*above ground and will represent a loading tank. The tank will be approximately half full of circulating water and will have a hinged lid which will allow for an opening of about 15 inches through which the chemical will be added."* (V1:26) The receiving containers for the residential portion of the study will consist of *"…large plastic troughs (100 to 600 gallon capacity) or children's wading pools…*" to simulate pools (V1:27). A simulated deck will be constructed around the simulated pool.

- **Pouring weight** – Table 1 (above) reports the range of anticipated AaiH to be handled in each of the Groups. V2:35-39 provides the best description of the pouring weights. However, AaiH has not yet been assigned to the individual MEs.
- **Use or non-use of a scoop** – Individual MEs will be assigned to either pouring the solid formulation or a combination of both pouring and scooping (V1:25). V2:36 provides the number of MEs to be assigned within each Group to perform the procedures of pouring and scooping (e.g., granules, occupational, Group 2, 3 MEs pour only, and 3 MEs pour & scoop). The sizes of the scoops have not been determined as of the writing of the protocol.

Various aspects of the study design incorporate randomization. The following is the description of the random design elements as provided in the protocol submission:

- *"Containers within each source container group: the number and size of containers used by each test subject will be randomly assigned prior to the start of monitoring. For example in the group 1 for consumers, there may be two 1 lb packets. Depending on availability of the containers it is possible that the appearance and opening of two same size containers may be different. The actual selection will depend on what is available commercially for the active ingredient that is selected. A description of the containers used in each ME will be entered into the field trial notebook and described in the final report.*
- *Order of pouring ME: the order (i.e. which one is done first) of the granular use scenario and the powder use scenario will be selected randomly for each test subject to avoid a potential systematic bias of someone becoming more proficient with pouring.*
- *Method of product transfer: how the MEs will transfer the product (pour, scoop, or pre-dissolve in the case of the consumer monitoring) will be randomly determined and assigned to each ME prior to the start of monitoring.*
- *The final randomization will be to assign each study participant to a scenario. The timing of participation will be dictated by the random order of the set combination to which they are assigned, although modifications may be necessary based on test subject availability.*

*Further details of the randomization process will be provided in the protocol when the availability of specific containers has been determined and defined."* (V1:27-28 and V2:36-37)

*"All MEs for the occupational monitoring study will be conducted indoors in one geographic location. The testing facility will be Ricerca Biosciences LLC located in Concord, Ohio. The purpose in conducting these MEs indoors (in a warehouse-type facility) is to mimic the environment where these products are typically used. Since the vast majority of antimicrobial products formulated as granules and powders are used in occupational settings such as materials preservation, pulp and paper manufacturing, and pesticide manufacturing, conducting the study in an indoor industrial environment simulates typical use conditions."* (V1:28)

*"The monitoring of subjects pouring into swimming pools [residential] will be done outdoors at one test location during the time of year that pools are typically treated in northern Ohio (June through September). Although these products are used throughout the United States, where temperatures and humidity differ, the amount of time it takes to open the container and pour the granules is so short that conducting the study at multiple sites to capture the influence of weather is not deemed necessary. Environmental conditions, including wind speed and direction relative to the test subjects, will be monitored."* (V1:28-29)

**3. Choice of Surrogate Material:** Cyanuric acid (1,3,5-triazine-2,4,6-triol) (CYA) at a concentration of 100 percent *"…was chosen as the surrogate chemical for the monitoring program because of its low mammalian toxicity, lack of glove requirement, availably as a powder and a granule, availability in a variety of container types and sizes, widespread use by consumers as a pool maintenance chemical, low environmental toxicity, and existing analytical methods. …[CYA] will allow monitoring to be done both with and without protective gloves. Since it is not a biocide, it does not need to be registered by EPA and thus has no EPA registration number. …[CYA] is used in the same manner as pour solid biocides and it does not require the use of gloves. … It is widely marketed as a chlorine stabilizer for swimming pools by forming a weak bond with chlorine in the water and protects the chlorine from degradation by the sun's ultraviolet rays. Granular CYA is sold in retail stores and on-line by a variety of distributors in a number of different container types and sizes, ranging from small 1 lb plastic pouches to 32 oz plastic bottles to 25 lb plastic pails to 90 lb plastic drums. These container types and sizes are the same or very similar to the containers used for EPA registered biocide products."* (V1:29-30)

*"The powder form of CYA is not marketed commercially due to its propensity to absorb moisture over time and cake; however it will be used in this study to allow for the monitoring of consumers handling a powder formulation without the use of gloves and workers handling a powder formulation with the use of gloves. … The powder form of CYA will be produced and packaged into commercial containers by Occidental Chemical Company for use in this study."* (V1:30)

## C. Summary Assessment of the Scientific Aspects of the Study Design

Supporting details are in Attachment 2.

1. **Statistical design*:*** *"…the AEATF II is employing a base case design (Governing Document, 2011) that was agreed upon with the US EPA at the initiation of this study program. The generation of a new, relevant, high quality "base set" of data will fill this data gap identified by the EPA. It is anticipated in some cases that after the base case is collected no additional data collection will be necessary as the data will be sufficient to meet regulatory needs. In other situations, the task force, in consultation with regulatory agencies, may determine that additional data are required. At that point, more rigorous statistical methods outlined in the Governing Document may be applied. This is the preferred approach when there are little or no existing data to statistically define data objectives or when the existing data are of poor or limited quality."* (V1:23).

   *"For this particular scenario the AEATF II is creating three groups to increase diversity based on amount of active ingredient handled. Some scripted diversity in container sizes will be incorporated to ensure a range of product handled; however the range of container sizes will be dictated by what is available commercially for the chosen surrogate chemicals. In addition there will be scripted diversity in the loading techniques to ensure that both pouring and scooping are monitored. There will be three groups, with 6 MEs per group, per use pattern scenario resulting in a total of 18 MEs for each of the three use scenarios."* (V1:24)

   The Joint Regulatory Committee (JRC) comprised of Health Canada, CA Department of Pesticide Regulation, and the USEPA has reviewed several iterations of the AEATF II's study design and has offered various recommendations to the AEATF II in the development of their final proposal. The following are a few of the alternative considerations that were made during the JRC review of this final protocol:

   - **Consideration was given to stratifying the sample based on the active ingredient concentration instead of AaiH:**

     The JRC has selected AaiH as the normalization variable for the unit exposures, previous HSRB meetings have discussed obtaining the range of AaiH by using a range of AI concentrations. The JRC did not recommend this modification to this particular study design (Note: we are investigating a range of concentrations in another protocol design for a different exposure scenario) for solid pour for several reasons including: (1) the surrogate compound is not available in a wide range of concentration; (2) switching to a different surrogate compound may require the need for personal protective equipment for the residential scenario (e.g., gloves); and (3) if we stratified the sample based on percent active ingredient we would need to control the other variables (hold them fixed) to be able to analyze the effect concentration has on exposure. We do not know with high confidence what variables ultimately

drive exposure and many of these potential variables cannot be controlled (regulated) on pesticide labels. Within the marketplace a single pesticide label can be placed on any size container; but the container size itself is not usually regulated as an exposure mitigation option. It is important to include various size source containers in the sampling design that consumers may handle in the market place (along with bags and jugs). Therefore, the diversity of the variables selected by the AEATF II (e.g., range of source container sizes from 1 to 90 pounds; size and type of receiving container; use of scoops; etc) can be reasonably assumed by the JRC to provide a design that includes rough estimate of the high end of exposure.

- **Consideration was given to the use of gloves, or not, by the residential study participants:**

  The scenario for the occupational pouring of powders with the use of gloves was originally suggested to be used for consumer uses of powders too. The rationale provided by the AEATF was that most of the consumer use of powders is for pools/spas and those existing labels include gloves. However, risk assessments for consumers conducted by the JRC are based on no chemical resistant gloves regardless of the labeling for gloves (in some instances potential risks with and without gloves have been provided to risk managers). The assessments are done in this fashion because it is assumed that not all consumers will actually use the gloves (e.g., no enforcement, etc). If gloves do end up on the consumer label, it is there based on product labeling (i.e., acute tox studies such as dermal irritation, corrosive nature, etc.). The JRC recommended that the powder scenario be conducted with and without chemical resistant gloves. This recommendation has been incorporated.

- **Consideration was given to the experience level of the residential pool owners:**

  Initially one of the study participant selection criteria was to include a specific number of years of pool ownership/experience with pool chemicals. It was ultimately decided not to reject participants based on levels of experience and instead to allow for monitoring a test population with a range of experience.

2. **Proposed pattern of human exposure:** The AEATF II proposes to select study participants for the occupational scenario from individuals with experience pouring solid formulations as part of their job. *"To qualify for the occupational granule scenario and the occupational powder scenario, individuals with occupational experience pouring granular or powder formulations as part of their job will be recruited. Because pour solid formulations are not as prevalent as liquid formulations and due to the majority of them having a high percentage of active ingredient and being corrosive or acutely toxic, some skill is needed to properly handle and load them. Only people experienced with handling pour solid*

*formulations will be recruited. However, to ensure that workers with a range of experience are recruited, no minimum months or years of experience will be specified. Since no differences in solid pouring techniques are expected as a function of the specific industry or occupational setting, no particular industry will be targeted during the recruitment. However, based on where the majority of granular and powder antimicrobial products are used, it is anticipated that the majority of workers with this skill will be from the manufacturing (textiles, pulp and paper treatment, paint), cooling tower, and water treatment industries because they use antimicrobial products frequently in these industries."* (V1:29)

The selection of study participants for the residential portion of the study includes the consideration of the following*: "To participate in the residential pouring scenario, prospective subjects must live (or have lived within the past 5 years) in a home with a swimming pool and must have experience using granular or powder chemicals to treat and maintain their pools. There are a wide range of pool chemicals formulated as granules and available to the consumer which should allow for a large sampling population."* (V1:29)

The physical aspects of pouring include...*"Consumer products may be poured or scooped and broadcast from a standing position, a bent position, or a kneeling position. Typically labels recommend adding product to the deep end of the pool while walking to ensure dispersion. Some products specify the use of a bucket to dissolve the product before adding it to the pool. Less variation in pouring positions are expected in occupational settings where product is transferred from a bucket, box, or drum to a tank or vat."* (V1:16)

The duration of pouring will be based on how long it takes each study participant to pour the prescribed amount as instructed. Although there is no prescribed duration, *"...handling the test chemical is expected to be between 6 to 40 minutes..."* (V2:48) The study researchers will instruct the study participants to *"pour the way they would normally pour"* (V1:32).

Step-wise descriptions of the interactions of the study researchers and participants (e.g., source container placement, instructions on how much to pour, etc) and sample collection (e.g., private changing area, etc) are described in V2:50-55.

Although the study researchers plan to measure the air exchange rates for the indoors portion of the study (i.e., occupational pouring), additional considerations need to be accounted for as per the HSRB comments on the previous liquid pour study. The HSRB's written comments on the liquid pour study concerning the ventilation indicated: *"... the focus of interest in ventilation should be on the local air flow between the pouring operation (the source of exposure) and the handler." Further, the Board suggested that "...at the very least, that pattern should be measured before and/or after exposures and the orientation between the source and each handler should be documented for each ME. Alternatively, the room's setup and the orientation between the source and handler could be varied (e.g., rotated 90°) either*

*within or among MEs" (HSRB, October 2011 Meeting Report, 11).*" The Board's comment was made so that users of the data would be able "*…to evaluate the potential for a consistent airflow direction or orientation to have caused the average inhalation route to be either higher or lower than would have been caused by random or variable airflows."*

The EPA believes that the AEATF II solid pour study will represent typical worker and/or consumer methods of pouring granules and powders from source containers. The selection of occupational and residential subjects, test materials, source container sizes, receiving containers, and associated activities (e.g., use of a scoop) as described in the protocol is justified.

3. **Endpoints and Measures:** The AEATF II proposes to measure dermal and inhalation exposures resulting from manually pouring granules and powder formulations. Dermal and inhalation exposure will be measured using whole-body dosimeters (WBD) (inner and outer), hand and face washes, and personal air monitors (V2:52-55). For the WBD, the Agencies are most interested in the inner dosimeters to assess potential exposure. The outer dosimeters will add to the existing data base on the development of protection factors for single layer of clothing. The potential for foot exposure is minimal and the feet will not be monitored. The hand and face wash is an appropriate method to determine exposure to the hands and face. The personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). A SKC Inc. IOM inhalable particulate sampler will be used to trap and measure particulates up to 100 um along with respirable particles of 4 um or less. Flow rates will be approximately 2 L/min (SOP AEATF II-8D).

   *"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. 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 exchange rate. 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."* (V2:56)

4. **QA/QC Plan:** The study will be conducted under the FIFRA GLP Standards (40CFR160) (V2:67). The AEATF II QA/QC plan for the solid pour study is described in sufficient detail and is adequate to ensure that the measurements are accurate and reliable. The QA/QC plan includes field recovery analyses, storage stability studies, and break-through analyses of the air samplers. Method validation results should be included in the final study report as per AEATF II SOP 9I (V4:121).

Primary components of the field recovery analyses include (V2:57-59): samples to be fortified every other day of monitoring; two fortification levels per matrix with the low level 3 to 4x the LOQ (V2:58), triplicate samples per fortification level (V2:58), fortified samples exposed to ambient conditions for the maximum duration of exposure, and WBD not covered during exposure duration. Field recovery samples will be fortified in the "field" and stored in the same was as the actual study samples, and will be analyzed concurrently with the actual exposure samples. Correction for loss in field recoveries will correct for all phases of potential losses.

5. **Statistical Analysis Plan:** The results of monitoring data will be provided in the final report. The AEATF II will not statistically analyze the monitoring data. The EPA proposed statistical model for these data differs from the mixed effects modeling used for the earlier mop and wipe studies, and instead will be similar to the models used for the liquid pour study, because the group variable represents a fixed effect rather than a random effect. In the mop and wipe studies, the location/building/room was treated as a random effect variable since the clusters can be assumed to have been randomly selected from a large universe of potential location/building/room combinations and we can represent this source of variability as a random effect. For this solid pour study, each group consists of a small set of container sizes and the three groups should not be regarded as having being selected from a large universe of possible container size groups. Instead we regard each group as providing its own intercept to the exposure equation. Statistically this is modeled using simple linear regression with dummy variables for each of the three groups, or, equivalently, as a one-way analysis of variance model. Assuming the normalized exposure is a sum of the group intercepts and a random error, the fitted model will be used to estimate the arithmetic means, geometric means, and $95^{th}$ percentiles of the normalized exposure for each group, together with bootstrap confidence intervals. The bootstrap confidence intervals will be used to assess the fold relative accuracy against a goal of 3-fold relative accuracy. Another crucial statistical test will be to test whether the group intercepts are statistically significantly different. We will also investigate alternative models where the groups can have different variances. It will also be important to test the proportionality assumption against independence by assuming that the logarithm of exposure is the sum of the group intercept, the slope multiplied by the logarithm of the amount of active ingredient, plus the error term; confidence intervals for the slope will be used to determine if the slope is significantly different from 1 (proportionality) or from 0 (independence). The statistical analysis plan also includes the development of summary tables of the data, and various graphs of the data including exposure plotted against the amount of active ingredient showing the fitted regression models and the different size groups, and Q-Q plots of the residuals (to assess the lognormality assumption) and of the studentized residuals (to assess the model performance of the final model).

## D. Compliance with Applicable Scientific Standards

This protocol adequately addresses the following elements according to applicable scientific standards:

- Scientific objective
- Experimental design for achieving objectives
- Quantification of the test materials
- Data collection, compilation and summary of test results
- Justification for selection of test substance and dilution rate
- Justification for sample size
- Fortification levels and number of samples for laboratory, field, and storage stability samples

Additionally, the AEATF II has addressed the technical aspects provided in the applicable exposure monitoring guidelines (i.e. Series 875 Group A and OECD Applicator Guidelines) as well as Good Laboratory Practices (GLPs).

**Recommendations:**

EPA recommends that the study researchers provide additional details about how the airflow is oriented between the pouring and the test subject within the indoor environment (e.g., is the airflow in the room blowing the powder into the test subject, or away from the test subject?) before the research goes forward.

Although the estimated inhalation risks do not indicate a risk of concern, EPA still believes it to be prudent for the researchers to require that the consumer test subjects wear respiratory protection (e.g., N95 respirator) as was done in previous AEATF II exposure studies. The protocol already specifies that occupational test subjects will be required to wear respiratory protection.

It is also noted that the number of scoops (and size) and pours from the containers as well as the individual assignment of AaiH for each ME are not provided; only the range of the total amount of active ingredient in each Group is reported. The AEATF II has indicated that these items will be assigned once the containers and scoops are purchased (availability issues).

The AEATF-II will need to provide hand wash removal efficiency information, possibly a hand wash removal efficiency study, to allow EPA to correct for incomplete residue removal from the hand sampling.

In future protocols, the AEATF-II is advised to provide detailed calculations about the anticipated risks from exposure to the test substance and the likelihood of occurrence of these risks. EPA performed these calculations in its review, but the AEATF-II should provide this type of information in future protocols

## E. Summary Assessment of Ethical Aspects of the Proposed Research

Supporting details are in Attachment 2.

1. **Societal Value of Proposed Research:** The purpose of the proposed monitoring study is to determine potential dermal and inhalation exposures to occupational workers and consumers associated with the manual pouring of solid formulation antimicrobial products (granules and powders). Because many consumers and workers pour granule or powder formulations of antimicrobial products, the research question is important; it cannot be answered with confidence without new monitoring data meeting contemporary standards of quality and reliability.

2. **Subject Selection:** Forty adult subjects will be recruited from the Concord, Ohio and Lake County, Ohio area – 20 for the "occupational" portion of the study and 20 for the "consumer" portion of the study. Participants will self-identify in response to newspaper advertisements in three different newspapers, including a Spanish-language paper (the News-Herald of Northern Ohio, the Star Beacon, and Hola Today). Callers responding to the newspaper advertisements will be screened, scheduled for informed consent meetings, and enrolled.

   While it is possible that people who respond to the advertisements are different in some unknowable ways from those who do not respond, there is no reason to think that respondents in the Concord/Lake County, Ohio area are not typical of people who would respond to these types of advertisements in other areas of the United States. Placing advertisements in three newspapers with different circulations furthers the goal of minimizing bias and achieving as much diversity as possible among respondents and subjects.

   For the occupational portion of the study, the researchers will recruit subjects who are currently employed in a position where they handle and pour powder or granular formulated chemicals. For the consumer portion of the study, the researchers will recruit subjects who currently live or have lived within the past five years in a home with a pool and who have experience handling and pouring powder or granular formulated pool maintenance chemicals. To ensure that people with a range of experience are included in the study, no minimum amount of experience is required.

   The inclusion/exclusion criteria are complete and appropriate except that "skin conditions on the face/neck" should be added to the list of exclusions. Pregnant or nursing women are excluded from participation. Employees or relatives of employees of the investigators, of any of the companies that are members of the AEATF-II task force, or of the American Chemistry Council are also excluded from participation.

   No potential subjects are from a vulnerable population. Recruitment materials and interactions with potential subjects will be conducted in English or Spanish, depending on subject preference. Subjects will be recruited through newspaper

advertisements, not through employers, which will minimize the potential for coercion or undue influence.

3. **Risks to Subjects:** The proposed test material is of low toxicity to mammals and will be used in a manner that is consistent with its normal use as a chlorine stabilizer. Risks to subjects include the risk of a reaction to the test material or the soapy mixture that will be used to wash the hands and face/neck; the risk of discomfort and possibly heat-related illness associated with wearing two layers of clothing while doing physically demanding work; the risk of discomfort or inconvenience from wearing the air sampling device; the risk of embarrassment from undressing in the presence of a research technician; and the risk of an unexpected result of pregnancy testing. All identified risks are characterized as of low probability.

   Risks are minimized by exclusion of candidates known to be allergic or sensitive to chemical-based products particularly cyanuric acid and soaps, in poor health, or with broken skin on hands or face/neck; alerting subjects to signs and symptoms of heat stress; monitoring heat index with associated stopping rules; allowing subjects to rest whenever they want or need to; medical professional on-site observing the subjects; incorporation of procedures to keep the results of pregnancy testing private and to permit discrete withdrawal; private changing area; provision of appropriate protective clothing and personal protective equipment (eye protection and respiratory protection for all subjects; and chemical-resistant gloves for subjects in the occupational portion of the study).

4. **Benefits:** This research offers no direct benefits to the subjects. The principal benefit of this research is likely to be reliable data about the dermal and inhalation exposure of people pouring solid formulations of antimicrobial products. These data are intended to be used by EPA and other regulatory agencies to support exposure assessments for a wide variety of antimicrobial products and their uses.

5. **Risk/Benefit Balance:** Risks to subjects have been thoughtfully and thoroughly minimized in the design of the research. The low residual risk is reasonable, in light of the likely benefits to society from new data supporting more accurate exposure assessments for antimicrobial products.

6. **Independent Ethics Review:** The proposed research has been reviewed and approved by the Schulman Associates IRB. The submitted materials include a full record of correspondence between the investigators and the IRB.

7. **Informed Consent:** Informed consent will be obtained from each prospective subject and appropriately documented in the language preferred by the subject. Literacy in English or Spanish is a requirement for inclusion in the study.

   All written recruitment, consent, and risk communication materials will be available in both English and Spanish. In order to ensure effective communication and thorough comprehension by anyone preferring Spanish over English, a Spanish-

speaking member of the research team will be present at the meetings at which candidates are qualified and sign consent forms.

8. **Respect for Subjects:** Subject-identifying information will be recorded only once; all subsequent data records and reports will refer to individual subjects only by an arbitrary code. Provision is made for discrete handling of the pregnancy testing that is required of female subjects on the day of testing. Candidates and subjects will be repeatedly informed that they are free to decline to participate or to withdraw at any time for any reason, without penalty.

## F. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

A detailed evaluation of how this proposal addresses applicable standards of ethical conduct is included in Attachments 2-5 to this review.

**EPA Ethics Comments**

Before the research is conducted, the documents should be revised as follows and resubmitted for review by the approving IRB:

- Add skin conditions of the ***face/neck*** to the exclusion criteria listed in the protocol.

- 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.]

- Revise the Residential Monitoring consent form to explain that subjects will need to wear a particulate dust mask as a safety precaution.

- 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 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 the requirement clear.

The AEATF should incorporate the forthcoming guidance from the HSRB about how to provide personal exposure results to subjects.

**EPA Ethics Conclusions**

40 CFR 26 Subpart L, at §26.1703, as amended effective April 15, 2013, provides in pertinent part:

> EPA must not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

The protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA to rely on a study executed according to this protocol.

If the comments noted above are addressed and the amended protocol is approved by the overseeing IRB, this research should meet the ethical standards of FIFRA §12(a)(2)(P) and 40 CFR 26 subparts K and L.

Attachments:

1. Summary Review of AEATF II Solid Pour Scenario Design dated June 6, 2013
2. Summary Review of AEATF II Protocol AEA07 dated June 6, 2013
3. §26.1111 Criteria for IRB approval of research
4. §26.1116 General requirements for informed consent
5. §26.1117 Documentation of informed consent
6. §26.1125 Criteria for Completeness of Proposals for Human Research

**EPA Scenario Review: AEATF-II Solid Pour Scenario/Protocol**

**Title:** **SOLID POUR SCENARIO: RATIONALE FOR STUDY DESIGN**
(AEATF-II Volumes I and II)

**Date:** June 6, 2013

**Sponsor:** American Chemistry Council
Antimicrobial Exposure Assessment Task Force II
c/o Hasmukh Shah, Ph.D.
1300 Wilson Blvd
Arlington VA 22209

## 1. Scope of Scenario Design

### (a) Is the scenario adequately defined?

*"The objective of this study is to obtain a diverse set of pouring task conditions based on a number of potential variables when a solid antimicrobial is poured in order to capture the diversity of pouring situations across all consumer and occupational uses. The number of combinations of variables makes it impractical to create candidate MEs corresponding to every possible pouring situation. A more pragmatic approach is to consider a reasonable set of candidate conditions based on characteristic configurations common to solid pouring task characteristics."* (V1:16) The AEATF II solid pour design appropriately proposes to diversify the sampling characteristics by selecting various source container types (bags, cans, pails, and drums (V2:36)) and sizes; receiving container types; height of pouring; pouring amount; and the use or non-use of a scoop (V1:16-19).

Preliminary versions of the AEATF II solid pour study protocol have been reviewed by EPA, PMRA, and CDPR to determine the appropriate study design to assess exposure as accurately as possible, while ensuring that any uncertainty does not underestimate exposure. Antimicrobial products that are in a solid form can be formulated as granules, powders, crystals, flakes, pellets, tablets, rods, sticks, etc and packaged in different size containers. The solid pour formulations in this study are limited to those that can be poured, rather than placed (e.g., rods). Of the solid formulations that can be poured, this study will measure exposure to powders and granules.

*"Pouring and scooping solid formulations in commercial, industrial, and residential settings is quite diverse, especially with respect to the conditions impacting biocide exposure to individuals. A major difference between the occupational, commercial, and industrial uses and residential use of these products is that the occupational use occurs primarily indoors, in manufacturing facilities. The vast majority of residential pour solid products are pool and spa chemicals which means that they are most frequently used outdoors (indoor pools exist, but are outnumbered by outdoor pools). Another key*

*difference between occupational and residential use is the size of containers, with larger containers (25 lbs and up) used in occupational settings and smaller containers (1 lb to 20 lbs) sold into the consumer market. In industrial settings with manual chemical loading, a scoop may be used when product is packaged in a large box or drum. The amount of chemical handled on a daily or weekly basis is likely to be different when comparing residential use to occupational use."* (V1:6)

**(b) Is there a need for the data? Will it fill an important gap in understanding?**

*"Some pour solid data do exist in both the Pesticide Handlers Exposure Database (PHED) database as well as the Chemical Manufacturers Association (CMA – now the American Chemistry Council - ACC) data set. However, these data have only limited relevance to the pouring of antimicrobial products and often have poor quality from an analytical standpoint (e.g. poor recovery rates and high detection levels). The largest set of exposure monitoring data for the pour solid scenario currently available comes from PHED (EPA, 1998). The pour solid formulation types available in PHED are powders, granules, and dry flowables (also known as water dispersible granules). However, these data are based on the mixing and loading of agricultural pesticide formulations and do not necessarily represent antimicrobial formulations or how pour solid antimicrobials are typically used. For example, a key difference between agricultural granules and antimicrobial granules is that agricultural granules are designed to be applied dry, directly to the soil surface – they are not mixed with water. Agricultural granules are made up of carrier particles (such as clay, corn cob, or sand) to which the active ingredient is sorbed. This contrasts with antimicrobial granules which, with very few exceptions, are designed to be added to water (i.e. swimming pool) or some other liquid process such as paint or polymer and thus do not contain an inert carrier. In addition, all the mixing/loading data in PHED was generated outdoors since product was being transferred to agricultural spray tanks; this does not reflect the indoor environment where the majority of pour solid antimicrobial formulations which are used.*

*Another key difference is that agricultural granules and powders typically contain low concentrations of active ingredients (for example Bolero® Ultramax Herbicide is a granular herbicide containing 15% thiobencarb) while solid antimicrobials contain a much higher percent active ingredient (for example BOWCIL™ 150 Antimicrobial is a powder formulation containing 96% cis-CTAC and Fungaflor 75 WSG is a water soluble granule for postharvest treatment of citrus fruit containing 100% imidazole sulfate) As such, the existing PHED data poorly reflect products and loading methods used for antimicrobial products.*

*In addition to the poor quality of the exposure data currently available, the agricultural pour solid formulations do not match those used in the antimicrobial industry. Because of these key differences in the formulations, a new set of pour solid exposure data generated using antimicrobial-containing products is needed.*" (V1:9)

Based on the PHED and CMA data limitations, the Antimicrobial Division is requiring dermal and inhalation exposure data in many of its assessments to fill this data gap for solid pouring.

**2. Rationale for Scenario Sampling Design**

**(a) Are the variables in the solid pour scenario designs likely to capture diverse exposures at the high-end?**

The design choices in the four solid pour scenarios to provide diversity in sampling include (1) source container type and size; (2) receiving container type, size, and contents; (3) height of pouring; (4) pouring amount; (5) transfer process of pouring and scooping; and (6) using different workers/consumers for each monitoring event within a scenario (the same worker/consumer will complete a ME for both occupational granule and powder and for both consumer granule and powder and these four scenarios will be represented by their unique unit exposure (UE)). Additional descriptions of these key variables are provided:

**Source Containers.** Source containers for the occupational scenarios will be 25 lb pail and 50 and 90 lb drums. For the consumer scenarios the containers will be 1 lb cans, 2 and 6 lb cans, and 25 lb pails. (V2:36)

**Receiving Containers.** *"There are a variety of possible characteristics of receiving containers into which a person could pour an antimicrobial product. However, for the most part, pour solid products used in occupational settings are being added to tanks or vats at the beginning of an industrial process. In order to simulate this for the occupational scenarios, the receiving containers used in this study will consist of a 100 to 200 gallon capacity cylindrical plastic tank. The dimensions of the tank will be approximately 30 inches in diameter and 36 inches above ground and will represent a loading tank. The tank will be approximately half full of circulating water and will have a hinged lid which will allow for an opening of about 15 inches through which the chemical will be added. This design was chosen to characterize how product is typically used in occupational situations.*

*This will also represent loading systems where sanitizers are used in commercial and industrial food handling establishments. For this use pattern, two scoops of product is typically added to a wide, open top tank at waist height where water is being recirculated through jet type nozzles at the bottom of the tank, pointing across the bottom of the tank. The use of the cylindrical tank containing water as the receiving container will simulate the typical use pattern associated with the manufacturing and industrial uses of pour solid biocide formulations.*

*To simulate the treatment of swimming pools for the consumer pouring of granules and powders, large plastic troughs (100 to 600 gallon capacity) or children's wading pools will be used. To further simulate a homeowner pouring into an in-ground pool, a deck will be constructed so that the lip of the pool or trough will be flush with the*

*walking surface. This will maximize the distance between the subject and the pool. The pool(s) or troughs will contain water in order to mimic the actual recreational water treating process, and subjects will follow label directions which normally recommend that product be dispersed along the deep end of the pool. In order to simulate use directions for certain granular and powder products and to achieve diversity in pouring techniques, some subjects will pre-dissolve product in buckets while others will pour directly from containers or scoop product into the pools."* (V1:17-18)

**Height of Pouring.** The height at which the workers will pour is based on the simulated 36 inch tall receiving container versus the height of the test subject. For the consumers pouring into the simulated pool, a simulated deck will be included to have the subject pour into the receiving container at a floor level.

**Pouring Amount.** The amount (weight) of solid poured will be based on 3 Groups (V1:15). Table 1 above illustrates the amount of active ingredient to be poured in each Group. In summary, occupational granules & powders: Group 1 will handle between 5 and 20 lbs; Group 2 will handle between 20 and 50 lbs; and Group 3 will handle between 50 and 100 lbs. Likewise, consumers will handle: Group 1, 1 to 10 lbs; Group 2, 10 to 30 lbs; and Group 3, 30 to 50 lbs.

**Transfer Process.** *"When product is scooped, rather than poured, from a container, a scoop of pre-defined volume will be used. Several different scoops will be purchased for the study so that the appropriate sized scoop can be used relative to the amount that needs to be transferred. Use of volumetric measuring devices is consistent with the use instructions on consumer and many professional product labels."* (V1:18)

**(b) How have random elements been incorporated into the scenario sampling design?**

Random elements have been incorporated into the design as follows:

- Number and size of source containers will be randomly assigned to each participant in all four scenarios (V1:18 and V2:34-35)
- The pre-dissolving of the granules and powders for the consumer scenarios will be randomly assigned to participants. (V2:35)
- The order of the granules versus powder scenarios for each study participant will be randomly selected (e.g., the same participant will pour an occupational powder and an occupational granule, the order in which they pour will be randomly selected). (V1:19)
- The transfer by scoop or pour will be randomly assigned to study participants. (V1:19)
- Study participants will be assigned as follows: *"A total of 40 subjects will be recruited for this study. Twenty subjects will be recruited for the occupational phase and twenty will be recruited for the consumer phase. Each subject will be assigned a unique identification number starting at AEA07-01 and ending*

*with AEA07-40. The people in the occupational monitoring will be designated by placing the letter "OC" after their identification number. The subjects in the consumer monitoring group will have the letter "CN" after their identification number. The subject numbers for each group will be randomized using a research randomizer program accessible at the following internet website: http://randomizer.org. The first 18 numbers in the generated randomized list for each group will determine the participating subjects, while the two remaining subjects will be held as alternates. The alternate subjects will be on-call for the duration of the study. Alternates will get compensated as if they participated in the study.*

*Each subject will be randomly assigned to one of the three AI handled groups for powder and for granules. Randomly assigning subjects to each group means that they may not necessarily be handling the same amount of chemical.*

*For purposes of assigning subject numbers to AI handled groups during the study, the following table will be used. Based on the randomly assigned subject identification number, each subject will be assigned to one of the three AI handled groups for each type of solid formulation (powder and granular). Note that that each participant will be assigned to two randomly selected subject identification numbers, one for pouring powders and one for pouring granules. The randomly selected subject identification numbers will correspond to a ME."* (V2:36-37)

| Amount of AI Handled Group | Subject Identification Number |
|---|---|
| Occupational Use Pattern | |
| 1 | 1 – 6 |
| 2 | 7 – 12 |
| 3 | 13 - 18 |
| Consumer Use Pattern | |
| 1 | 1 – 6 |
| 2 | 7 – 12 |
| 3 | 13 - 18 |

**(c) What feasible opportunities to incorporate random elements in the design—if any—have been overlooked?**

None.

**(d) What typical patterns of exposure will likely be included by the sampling design?**

"*Consumer products may be poured or scooped and broadcast from a standing position, a bent position, or a kneeling position. Typically labels recommend adding product to the deep end of the pool while walking to ensure dispersion. Some products specify the*

*use of a bucket to dissolve the product before adding it to the pool. Less variation in pouring positions are expected in occupational settings where product is transferred from a bucket, box, or drum to a tank or vat."* (V1:7)

**(e) What typical patterns of exposure will likely be excluded by the sampling design?**

Previous AEATF II studies only monitored professional participants and only indoors. This solid pour study proposes to monitor both occupational and consumer subjects as well as indoors and outdoors.

*"Exposure monitoring data for the pour solid antimicrobial scenarios will be represented by data generated during the pouring of granules and powders. Less common solid pour formulations described as flakes and crystals exist. Crystals and flakes are not defined by particle size, but rather by particle structure. A compound could exist in both a crystal or a flake and an "amorphous" powder form. Crystals are composed of ordered, repeating structures that form regular shapes. The average particle size of flakes is larger than powders. Flakes are almost exclusively produced by flattening either isometric particles or agglomerates of primary particles through a milling process to result in uniformly shaped particles called flakes. Based on these definitions and the anticipated similarity in terms of pouring to granules, exposure to workers pouring crystals and flakes will be covered by exposure data generated for granules."* (V1:6)

The solid pouring scenarios exclude the task of application of the pour product. Most uses of solid formulations are for pools and into industrial systems which do not require a separate application. For those instances were the solid formulation is poured into a solution for subsequent application, the exposures to applicators will be monitored in separate studies as outlined in the AEATF II Governing Document.

**3. Is the proposed test material an appropriate surrogate?**

The test substance, cyanuric acid, is an appropriate choice for the development of surrogate exposure data because it is stable, characterized by low vapor pressure, and has a low analytical limit of detection.

*"The choices for test substances are somewhat limited due to the desire to use a product with low mammalian toxicity (signal word Caution or Warning) and that can be relatively easily identified analytically. After reviewing many labels, cyanuric acid (1,3,5-triazine-2,4,6-triol) was identified as the top candidate. Cyanuric acid was chosen as the surrogate chemical for the monitoring program because of its low mammalian toxicity, lack of glove requirement, availably as a powder and a granule, availability in a variety of container types and sizes, widespread use by consumers as a pool maintenance chemical, low environmental toxicity, and existing analytical methods. Therefore, it was decided to use this product for both the consumer and occupational monitoring programs as this product will allow monitoring to be done both with and without protective gloves. Since it is not a biocide, it does not need to be registered by EPA and thus has no EPA registration number. The use of CYA as a surrogate chemical was selected for use in this*

*study as it is used in the same manner as pour solid biocides and it does not require the use of gloves. CYA is used as a component in bleaches, disinfectants, and herbicides. It is widely marketed as a chlorine stabilizer for swimming pools by forming a weak bond with chlorine in the water and protects the chlorine from degradation by the sun's ultraviolet rays."* (V1:20)

*"The powder form of CYA is not marketed commercially due to its propensity to absorb moisture over time and cake; however it will be used in this study to allow for the monitoring of consumers handling a powder formulation without the use of gloves and workers handling a powder formulation with the use of gloves. Production will be timed to minimize the period between manufacturing the powder form and the monitoring study, so that caking of the material will not be a problem. The powder form of CYA will be produced and packaged into commercial containers by Occidental Chemical Company for use in this study."* (V1:21)

**4. What is the rationale for the proposed cluster design and sample size?**

*"…existing data are either of poor quality or only marginally relevant to the pouring of antimicrobial containing solids. Consequently, no reliable estimates of ME-to-ME variation are available for a statistical determination of the necessary number of MEs to meet specific data objectives. As a result the AEATF II is employing a base case design (Governing Document, 2011) that was agreed upon with the US EPA at the initiation of this study program. The generation of a new, relevant, high quality "base set" of data will fill this data gap identified by the EPA. It is anticipated in some cases that after the base case is collected no additional data collection will be necessary as the data will be sufficient to meet regulatory needs. In other situations, the task force, in consultation with regulatory agencies, may determine that additional data are required. At that point, more rigorous statistical methods outlined in the Governing Document may be applied. This is the preferred approach when there are little or no existing data to statistically define data objectives or when the existing data are of poor or limited quality (V1:14)."*

**EPA Protocol Review: AEATF II Solid Pour Scenarios/Protocol**

**Title:** A Study For Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial

**Date:** June 6, 2013

**Principal Investigator:**
Leah Rosenheck

**Testing Facility Management Representative**
Bryce D. Landenberger, Ph.D.
Science & Technology Leader
The Dow Chemical Company
1803 Building
Midland, MI 48674

**Participating Laboratories:**
Ricerca Biosciences LLC
7528 Auburn Road
Concord, Ohio 44077

**Sponsor:** American Chemistry Council
Antimicrobial Exposure Assessment Task Force II
c/o Hasmukh Shah, Ph.D.
700 2nd Street, NE
Washington, DC 20002

**Reviewing IRB:** Schulman Associates IRB
1550 Sawgrass Corporate Parkway, Suite 120
Sunrise, FL 33323

## 1. Societal Value of Proposed Research

### (a) What is the stated purpose of the proposed research?

*"This study is being conducted to determine potential dermal and inhalation exposures to occupational workers and consumers associated with the manual transfer (pour and/or scooping ) of solid formulation antimicrobial products. ….. The data generated from this study is expected to be sufficient to complete the data set for the AEATF II pour solid scenario."* (V2:8)

*"The purpose of this study is to find out how much chemical gets onto your skin and in the air when you pour or scoop a dry biocide product from a container."* (V2:114 of 183)

**(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?**

*"This study is being conducted to determine potential dermal and inhalation exposures to occupational workers and consumers associated with the manual transfer (pour and/or scooping ) of solid formulation antimicrobial products. ….. The data generated from this study is expected to be sufficient to complete the data set for the AEATF II pour solid scenario."* (V2:8)

*"The AEATF II monitoring program, as described in the Governing Document (2011), intends to develop a database of exposure monitoring data that can be used to support practical regulatory decisions about future exposures to antimicrobial active ingredients used in various products* (V2:10)."

*"Currently, US EPA relies upon surrogate exposure monitoring data located in the Pesticide Handlers Exposure Database (EPA, 1998) from primarily agricultural handler studies conducted more than 15 years ago to characterize exposure from the manual pouring of antimicrobial products. In addition to some inherent differences that exist between agricultural pesticide mixing and loading which is done outside and the handling of antimicrobial chemicals in industrial and residential settings, there have been a number of changes in the past 15 years including increased sensitivity of the analytical methods, changes in exposure dosimetry methods, and changes in regulatory needs. EPA has requested confirmatory exposure monitoring data for a number of antimicrobial use scenarios in Registration Eligibility Decision (RED) documents issued since 2004* (V2:15)."

**(c) How would the study be used by EPA?**

EPA will consider the data from this study in assessing exposures of occupational or residential handlers of antimicrobial products that are packaged as solid formulations and poured into other containers.

**(d) Could the research question be answered with existing data? If so, how?**

Due to the limitations of existing data, the research question cannot be answered with confidence relying on existing data.

**(e) Could the question be answered without newly exposing human subjects? If so how? If not, why not?**

*"Human subjects are required in this study because they will normally conduct these activities when performing their routine job function. There are no acceptable methods*

*or models that could be used to extrapolate exposure for this type of human activity* (V2:17).*"*

**(f) Is the research likely to produce data that address an important scientific or policy question that cannot be resolved on the basis of animal data or human observational research?**

Yes. The purpose of monitoring of test subjects is to measure dermal and inhalation exposure while the individuals pour solid formulations. To capture the key parameters that may result in exposure to the users, a range of container shapes and sizes, amount of active ingredient handled, and use of a scoop and/or pouring directly from a container need to be included in the study design. To be able to capture these key parameters the study needs to include this type of scripting, rather than observational (e.g., finding people that intermittently pour solid formulations into their backyard pools).

**2. Study Design**

**(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?**

*"This study is being conducted to determine potential dermal and inhalation exposures to occupational workers and consumers associated with the manual transfer (pouring and/or scooping) of solid formulation products. ….. The data generated from this study is expected to be sufficient to complete the data set for the AEATF II pour solid scenario* (V2:8).*"*

"*A confidence interval based approach will be used to determine the realized relative accuracy for the arithmetic mean and 95$^{th}$ percentile of exposure normalized by amount of ai handled. If the benchmark accuracy goal (i.e., k=3) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional monitoring events may be considered (V2:64)"*

No hypothesis is stated, nor is the study designed to test a hypothesis.

**(b) Can the study as proposed achieve that objective or test this hypothesis?**

The objective cited above can be achieved by the study as proposed (with the few minor recommendations noted above).

## 2.1 Statistical Design

### (a) What is the rationale for the choice of sample size?

*"In an ideal situation the determination of sample size would be based on an objective statistical approach. This approach would leverage existing data to estimate the variability that must be accounted for to specified confidence requirements. Such an approach was used for the initial few studies of the AEATF II. However, as the AEATF II began to work on implementing additional studies it became evident that either such data did not exist or that it was not relevant to current practices and methodologies. Attempts to use existing data from poor quality or only marginally relevant studies produced sample sizes that were logistically impractical to implement and unaffordable for the task force to complete. There is also concern that post collection analysis of newly collected data would indicate more samples had been collected than required to meet the confidence requirements. This would imply that subjects had been unnecessarily used and exposed in the data collection process (AEATF Governing Document 2011, pages 56-57)."*

*"As a result, the determination was made that a new, relevant, high quality "base set" of data needs to be created prior to applying a more statistically rigorous design process. To inform this approach, the AEATF II is relying on existing EPA guidelines on exposure studies (Series 875 - Occupational and Residential Exposure Test Guidelines). These guidelines call for essentially three groups of five observations per group. It is the intention of the AEATF II to collect 15 to 20 MEs per scenario to create a base-case data set. The exact number will depend on the number of levels of key factors that are considered likely to impact exposure (AEATF Governing Document 2011, pages 56-57)."*

*"It is anticipated in some cases that after the base case is collected no additional data collection will be necessary as the data will be sufficient to meet regulatory needs. In other situations, the task force, in consultation with regulatory agencies, may determine that additional data are required. At that point, more rigorous statistical methods as used in the first few studies, and outlined in Appendix E, may be applied. The exact steps will be determined after this joint evaluation, and with consideration for how the data will be used (AEATF Governing Document 2011, pages 56-57)."*

### (b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

No positive or negative controls are proposed. This is appropriate for the study design and statistical analysis plan.

**(c) How is the study blinded?**

The study is not blinded.

**(d) What is the plan for allocating individuals to treatment or control groups?**

"A total of 40 subjects will be recruited for this study. Twenty subjects will be recruited for the occupational phase and twenty will be recruited for the consumer phase. Each subject will be assigned a unique identification number starting at AEA07-01 and ending with AEA07-40. The people in the occupational monitoring will be designated by placing the letter "OC" after their identification number. The subjects in the consumer monitoring group will have the letter "CN" after their identification number. The subject numbers for each group will be randomized using a research randomizer program accessible at the following internet website: *http://randomizer.org*. The first 18 numbers in the generated randomized list for each group will determine the participating subjects, while the two remaining subjects will be held as alternates. The alternate subjects will be on-call for the duration of the study. Alternates will get compensated as if they participated in the study.

*Each subject will be randomly assigned to one of the three AI handled groups for powder and for granules. Randomly assigning subjects to each group means that they may not necessarily be handling the same amount of chemical.*

*For purposes of assigning subject numbers to AI handled groups during the study, the following table will be used. Based on the randomly assigned subject identification number, each subject will be assigned to one of the three AI handled groups for each type of solid formulation (powder and granular). Note that that each participant will be assigned to two randomly selected subject identification numbers, one for pouring powders and one for pouring granules. The randomly selected subject identification numbers will correspond to a ME."* (V2:36-37)

| Amount of AI Handled Group | Subject Identification Number |
|---|---|
| Occupational Use Pattern | |
| 1 | 1 – 6 |
| 2 | 7 – 12 |
| 3 | 13 - 18 |
| Consumer Use Pattern | |
| 1 | 1 – 6 |
| 2 | 7 – 12 |
| 3 | 13 - 18 |

**(e) Is the proposed research designed in accordance with current scientific standards and practices to include representative study populations for the endpoint in question?**

Yes, the proposed research includes developing unit exposures for both the occupational and consumer populations. Powders and granule formulations are sold to and used by workers and by consumers and the study participants in this study will be recruited from those two populations.

**(f) Can the data be statistically analyzed?**

The results of the analysis from the sampling will be provided in the final report and will be analyzed by EPA.

**(g) What is the plan for statistical analysis of the data?**

"The AEATF II will not statistically analyze the monitoring data in order to characterize exposure or investigate the relationship between exposure and other factors (e.g., container size, amount of active ingredient handled, and conventional pour versus reduced splash). However, regulators and other users of the constructed database (BHED) may choose to conduct such analyses. The extent of AEATF II's data analyses will be limited to the statistical characterization of data adequacy for inclusion in BHED scenario monographs (V2:64)."

"A confidence interval based approach will be used to determine the realized relative accuracy for the arithmetic mean and 95th percentile of exposure normalized by amount of ai handled. If the benchmark accuracy goal (i.e., k=3) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional monitoring events may be considered (V2:64)."

**(h) Are proposed statistical methods appropriate to answer the research question?**

Yes.

**(i) Does the proposed design have adequate statistical power to definitively answer the research question?**

Because of its Purposive Diversity Sampling Design, rather than completely random design, the study will support only limited inferences. EPA believes, nonetheless, that it is likely to characterize reliably the high end of exposures that occur while individuals pour a solid formulation. EPA is confident that this design will provide data on solid pour exposures more accurately and reliable than currently available data.

**(j) Does the investigator propose to conduct the research in accordance with recognized good research practices, including, when appropriate, good clinical practice guidelines and monitoring for the safety of subjects?**

This study is proposed to be conducted in accordance with recognized good research practices. This is not a clinical study and therefore good clinical practice guidelines are not applicable.

**2.2 How and to what will human subjects be exposed?**

*"Subjects will be brought to the monitoring area containing the containers they are expected to pour and the appropriate receptacle container(s). If there are multiple source containers they will be placed in a group so that not to bias the order in which the test subject pours them. The test subject will be free to position him/herself as he wants with respect to the receiving container(s). The subjects will be informed as to how much to pour and whether they should use a scoop or pour directly from the container(s) or whether they will need to pre-dissolve the product in a bucket. .... Subjects will be asked to begin opening the container(s) and pouring the way they normally do on the job (V2:48).*"

Each test subject will be exposed to cyanuric acid.

**(a) What is the rationale for the choice of test material and formulation?**

The choice of the formulation type (i.e., solid) is to collect data for pouring of solid formulations.

*"The choices for test substances are somewhat limited due to the desire to use a product with low mammalian toxicity (signal word Caution or Warning) and that can be relatively easily identified analytically. After reviewing many labels, cyanuric acid (1,3,5-triazine-2,4,6-triol) was identified as the top candidate. Cyanuric acid was chosen as the surrogate chemical for the monitoring program because of its low mammalian toxicity, lack of glove requirement, availably as a powder and a granule, availability in a variety of container types and sizes, widespread use by consumers as a pool maintenance chemical, low environmental toxicity, and existing analytical methods. Therefore, it was decided to use this product for both the consumer and occupational monitoring programs as this product will allow monitoring to be done both with and without protective gloves. Since it is not a biocide, it does not need to be registered by EPA and thus has no EPA registration number. The use of CYA as a surrogate chemical was selected for use in this study as it is used in the same manner as pour solid biocides and it does not require the use of gloves."* (V1:20)

**(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?**

The total amount of product poured by each subject per ME will range from 1 to 50 pounds for the consumer scenarios and from 5 to 100 pounds for the occupational scenarios.

*"Some scripted diversity in container sizes will be incorporated to ensure a range of product is handled; however the range of container sizes will be dictated by what is available commercially for the chosen surrogate chemical as well as what is typical for pour solid antimicrobial formulations. In order to achieve diversity in the pouring conditions with respect to the amount of product poured, subjects will be placed into one of three groups. There will be three groups, with 6 MEs per group, per use pattern scenario resulting in a total of 18 MEs for each of the four use scenarios. This will ensure a range of amount of chemical handled to generate a distribution of exposure data for this pour solid scenario. In addition there will be scripted diversity in the loading techniques to ensure that both pouring and scooping are monitored. The groups are defined in the following table.*

| | ***Use Pattern Scenarios*** | | | |
|---|---|---|---|---|
| | ***Granules – Occupational*** | ***Powders – Occupational*** | ***Granules - Consumer*** | ***Powders- Consumer*** |
| *Group 1* | *Range of AI Handled: 5 – 25 lbs* | *Range of AI Handled: 5 – 25 lbs* | *Range of AI Handled: 1 – 12 lbs* | *Range of AI Handled: 1 – 12 lbs* |
| *Group 2* | *Range of AI Handled: 25 – 50 lbs* | *Range of AI Handled: 25 – 50 lbs* | *Range of AI Handled: 12 – 30 lbs* | *Range of AI Handled: 12 – 30 lbs* |
| *Group 3* | *Range of AI Handled: 50 – 100 lbs* | *Range of AI Handled: 50 – 100 lbs* | *Range of AI Handled: 30 – 50 lbs* | *Range of AI Handled: 30 – 50 lbs* |

*Within these groups other characteristics will be varied to the extent feasible to provide for diversity in exposure. The purpose of creating these groups is to force diversity in the amount of active ingredient handled, not to conduct a side-by-side comparison. The data from all three groups within each use pattern scenario will be combined to generate a single unit exposure per use pattern. The study will generate four sets of unit exposure values for dermal and inhalation, one for each use pattern scenario."* (V2:13-14)

**(c) What duration of exposure is proposed?**

Each predefined ME will pour different volumes of the formulated product. Therefore, the volume of product poured is proposed, not specific time durations. The AEATF II does anticipate that the duration to pour the specified volumes will range from 6 to 40 minutes (V2:45).

## 2.3 Endpoints and Measures

**(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?**

Potential dermal exposure to the test substances will be measured using passive dosimetry techniques including whole body inner and outer dosimeters, hand washes, and face/neck wipes. All monitored subjects will wear the outer dosimeter (representative outer clothing consisting of cotton long pants and cotton long sleeve shirts) directly over the inner dosimeter (consisting of 100% cotton long underwear). Inner and outer dosimeters will be provided by AEATF II. Hand exposure will be measured by rinsing the hands with a solution of 0.01% Aerosol OT-75 surfactant distilled water solution (SOP AEATF II-8B). Face and neck exposure will be measured by wiping the face and neck (twice) with two gauze pads moistened with 0.01% Aerosol OT distilled water (SOP AEATF II-8C). (V2:51).

The amount of active ingredient handled will be determined by weighing the source containers before and after each ME (V2:35)."

"*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. 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 exchange rate. 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." (V2:53)*

These and other measurements cited within the protocol and SOPs are appropriate for this type of study. As per the HSRB's written comments on the AEATF II's liquid pour study, additional details on the airflow within the indoor environment need to be recorded.

**(b) What steps are proposed to ensure measurements are accurate and reliable?**

"*This study will be conducted according to FIFRA GLP Standards (40 CFR 160). This protocol will be audited by the Field and Analytical quality assurance units prior to finalization. In-life field phase of this study will be monitored by the study QA while the analytical phase will be audited by the Ricerca QA to ensure compliance with the FIFRA GLP regulation and adherence to this protocol and relevant SOPs. The QAU(s) will submit copies of their inspection reports to the Study Director, Test Facility Management, and AEATF Sponsor Representative and Sponsor Monitor(s) (40 CFR part 160.35 [4]). The final report will be audited by the study QAU to ensure that the contents of the report accurately describe the conduct and findings of*

*the study. Results of the audit will be transmitted to the Study Director, Test Facility Management, the Principle Analytical Investigator, the Sponsor's Representative, and the Sponsor Monitor(s). QAU organization and responsibilities will follow current AEATF II SOPs and Ricerca SOPs as applicable. The final report will contain a signed Quality Assurance Statement from the QAU of each contributing facility conducting QA audits* (V2:64)."

The AEATF II SOPs provide specific procedures to ensure accurate measurements such as calibration of inhalation monitoring devices (SOP 10G).

*"GLP purity analysis (content of active ingredient in the test substance) will be performed on each lot of product prior to use in the study and a Certificate of Analysis will be kept in the raw data file. Retained samples from each lot of test substance used in the study will be archived at the analytical laboratory (V2:24)."*

**(c) What QA methods are proposed?**

*"This study will be conducted according to FIFRA GLP Standards (40 CFR 160). This protocol will be audited by the Field and Analytical quality assurance units prior to finalization. In-life field phase of this study will be monitored by the study QA while the analytical phase will be audited by the Ricerca QA to ensure compliance with the FIFRA GLP regulation and adherence to this protocol and relevant SOPs. The QAU(s) will submit copies of their inspection reports to the Study Director, Test Facility Management, and AEATF Sponsor Representative and Sponsor Monitor(s) (40 CFR part 160.35 [4]). The final report will be audited by the study QAU to ensure that the contents of the report accurately describe the conduct and findings of the study. Results of the audit will be transmitted to the Study Director, Test Facility Management, the Principle Analytical Investigator, the Sponsor's Representative, and the Sponsor Monitor(s). QAU organization and responsibilities will follow current AEATF II SOPs and Ricerca SOPs as applicable. The final report will contain a signed Quality Assurance Statement from the QAU of each contributing facility conducting QA audits* (V2:64)."

**(d) How will uncertainty be addressed?**

"*A confidence interval based approach will be used to determine the realized relative accuracy for the arithmetic mean and 95th percentile of exposure normalized by amount of ai handled. If the benchmark accuracy goal (i.e., k=3) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional monitoring events may be considered* (V2:64)."

## 3. Subject Selection

### 3.1 Representativeness of Sample

#### (a) What is the population of concern? How was it identified?

The target population is the distribution of future handler/days of anyone who needs to use antimicrobial products that require "pouring" for proper use. This includes pouring solid antimicrobial products into swimming pools or into treated materials at manufacturing settings, etc.

The community of individuals that may need to pour an antimicrobial product formulated as a solid is enormous and includes millions of workers and residents in the United States.

#### (b) From what populations will subjects be recruited?

Occupational Portion of Study:

*"In order to obtain a subject pool who is familiar with handling and pouring solid antimicrobial products in an occupational setting, adult subjects who are employed in a position where they are required to handle and pour powder or granular formulated chemicals will be recruited from Concord (Lake County), Ohio and the surrounding counties. Since no differences in solid pouring techniques are expected as a function of the specific industry or occupational setting, no particular industry will be targeted during the recruitment. However, professional pool service workers will be excluded because the focus of this occupational scenario is on loading of chemicals in indoor industrial or manufacturing processes. Based on where the majority of granular and powder antimicrobial products are used, it is anticipated that the majority of workers with this skill will be from the manufacturing (textiles, pulp and paper treatment, paint), food and beverage processing, cooling tower, and water treatment industries.*

*Because solid biocide formulations typically contain high percentages of active ingredient and tend to be corrosive, only people that have experience with handling pour solid formulations will be recruited. However, to ensure that people with a range of experience are included in the study, no minimum number of months or years of experience will be specified. In order to adequately capture the ethnic diversity in the area, recruitment materials and all communications with potential subjects will be available in English and Spanish as it is anticipated that the population of interest may include some Spanish-speakers."* (V2:40-41)

Consumer Portion of Study:

*"In order to obtain test subjects who are familiar with handling and pouring solid antimicrobial products used in and around the home, adult subjects who currently*

*live, or have lived within the past five years, in a home with a pool and who have experience handling and pouring powder or granular formulated pool maintenance chemicals will be recruited from Concord, Ohio and the surrounding counties. Information from County Tax Appraisal data shows that there are over 10,000 homes with pools in Lake and Ashtabula counties (www.datamasters.org).*

*There are a wide range of pool chemicals formulated as granules and sold to consumers which should allow for a large sampling population. People having experience with either granular products or powder products will be eligible to participate in both the pouring of powders and granules monitoring. To ensure that people with a range of experience are included in the study, no minimum number of months or years of experience will be specified. Recruitment materials and all communications with potential subjects will be available in English and Spanish as it is anticipated that the population of interest may include some Spanish-speakers*." (V2:41)

**(c) Are expected participants representative of the population of concern? If not, why not?**

*"Advertisements will be posted in several local newspapers including one Spanish language paper. The following papers will be contacted regarding the posting of the advertisement: the News-Herald of Northern Ohio, the Star Beacon, and Hola Today. In addition to printing the ad in the paper, the ads will also be posted on the newspapers' on-line web sites. Recruitment for the occupational monitoring may or may not take place at the same time as recruitment for the consumer monitoring. The consumer monitoring will take place in the summer months whereas the occupational monitoring is not tied to any particular season.*

*"The advertisements will contain a toll-free number where interested respondents can leave a message either in English or Spanish. The messages will be automatically forwarded to the Study Director or bilingual researcher*." (V2:42)

Expected participants will self-identify in response to advertisements placed in local newspapers. The placement of advertisements in newspapers targeting different demographic groups should minimize bias and achieve diversity among respondents and subjects. While individuals who express interest in response to a newspaper advertisement about this study may differ in unknowable ways from other individuals who do not step forward, there is no reason to think that respondents in the Concord, Ohio and/or Lake County, Ohio area are atypical of similar individuals in any other area of the United States.

Experience Issue

The protocol specifies that subjects for both the consumer and residential portions of the study must have experience performing the activity being monitored. Subjects for the occupational portion must be currently employed in an industry where they pour

solid formulation antimicrobial products as a part of their job, and subjects for the consumer portion must own a pool or have owned a pool in the past 5 years and have experience treating the pool with solid formulation antimicrobial products. The recruitment of test subjects who have experience with the activity, product, or equipment being evaluated is a basic premise of exposure monitoring studies. The EPA OCSPP Series 875 Occupational and Residential Exposure Test Guidelines 875.2000 state the following:

> "Ideally, the test population should be involved in the type of work on a regular basis and be familiar with the activities and purpose of the study. For example, test subjects should be normal workers and not inexperienced volunteers. Likewise, for residential studies, the test populations should be representative of the exposed homeowners/residents population." (page B2-9 of EPA Guideline 875.2000)

In this case, individuals who would be representative of the exposed population would be workers who pour these types of products as part of their job, and homeowners who have their own swimming pool and who have used granular pool chemicals to treat their pool. The number of brand-new employees or first-time pool owners is a small percentage of the overall population, and it would not be appropriate to skew the dataset to these inexperienced users. Moreover, for an unskilled task like pouring granules and powders, individuals with no experience will not necessarily have higher exposure than those with experience. In fact, users with no experience may be more careful than those who regularly use the products and who may become increasingly sloppy over time. In order to ensure that the test population has a range of experience, no minimum amount of experience is required.

**(d) Can the findings from the proposed study be generalized beyond the study sample?**

*"The AEATF II monitoring program, as described in the Governing Document (2011), intends to develop a database of exposure monitoring data that can be used to support practical regulatory decisions about future exposures to antimicrobial active ingredients used in various products. Generic exposure data will be developed on a broad range of use patterns and associated application methods, as well as post application exposures to support registration and re-registration by its member companies of such uses for antimicrobial ingredients. The data will reflect both occupational and consumer activities and methods used in the handling of antimicrobial products."*(V2:13)

### 3.2 Equitable Selection of Subjects

**(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?**

Inclusion/exclusion criteria are complete and appropriate, except that "skin conditions on the surface of the ***face/neck***" should be added to this list of exclusions.

The inclusion/exclusion criteria are listed in Volume 2, page 22-23, and below:

"*Inclusion Criteria*

- *Males or females, at least 18 years of age as verified by government issued photo ID*
- *Self-identified as being in good health.*
- *Willingness to sign the Informed Consent Form and the Subject Qualification Worksheet*
- *Speak and read English or Spanish*
- *Occupational Monitoring: currently employed in a manufacturing, water treatment, food or beverage processing or other industrial type company in a position that requires the handling and pouring (or scooping) of granular or powder chemical formulations*
- *Occupational Monitoring: physical ability to lift and pour up to four containers weighing 50 pounds each*
- *Consumer Monitoring: residence at a home (either current or within the last 5 years) with a swimming pool and experience with using granular or powder pool chemicals*
- *Consumer Monitoring: physical ability to lift and pour up to two containers weighing 25 pounds each*

*"Exclusion Criteria*

- *Skin conditions on the surface of the hands (e.g., psoriasis, eczema, cuts or abrasions) as determined by a visual inspection*
- *Pregnant, as shown by a urine pregnancy test*
- *Nursing*
- *Allergies or sensitivities to chemical-based products, particularly cyanuric acid and soaps*
- *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"* (V2:22-23)

**(b) What, if any, is the relationship between the investigator and the subjects?**

Employees and spouses of employees of the investigators are excluded from participation as subjects. (V2:22-23)

**(c) Are any potential subjects are from a vulnerable population?**

No potential subjects are from a vulnerable population.

**(d) What process is proposed for recruiting and informing potential subjects?**

The recruiting process is described in V2:42-45.

**(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?**

Subjects will be recruited through advertisements in local newspapers. There will be no connection or communication between the researchers and the potential subjects' employers, which minimizes the potential for coercion or undue influence.

### 3.3 Remuneration of Subjects

**(a) What remuneration, if any, is proposed for the subjects?**

*"A small compensation for the time and inconvenience spent on this study will be provided to the subjects. Potential subjects who attend the informed consent meeting whether they decide to participate or not will be paid $20 in cash for their time and inconvenience. Subjects who qualify, sign the consent form, and report to the study site on their assigned day will receive $100 for their time and inconvenience when they leave the study site, whether they are monitored or not."* (V2:45)

**(b) Is the remuneration consistent with the principles of justice and respect for persons?**

Yes. The proposed payment amount is fair and reasonable compensation for the subjects' time and inconvenience. "*The value for remuneration is based roughly on a day's wage of $100 and represents potential lost time from secondary sources of employment, travel time and incidental expenses incurred in study participation. Compensation will be provided to individuals who complete their assigned participation or who need to withdraw for whatever reason."* (V2:45)

**(b) Is proposed remuneration so high as to be an undue inducement?**

No

**(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects?**

No

**(d) How and when would subjects be paid?**

Compensation will be in the form of cash (U.S. currency). *"Potential subjects who attend the informed consent meeting whether they decide to participate or not will be paid $20 in cash for their time and inconvenience. Subjects who qualify, sign the consent form, and report to the study site on their assigned day will receive $100 for their time and inconvenience when they leave the study site, whether they are monitored or not.*" (V2:45)

## 4. Risks to Subjects

### 4.1 Risk characterization

**(a) Is adequate information available from prior animal studies or from other sources to assess the potential risks to subjects in the proposed research?**

Although cyanuric acid (CAS No. 108-80-5) is not an EPA-registered product, isocyanuric acid (CAS No. 108-80-5) is used to formulate chlorinated isocyanuric acid registered products and is also a break-down product of other registered pesticides. As such, EPA has toxicity data from animal studies with isocyanuric acid. Even though, as the protocol indicates, cyanuric acid is generally characterized by "low" toxicity, EPA is using the results of an oral developmental toxicity study based on monosodium isocyanurate as the endpoint for the dermal and inhalation routes. The monosodium isocyanurate is not chlorinated, and therefore, is used to represent cyanuric acid. The endpoint derived from the rat developmental (oral) study is increased incidence of hydrocephaly. The NOAEL from this study is discussed in subsequent sections.

The MSDS for cyanuric acid indicates that it *"may cause slight skin irritation"* and *"may cause mild eye irritation.*" During the EPA protocol review, questions arose concerning the skin irritation potential for the consumers who will pour the solid formulations without gloves. Although the MSDS indicates "slight" skin irritation, there is a statement on the MSDS that states: *"Hand Protection: Wear appropriate chemical resistant gloves"*. Therefore, to clarify the need (or not) for the gloves given the "slight" skin irritation versus the MSDS statement to wear gloves, the researchers provided the following information to EPA: *"…background about why the Occidental Chemical Corporation (OxyChem) MSDS for cyanuric acid recommends the use of protective gloves. It is standard procedure at OxyChem to place a glove recommendation on the MSDS even for products where the dermal toxicity and dermal irritation do not warrant it, for example with inert ingredients. The reason for this standard language is that it is protective, reflects best chemical handling practices, and it protects people who might have cuts or open sores on their hands against unanticipated irritation. In our study, the hands of each volunteer will be examined for the presence of cuts or open sores prior to them participating in the study. The presence of cuts or open sores is an exclusion criterion. Given this precautionary study measure, the data from the dermal irritation studies, and the fact*

*that CYA product labels don't require gloves, we feel that we are not putting the volunteers in the consumer portion of the study at any additional risk by asking them to handle and pour product without the use of gloves. We will be requiring volunteers in the occupational portion of the study to wear gloves as the exposure data we generate for workers needs to be representative of the bulk of occupational product labels which do require chemical-resistant gloves."* (Email from Leah Rosenheck (study director) to Timothy Leighton (EPA), August 30, 2013).

In addition, on September 4, 2013, the AEATF-II provided additional study summaries on the acute inhalation toxicity and dermal irritation potential of cyanuric acid in response to EPA's concerns regarding the hazard potential of cyanuric acid from acute inhalation and dermal exposures. (See *AEATF Supplemental Submission of Toxicity Study Summaries for Cyanuric Acid.* This document is among the background materials provided to the HSRB).

The summary information for acute inhalation toxicity indicates that there is minimal toxicity of cyanuric acid following acute inhalation exposures in rats. The submitted summary for dermal irritation of cyanuric acid indicates that an applied dose of 500 mg to the skin of rabbits is non-irritating to intact skin.

Additional discussion is provided below on the comparison of the hazard and anticipated exposures for the test subjects in this study.

**(b) What is the nature of the risks to subjects of the proposed research?**

Risks are of a reaction to the test materials; of discomfort and possibly heat-related illness associated with wearing two layers of clothing; of discomfort or inconvenience from wearing the air sampling device; of embarrassment from disrobing in the presence of a research technician; of an unexpected result of pregnancy testing.

Risks discussed in the consent forms include risk of a reaction to the test materials, risk of stinging from the soapy mixture that will be used to wash hands and face, risk of physical stress from lifting up to two 25-pound containers, the possibility of heat stress, risk of discomfort, risk of embarrassment, possible surprise at the results of a pregnancy test, and the potential for a breach of confidentiality. (V2:108-9; 119-120)

**(c) How do proposed dose/exposure levels compare to the established NOAELs for the test materials?**

Anticipated exposure levels to the test subject are based on the wettable powder data in EPA's Pesticide Handler's Exposure Database (PHED). The PHED data are not directly comparable to the proposed exposures in this study because the PHED data are based on agricultural applications along with other limitations (hence this AEATF- II study is being proposed for future use to evaluate exposure to solid antimicrobial products). Currently, PHED data are the only source of exposure data to estimate the potential risks. Based on the PHED data, the unit exposure for

inhalation is 0.0434 mg/lb ai. Within the PHED database, the mean AaiH handled during the sampling for the 43 inhalation measurements is 30 pounds (range 0.03 to 264 pounds). The dermal unit exposure for single layer and no gloves is 3.7 mg/lb ai and for single layer with chemical resistant gloves the unit exposure is reduced to 0.17 mg/lb ai. The number of dermal samples range from 22 to 45 for the body (a range is reported because of the incomplete body part measurements), 7 hand samples for subjects wearing no gloves, and 24 hand samples for subjects wearing chemical resistant gloves.

A comparison of the anticipated dermal exposures to the point of departure (POD) from the developmental (oral) study in rats (NOAEL = 200 mg/kg/day) indicates that for the occupational powder scenario (gloves and maximum of 100 lbs ai poured), the estimated margin of exposure (MOE) is 82,000 (i.e., (NOAEL 200 mg/kg/day) / (0.17 mg/lb ai x 100 lbs ai x 0.01 dermal absorption x (1/70 kg BW)) = 82,000). For the consumer powder scenario (no gloves and maximum of 50 lbs ai poured), the estimated dermal MOE is 7,600 (i.e., (NOAEL 200 mg/kg/day) / (3.7 mg/lb ai x 50 lbs ai x 0.01 dermal abs x (1/70 kg BW)) = 7,600). The MOE is the unitless ratio of the POD/dose where the target MOE is 100 (10x interspecies extrapolation and 10x intraspecies variation).

A comparison of the anticipated inhalation exposures to the POD indicates that for the occupational powder scenario (100 lbs ai poured) the estimated margin of exposure (MOE) is 3,200 without a respirator (i.e., MOE = (NOAEL 200 mg/kg/day) / (0.0434 mg/lb ai x 100 lbs ai) = 3,200). The inhalation MOE for the consumer powder scenario (maximum of 50 lbs ai poured) is 6,500 (i.e., MOE = (NOAEL 200 mg/kg/day) / (0.0434 mg/lb ai x 50 lbs ai) = 6,500). The MOE is the unitless ratio of the POD/dose where the target MOE is 1000 (i.e., 10x interspecies extrapolation, 10x intraspecies variation, and an additional 10x data base uncertainty factor for the route-to-route extrapolation from the oral toxicity endpoint to the inhalation route of exposure). The potential exposure to the test subjects in the occupational scenarios is less than estimated above because they will be wearing N95 respirators.

Based on the comparisons of the anticipated exposures and subchronic endpoints selected, there are minimal dermal and inhalation risks of concern. Nonetheless, it is prudent for the researchers to provide the consumer test subjects, in addition to the occupational test subjects, with respiratory protection (i.e., it is prudent to wear respiratory protection when pouring up to 50 pounds of any type of powder).

**(d) Does the research proposal adequately indentify anticipated risks to human subjects and their likelihood of occurrence? How was this likelihood estimated?**

The potential dermal and inhalation risks have been evaluated by EPA through a comparison between the NOAEL and the anticipated dermal and inhalation exposure. The comparison indicates minimal dermal and inhalation risks. Please see part 4.1(c) (above) for details. These calculations are not explicitly presented in the protocol. The study sponsors are advised to provide these calculations in future protocols.

**(e) If any person with a condition that would put them at increased risk for adverse effects may become a subject in the proposed research, is there a convincing justification for selection of such a person and are there sufficient measures to protect such subjects?**

Subjects who might be at an increased risk for adverse effects are excluded from the study. Individuals known to be allergic or sensitive to chemical-based products particularly cyanuric acid and soaps, subjects in poor health, or with broken skin on hands or face/neck are not eligible to become subjects in this study.

## 4.2 Risk Minimization

**(a) What specific steps are specified in the protocol to minimize risks to subjects?**

The protocol indicates that all of the test subjects will wear eye protection and two layers of clothing (long sleeved shirt and long pants over long underwear). In addition, the occupational test subjects will wear chemical resistant gloves as well as respiratory protection.

The protocol currently states that subjects in the consumer portion of the study will be given the option – but not required – to wear respiratory protection. However, EPA is requiring that the researchers require all subjects – both in the occupational portion and residential portion of the study – to wear respiratory protection (a particulate dust mask) as an additional protection.

Other protections include:

- Candidates known to be sensitive to chemical-based products, particularly cyanuric acid and soaps, are excluded (V2:22)
- Candidates who are pregnant, nursing, in poor health, or who have broken skin on their hands are excluded (V2:22)
    - *EPA is recommending that the sponsors add "skin conditions of the face/neck" to the list of exclusions*
- The consent form alerts subjects to signs and symptoms of eye and skin reactions and advises them to stop the activity if they experience muscle fatigue, muscle strain, or if they feel faint or too hot (V2:108-9; 119-20)
- The ambient temperature will be monitored, and subjects will be observed for signs of heat stress. There are appropriate stopping rules if the heat index becomes unsafe (SOP 11B.1, Heat Stress). (V4:143-154)
- A medical professional (nurse, EMT, or Physician Assistant) will be hired for this study and will be present during the monitoring events. This individual will be responsible for examining hands and face/neck of each subject before the study for open cuts or abrasions or certain skin conditions and for examining the subjects' hands and face/neck for possible signs of dermal irritation following completion of the monitoring events. (V2:30)

- Following completion of monitoring, each subject will be asked to wash their hands and face thoroughly with soap and water. (V2:30)
- The protocol minimizes the risk of psychological harm related to the pregnancy tests by providing a private place for women to take the test and following procedures designed to protect the confidentiality of any test result. (V2:25)

**(c) What stopping rules are proposed in the protocol?**

Heat stress index above 95 (V2:46)

Other medical reasons (V2:47)

"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." (V2:47)

**(d) How does the protocol provide for medical management of potential illness or injury to subjects?**

SOP 11.B.1 for Management of Heat Stress (V4:143-154)
SOP 11.C.3 for Emergency Procedures (V4:155-159)

**(e) How does the protocol provide for safety monitoring?**

*"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 medical professional will determine whether medical treatment is necessary.*

*"The extra layer of clothing (inner dosimeter) worn by subjects may increase the risk of heat-related illness. However, the possibility of heat stress will be minimal for subjects in this study due to the location of the study and the short amount of time the subject will be working. Research personnel will monitor the heat index, and stop subjects' work if the heat index exceeds 95. The SOP AEATF II-11B describes the procedure for identification and control of heat stress. The poster "Controlling Heat Stress Made Simple" will be posted in the subject dressing area and the information contained on the poster available to subjects and research personnel at the field site.*

*"In brief, researchers will observe subjects for possible signs of early heat illness such as fatigue, dizziness, irritability, or decreased concentration. If these symptoms are observed, the subjects will be asked whether they would like to rest for a moment. If they answer affirmatively, they will stop working, be given their choice of water or a sports drink and a chair, and the Study Director and medical professional will be immediately contacted for further medical management instructions. If they answer*

*negatively, they will be permitted to continue working, and frequently thereafter asked whether they would like to rest for a moment. Any affirmative answer will be handled as described above.*

*"If subjects develop visible signs or report symptoms of distress such as pronounced fatigue, headache, cramps, feeling faint, increased pulse, muscle spasms, heavy sweating (or dry skin if previously sweating), extreme thirst, or rapid breathing, the subjects will be required to stop working immediately, and given their choice of water or a sports drink and a chair. A medically qualified person will be on site and will assess the situation. If the worker's condition appears to be serious, a member of the study team or the medic will call 911 and allow emergency medical personnel to respond and treat the subject.*

*"Study personnel will be instructed to inform the Study Director and medical professional 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.*

*"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."* (V2:46-47)

**(f) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?**

The consent forms state: *"If you experience an eye reaction 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."* (V2:110, 120-121)

*"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 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."* (V2:47) (SOP 11C-3 is located in Volume 4, pages 155-9)

**(g) How and by whom will medical care for research-related injuries to subjects be paid?**

The informed consent forms state: *"If you get hurt or sick while you are participating in this study, a nearby medical facility that knows about this study 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."* (V2:109, 120)

**5. Benefits**

**(a) What benefits of the proposed research, if any, would accrue to individual subjects?**

There are no benefits to the subjects of participating in this research study.

**(b) What benefits to society are anticipated from the information likely to be gained through the research?**

*"Measuring exposure of workers in this research study will produce more reliable data about the potential dermal and inhalation exposure of workers and the general population performing these tasks. The resulting data will improve the completeness and accuracy of the database used by the EPA to assess exposure and risks to antimicrobial chemicals.*

*"The ability to accurately predict risk will allow a more accurate assessment of chemicals in the registration review process.*

*"Products containing antimicrobial chemicals formulated as granules and powders are used extensively in manufacturing, sanitizing, and water treatment (commercial and homeowner) industries. These products control mold, algae, bacteria, and viruses known to produce increased morbidity and mortality in humans, domestic animals, and pets. Society will benefit from continued ability to use antimicrobials that improve the quality of life."* (V2:25-26)

**(c) How would societal benefits be distributed? Who would benefit from the proposed research?**

Results from the study may benefit EPA by reducing uncertainty about the range of exposure experienced by consumers and workers handling antimicrobials. Registrants of antimicrobials will benefit because they will provide EPA with data on exposure that has

been made a condition of re-registration for a number of antimicrobials, and they may be aided in registering new antimicrobials using the data generated from this study.

**(d) What is the likelihood that the identified societal benefits would be realized?**

The research is very likely to produce more accurate and reliable information concerning exposure in the solid pour scenario, with resulting societal benefits in the form of more accurate and confident assessments of applicator exposure and risk.

**6. Risk/Benefit Balance: How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?**

The likely benefit to society in general, in the form of more accurate measurements of potential exposure to antimicrobial products, must be weighed against the risks to study participants. Antimicrobial products are widely used both by workers in occupational settings and the general public. Exposure data for this solid pour scenario meeting contemporary standards of reliability and quality will likely provide a significant benefit to society. Because the margins of exposure are acceptable for the product proposed for use in this research study, subjects are very unlikely to experience toxic effects, and because procedures will be in place to minimize these and other risks to participants, the likelihood of serious adverse effects is very small. In summary, the risks to study participants from participating in this study are reasonable in light of the likely benefit to society of the knowledge to be gained.

**7. Independent Ethics Review**

**(a) What IRB reviewed the proposed research?**

Schulman Associates IRB

**(b) Is this IRB independent of the investigators and sponsors of the research?**

Yes

**(c) Is this IRB registered with OHRP?**

Yes

**(d) Is this IRB accredited? If so, by whom?**

Schulman Associates IRB earned “Full Accreditation” from the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) in June 2008.

**(e) Does this IRB hold a Federal-Wide Assurance from OHRP?**

Yes.

**(f) Are complete records of the IRB review as required by 40 CFR 26.1125 provided?**

Yes.

**(g) What standard(s) of ethical conduct would govern the work?**

This is a protocol for third-party research involving what EPA has interpreted to be intentional exposure of human subjects to a pesticide. The study is being conducted with the intention of submitting the resulting data to EPA under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA). Thus, the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

**8. Informed Consent**

**(a) Will free and fully voluntary informed consent be obtained from each prospective subject?**

Yes.

**(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR §26.1117?**

Yes. See Attachment 5.

**(c) Do the informed consent materials meet the requirements of 40 CFR §26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research?**

Yes. See Attachment 4.

**(d) What is the literacy rate in English or other languages among the intended research subjects?**

Ability to speak and read English or Spanish is specified as a criterion for inclusion in the study. (V2:22)

**(e) What measures are proposed to overcome language differences, if any, between investigators and subjects?**

*"A member of the research team who is bilingual in English and Spanish will be present during monitoring events involving subjects whose preferred language is Spanish."* (V2:46)

Recruitment materials and all communications with potential subjects will be available in English and Spanish as it is anticipated that the population of interest may include some Spanish-speakers. (V2:41) In addition, a copy of the poster entitled "Controlling Heat Stress Made Simple" in English and Spanish will be posted in the subjects' dressing area. (V2:30)

**(f) What measures are proposed to ensure subject comprehension of risks and discomforts?**

All written recruitment, consent, and risk communication materials will be available in both English and Spanish (including label, MSDS, recruiting materials, flyers, and poster entitled "Controlling Heat Stress Made Simple").

The informed consent meetings are one-on-one meetings between the potential volunteer and the study staff unless family members or spouses wish to attend the meeting as well (SOP AEATF II-11I)…The Study Director or Research Associate will read the Informed Consent Form to the potential subjects. The experimental study and the inclusion and exclusion criteria will be described to each volunteer in detail, and potential subjects will be encouraged to ask questions or request clarification during the meeting and at any point during the rest of the study. The amount and form of compensation, the potential risks and discomforts and treatment and compensation for injury will be fully explained. Potential subjects will be allowed to take these forms and information home with them to discuss the study with family and friends. The Study Director or Research Associate will explain that they can withdraw from the study at any time without penalty or negative consequences. To make sure that the potential subjects understand what is being asked of them, a short list of standardized questions requiring a response will be asked of each potential subject (SOP AEATF II-11J.1). (V2:43-44)

SOP AEATFII-11J.1 provides the following with respect to ensuring subject comprehension:

*"3.0 Ensuring Comprehension*

> *"3.1 During the consent process, time will be allocated for questions and answers. The IRB-approved Consent Form (and all supporting documents, except product labels and MSDS forms) will be presented in English or an alternative language (e.g. Spanish if they cannot read English) to the subject. Alternative language specifications will be protocol specific and dependent on the demographics of where the study is conducted; further information is*

*provided in the Governing document of the AEATF II. All sections of the Consent Form must be explained in detail to the subject.*

*"3.2 When the person obtaining consent is finished, he/she must ascertain whether the potential subjects really understand the procedures, requirements, and risks associated with participation in the study. This assessment of comprehension will be done by asking specific questions of the potential subjects to indicate their understanding of key issues. The form in Attachment 11-J-1 will be used to establish general understanding of the informed consent form and what is being asked of the volunteer. This must be filled out for each study participant and retained with their signed consent form.*

*"3.3 If after this process the subject demonstrates comprehension of the material, meets the requirements, and wants to participate, he/she will be asked to sign and date the Consent Form. Once the form is signed, the person obtaining consent will provide a copy of the signed form to the subject. If the subject needs more time to decide on his participation, he can take the unsigned consent form home and set up a follow-up appointment.*

*"3.4 The Study Director (or designee) obtaining the consent will not sign the Consent Form unless he/she believes that the process has been free of coercion or undue influence and that the candidate fully understands the information presented."* (V4:169)

**(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?**

Please see SOP AEATFII-11J.1 (V4:167-171)

**(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?**

Recruiting will take place through advertisements in newspapers, not through the workplace, thus removing the possibility of coercion or undue influence exerted by an employer.

SOP AEATF II-11J.1 states: *"The Study Director (or designee) obtaining the consent will not sign the Consent Form unless he/she believes that the process has been free of coercion or undue influence and that the candidate fully understands the information presented."* (V4:169)

The consent forms state: *"If you decide to be in this study it will be because you want to. There will be no direct benefit to you if you do decide to participate and no harm to you if you decide not to. The choice is up to you."* (V2:110, 121)

**9. Respect for Subjects**

**(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?**

*"There are procedures in place to protect subject privacy during recruitment, consent, study conduct, and maintenance of study records. The consent form summarizes important confidentiality terms for subjects."* (V2:26)

*"Records correlating subject names to their identification codes and SISN will be retained separately from the study file in an area clearly marked "CONFIDENTIAL."* (V2:45)

*"If a subject is female, she will be taken to a private area and asked to take a urine pregnancy test using an over-the-counter pregnancy test kit purchased by the Sponsor…Results of the pregnancy test will be kept in confidence and they will be discussed only with the subject that provided the urine sample. Only a note indicating the expiration date of the test, lot number, and results of pregnancy test will be recorded in study records."* (V2:49)

**(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?**

The informed consent forms state:

*"If you decide to participate in this study it will be because you want to. There will be no direct benefit to you if you do decide to participate, and no harm to you if you decide not to. The choice is up to you."* (V2:110, 121)

*"You are free to withdraw from this study at any time, for any reason. Simply tell any member of the research team that you no longer want to participate. If you decide not to participate in this study or to withdraw from it at any time, you will not be penalized or reprimanded in any way. If you withdraw from the study after the exposure monitoring begins, you will still be paid for your time."* (V2:111, 122)

**(c) How will subjects who decline to participate or who withdraw from the research be dealt with?**

*"Potential subjects who attend the informed consent meeting whether they decide to participate or not will be paid $20 in cash for their time and inconvenience.Subjects who qualify, sign the informed consent form, and report to the study site on their assigned duty day will receive $100 for their time and inconvenience when they leave the study site, whether they are monitored or not…Compensation will be provided to individuals who complete their assigned participation or who need to withdraw for whatever reason."* (V2:45) Subjects who are withdrawn by the investigators—and all participating

subjects in the case that the entire study is stopped—are promised payment in full. (V2:45, 111, 122)

## § 26.1111 Criteria for IRB approval of research
## AEATF II Solid Pour Scenario/Protocol AEA07: June 6, 2013

| Criterion | Y/N | Comment/Page Reference |
|---|---|---|
| (a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. | Y | |
| (a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. | n/a | |
| (a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility. | Y | |
| (a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons. | Y | |
| (a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116. | Y | |
| (a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117. | Y | |
| (a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. | Y | |
| (a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. | Y | |
| (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects. | Y | |

## §26.1116 General requirements for informed consent
## AEATF II Solid Pour Scenario/Protocol AEA07: June 6, 2013

| Criterion | | Y/N | Comments |
|---|---|---|---|
| No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative | | Y | |
| An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence | | Y | |
| The information that is given to the subject or the representative shall be in language understandable to the subject or the representative | | Y | |
| No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence | | Y | |
| (a) In seeking informed consent the following information shall be provided to each subject | (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental | Y | |
| | (2) A description of any reasonably foreseeable risks or discomforts to the subject | Y | |
| | (3) A description of any benefits to the subject or to others which may reasonably be expected from the research | Y | |
| | (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject | n/a | |
| | (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained | Y | |
| | (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained | Y | Although research doesn't involve more than minimal risk, compensation and treatment of injuries are provided for |
| | (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject | Y | |
| | (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled | Y | |
| (b) When appropriate, one or more of the following elements of information shall also be provided to each subject | (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable | Y | |
| | (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent | Y | |
| | (3) Any additional costs to the subject that may result from participation in the research | Y | |
| | (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject | Y | |
| | (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject | n/a | |
| | (6) The approximate number of subjects involved in the study | Y | |
| (e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function. | | Y | |

## §26.1117 Documentation of informed consent
## AEATF II Solid Pour Scenario/Protocol AEA07: June 6, 2013

| Criterion | Y/N | Comments |
|---|---|---|
| (a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form. | Y | |
| (b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or | Y | |
| (b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form. | n/a | |

**40 CFR 26.1125 Prior submission of proposed human research for EPA review**
**AEATF II Solid Pour Scenario/Protocol AEA07: June 6, 2013**

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

| | Requirement | | Y/N | Comments |
|---|---|---|---|---|
| All information relevant to the proposed research specified by § 26.1115(a) | (1) Copies of<br>• all research proposals reviewed by the IRB,<br>• scientific evaluations, if any, that accompanied the proposals reviewed by the IRB,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | Y<br>n/a<br>Y<br>n/a | V2: 3-100, V3:18-158<br><br>V2:101-151 |
| | (2) Minutes of IRB meetings . . . in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution.+ | | Y | V3:369-374 |
| | (3) Records of continuing review activities. | | n/a | None |
| | (4) Copies of all correspondence between the IRB and the investigators. | | Y | V3:159-161, 163-168, 170-172, 271-276, 304-306, 324-328 |
| | (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;<br>• any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant. | | Y<br>Y | Provided separately to EPA |
| | (6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b). | | Y | Separately submitted to EPA under confidentiality claim |
| | (7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5). | | n/a | |
| The following Information, to the extent not already included: | §1125(a) a discussion of: | (1) The potential risks to human subjects | Y | V2:23-25 |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | V2:23-25, 29-30 |
| | | (3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue | Y | V2:25-26 |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | V2:18-20 |
| | | (5) The balance of risks and benefits of the proposed research. | Y | V2:26 |
| | §1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB. | | Y | Orig. V3:115-134, 307-312<br>Approved: V2:101-174 |
| | §1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used. | | Y | V2:40-45, 152-4 |
| | §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 | V2:26, 42-45 |
| | §1125(e): All correspondence between the IRB and the investigators or sponsors. | | Y | V3:159-161, 163-168, 170-172, 271-276, 304-6, 324-8 |
| | §1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB. | | Y | V2:181-3 |