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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

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MEMORANDUM

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

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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:

    - Allow random selection for two additional items: (1) randomize the order in which the randomly-selected source container sizes are poured; and (2) randomize the selection of which three subjects will use a measuring cup in Group 2.

    - Allow subjects to fill the spray bottles from the source container and with water in the order they *would normally do* as opposed to the researchers directing them to fill with water after pouring the concentrate from the measuring cup.

    - Provide a description of how the different size source containers will be randomly assigned to each ME.

    - Provide details about how the airflow in the laboratory room will be measured and what the target airflow will be (e.g., will the airflow be minimized?).

Ethics Review

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

- Before the research is initiated, the protocol and/or consent form should be revised as follows and resubmitted for review by the approving IRB:

    - 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.

    - Remove all generic references to "second alternate language" or "alternate language as appropriate to the area/population" and replace with "Spanish."

    - 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.

    - The AEATF should develop procedures for handling such a call and document those procedures in a new or existing SOP.

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

- Before submitting future protocols, the AEATF-II should develop a process for improving and verifying the accuracy of the Spanish translations, and articulate that process in an SOP or the protocol.

A. Responsiveness to Previous EPA and HSRB Comments

Applicable EPA and/or HSRB Comments from the January 2011 and April 2011 HSRB Meetings	Has the comment been address in this protocol?
1. Verify the appropriateness of, or make necessary improvements to, the Spanish translations of the consent form, product risk statements, and recruitment materials. Spanish translations should be written in common, simple Spanish, appropriate to the reading ability of potential Spanish speaking subjects	**NO.** The AEATF needs to develop a process to improve and verify the accuracy of the Spanish translations. This process should be documented in an SOP submitted along with future protocols.
2. Develop an SOP for clarifying the AEATF's health status reporting and inclusion criteria.	**Yes.** See section 2.8 in AEATF-II SOP-11J.0 (V4:170-171)
3. Develop an SOP for following up with participants who leave the study early because of illness.	**Yes**. See sections 2.5-2.8 in AEATF-II SOP-11C.2.

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)
- Liquid Pour Scenario: Study Design and Rationale (pp. 6-56)

Volume 2 of the submitted package includes the following documents:

- IIRB-approved protocol dated July 7, 2011 (pp. 3-116)
- IIRB Approval Letter dated July 13, 2011, and Supporting Documents (pp. 117-174)
    - Minutes of IIRB Meeting on July 12, 2011 (p. 121)
    - English Language Informed Consent Form (p. 125)
    - English Language Newspaper Advertisement (p. 148)
    - English Language Subject Qualification Worksheet (p. 150)
    - English Language Interview Script (p. 152)
    - Spanish Language Informed Consent Form (p. 155)
    - Spanish Language Newspaper Advertisement (p. 168)
    - Spanish Language Subject Qualification Worksheet (p. 171)
    - Spanish Language Interview Script (p. 174)

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)
- AEATF II Standard Operating Procedures (SOPs) referenced in the AEA05 liquid pour protocol.

C. Summary Assessment of the Scenario Design

Supporting details are in Attachment 1.

1. **Scenario Design:** The Antimicrobials Division (AD) 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 liquid product. Pesticide products that are formulated as a liquid in a container meant to be manually poured are packaged in containers from ounces (fluid) up to 5 gallon buckets. AEATF II defines this liquid open pour scenario as "…the manual transfer of a product that contains an antimicrobial active from a source container into a receiving container. Each transfer of a volume of liquid from a source container to a receiving container is considered a pour. In some situations (e.g. use of an antimicrobial concentrate) the product is poured into a measuring container before it is transferred into another, secondary container (e.g. a bucket). In some occupations (e.g. cleaning professionals) workers may pour from same or various containers multiple times per day." (V1:13)[1] The liquid pour scenario is further subdivided into two separate scenarios: pouring liquids from either conventional containers or engineered containers designed to reduce splashing. A set of two distinct unit exposure values will be developed for these two scenarios.

   The conventional containers have no mechanisms to reduce the splashing that may occur while pouring. The conventional containers represent the typical packaging for most liquid products (e.g., 1-gallon plastic milk jug is a conventional container). The reduced splash containers have a feature to reduce splashing (and thereby potentially reduce exposure) such as an air bypass. "There is no official definition of the term "reduced splash" or "no-glug". In the Container
   Rule (EPA Final Rule published in Federal Register, Vol. 71, No 158, 47330, 2006), two specific performance requirements for reduced-splash are specified for non-refillable containers used to products classified in EPA Toxicity Categories I and II. Containers of these products must do both of the following actions:

   1. Allow the contents of the non-refillable container to pour in a continuous, coherent stream (40 CFR 165.25 (e)(1)).

[1] This pagination convention is used throughout this review. "V1" refers Volume 1 of the AEATF II submission; "V2" refers to Volume 2; "V3" refers to Volume 3; "V4" refers to Volume 4. Entries after the colon are page references; many page images bear more than one page number. In Volume 1, the cited page number is always from the expression "p. N of 33" found at the bottom right-hand corner. Volume 2 page references are always from the expression "p. N of 177". Volume 3 page references are always from the expression "p. N of 224". Volume 4 page references are always from the expression "p. N of 173."

2. Allow the contents of the non-refillable container to be poured with a minimum amount of dripping down the outside of the container (40 CFR 165.25 (e)(2)).

These requirements apply to non-refillable containers with a capacity of 5 gallons (18.9 liters) or less that are not aerosols, pressurized containers or spray bottles. No formal list identifying specific containers as being reduced-splash exists since the definition is performance based rather than product-specific. Reduced-splash containers can include vented containers; pressure-activated containers such as the bag in the box technology; the use of a siphon to pull concentrated material out of a container; and manually operated positive displacement pumps and dispensing systems. More detail regarding the scope of currently available technology for reduced-splash containers in located in Appendix 1 (V1:13-14)." Appendix 1 is located V1:30-33. Figure 1 illustrates a photo of a reduced splash container (notice the air bypass on the right side of the opening).

Figure 1. Reduced Splash Container (V1:32)

EPA intends to use the data developed by the AEATF II for the liquid pour scenario to describe a typical occupational or residential handler's daily exposure to liquid antimicrobial concentrated products while pouring. The data must be generic enough to be useful for estimating exposures using various size source (product) containers and types of receiving containers. AD plans to use the data generated from the proposed liquid pour study generically to estimate dermal and inhalation exposures and risks for other non volatile antimicrobial ingredients where the product is packaged in conventional or reduced splash containers that are manually poured. EPA will combine the results from this proposed scenario with the results from different application scenarios (for example, moping or wiping) in order to assess the exposure from the overall use of these products.

Antimicrobial products have been grouped by EPA into the 12 Use Categories listed below as presented in the proposed 158W data requirements. Although liquid pouring of an antimicrobial product may occur in many Use Categories, most open pouring situations are expected to occur in Use Categories I, II, III, IV, V, VII, VIII, XI, and XII.

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 liquid pour scenario is well defined, and with some minor recommendations detailed below we expect that the resulting data will meet the needs of EPA and other regulatory agencies. The diversity of daily exposures under the liquid 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 liquid pour scenarios and has incorporated random elements where feasible, except for the following two recommendation: (1) randomize the order in which the source containers are poured to avoid potential bias such as by always pouring first from the smallest source containers into the smallest receiving containers; and (2) randomize the use of the measuring cup in Group 2 for the 3 of the 6 subjects. 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 liquid antimicrobial products packaged in conventional and reduced splash containers. The proposed sample size for each scenario is 3 container size groupings (small, medium, large) with 6 subjects in each grouping (n=18 monitoring events (MEs) for conventional pour and 18 MEs for reduced splash containers). 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 liquid pour conventional and reduced splash scenarios will consist of professional applicators from janitorial and property maintenance occupations pouring a liquid antimicrobial product from small, medium, and large container sizes. The study participants will pour these source containers (the term "source" container is used because the actual antimicrobial product in this study is diluted and then packaged by the study investigator into various size containers without pesticide labels) into receiving containers; including 32 fluid ounce trigger spray bottles, 2 and 4 gallon buckets, and 10+ gallon basins. The physical aspects of pouring include holding the source container, removing cap/lid and then manually pouring the contents into either measuring cups and then into receiving containers or directly from the source container into receiving

containers. The study participants will pour the concentrate into measuring cups and subsequently into the receiving containers. When the receiving container is the trigger spray bottle the activity will also include filling the bottle with water and shaking.

The sampling design is complex and it is difficult to follow just how many and what size source containers each individual will handle. The best description of the number and size containers that each ME will pour can be found at V2:33. Table 1 below summarizes the number and size of source containers to be poured by each study participant for each of the conventional and reduced splash scenarios. The multiple size source containers listed for each of the 3 Groups will be randomly selected. For the conventional scenario, each study participant assigned to Groups 1 and 2 will pour a total of 10 source containers; each study participant assigned to Group 3 will pour 4 source containers. For the reduced splash scenario portion of the ME, the study participant will also be randomly assigned to a specific number and size of source containers to pour. The process will be the same as that used for the conventional scenario except that study participants in Group 1 and 2 will be assigned to pour 15 source containers each and Group 3 participants will pour 6 source containers each (V2:33). The same study participants used in the conventional scenario monitoring will also participate in the reduced splash scenario monitoring while donning the same dosimeters. Therefore, each ME will represent both the conventional and reduced splash scenarios and by using 2 distinct active ingredients the exposures from each ME can be separated into the 2 unit exposures. The distinction between the two scenarios is made by the two active ingredient used.

Table 1. Summary of Study Design.

Scenario	Group	MEs	Source Container Size and Number to be Poured	Total Volume Potentially Poured[a]	Receiving Container[b]
Conventional	1	6	Each ME to pour 10 containers randomly selected from 24, 32, and 64 fluid ounce sizes	40 oz to 5 gallons[c]	32 oz spray bottles and 2 gal bucket
	2	6	Each ME to pour 10 containers randomly selected from 96, 128, and 180 fluid ounce sizes	7.5 to 14 gallons	2 and 4 gallon buckets and 10+ gal basin
	3	6	Each ME to pour four 5 gallon buckets	20 gallons	10+ gallon basin
Reduced Splash	1	6	Each ME to pour 15 containers randomly selected from 60 and 64 fluid ounce sizes	60 oz to 7.5 gallons	32 oz spray bottles and 2 gal bucket
	2	6	Each ME to pour 15 containers randomly selected from 96, 128, and 180 fluid ounce sizes	11.25 to 21 gallons	2 and 4 gallon buckets and 10+ gal basin
	3	6	Each ME to pour six 5 gallon buckets	30 gallons	10+ gallon basin

[a] Total volume potentially poured will depend on the random selection of the container sizes.
[b] Study participants filling spray bottles will use a measuring cup. Measuring cups will also be used by all of the Group 1 MEs to fill the bucket as well as for 3 of the 6 MEs in Group 2.
[c] The minimum amount handled for an individual ME is calculated from the study participant filling 10 spray bottles x 4 fluid ounce pours from the measuring cup for each spray bottle.

The amount of product to be poured during each monitoring event will be varied based on the size of the source container and the receiving container (V1:23-24). For source container sizes 180 fluid ounces or less a smaller pre-measuring cup will be used. This measuring cup will be used for the trigger spray bottles and buckets. A single pour into a measuring cup will be used for the spray bottles while two pours into the measuring cup will be used for the buckets. For the buckets, the study participant will pour the remaining concentrate from the container into the bucket after the two measuring cup pours. The focus on the professional handler is a practical necessity, given that residential consumer use of products needing to be poured are of shorter duration and smaller amounts. Thus, the residential consumer would have a greater chance that the samples would be at or below the limit of detection of the analytical methods used. Because of greater quantities of antimicrobial, professional handler exposure is expected to be greater than that of consumers.

The AEATF II liquid pour study is designed to be representative of the use of antimicrobials in the marketplace. There is a wide variety of uses of antimicrobial 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: 21-24):

- **Source container type and size** – an array of source container sizes (conventional and reduced splash) were selected by the AEATF II during a survey of their membership. Source container sizes to be included in the study are 24, 32, 60, 64, 96, 128, 180 fluid ounces as well as 5 gallon buckets. The actual results of the survey are not reported in the protocol but the size source containers selected are reasonable. The selected source containers are allocated into Group 1 (small), Group 2 (medium), and Group 3 (large). The AEATF II notes that the sizes of the source containers may be updated prior to the study based on new technologies and availability (V1:21).
- **Receiving container type, size, and contents** – study participants will manually pour the concentrated product from the source containers into four different types of receiving containers including 32 fluid ounce trigger spray bottles, 2 and 4 gallon buckets, and 10+ gallon shallow basins. These receiving containers will all be empty prior to the open pouring of the source containers. The AEATF II states that the neck opening of the spray bottle "…is typically the standard 28 mm regardless of the capacity (V1:22)."
- **Height of pouring** – the study participants pouring the small source containers (Group1) into spray bottles will be told to pour as they *normally would do*. The small source containers (Group 1) will also be poured into the 2 gallon receiving buckets placed (randomly assigned) either on the floor or at waist to chest height on a table. The medium (Group 2) source container sizes will be poured into the 2 and 4 gallon as well as 10+ gallon receiving containers randomly located at either the floor level or at table height. The large 5 gallon bucket source container (Group 3) will always be poured into the 10+ gallon basin located at floor level.

- **Pouring volume and number of pours** – V2:33 provides the best description of the pouring volumes and number of pours by each study participant. In summary, the total volume poured by each individual study participant for the conventional containers ranges from 40 fluid ounces up to 20 gallons. For the reduced splash scenario each individual study participant will also pour a range of 60 fluid ounces up to 30 gallons. Because the same study participant will be pouring for both scenarios, there is a chance that the same study participant will be assigned to both the Group 3s, and will thus pour a total of 50 gallons (i.e., four 5-gallon conventional buckets and six 5-gallon reduced splash buckets).
- **Use or non-use of a measuring cup** – "A measuring cup will be provided to all subjects in Group 1 and to 3 of the 6 subjects in Group 2 (V2:31)." A single pour from the measuring cup will be used to fill the spray bottle and two measuring cups will be used to fill the buckets. For the buckets, after the two measuring cups are used the study participant will be instructed to pour the remaining product from the source container into the receiving bucket.

The pour liquid scenario is limited to pouring. Study participants will not apply the resulting mixed dilution. The AEATF II is developing data under other scenarios (e.g., mop and spray & wipe scenarios) which can be considered along with the results of this study when the situation warrants.

Various aspects of the study design incorporate randomization. The following is a list of the random design elements (V1:24-25):

- **Source containers** – there are three sizes of the source containers in each of the small (Group 1) and medium (Group 2) size groupings, except for the Group 1 reduced splash scenario where there will be only two size source containers. The large (Group 3) source containers are always 5 gallon buckets. There will be 6 MEs in each group. Each ME in the conventional scenario Groups 1 & 2 will be assigned 10 source containers to pour and in Group 3 four 5-gallon buckets to pour. The size of each of these 10 source containers will be randomly assigned from the available sizes. A random selection will also occur for the source container sizes for the reduced splash scenario. The specifics of the random selection procedures are not detailed in the protocol (e.g., how will the random selection occur? Are the sizes of the source containers equally likely to be any of the available sizes (this is what we assume) or if some sizes will be deliberately over-sampled?). Note: See below for the EPA recommendation to also randomize the order in which the various size source containers are poured during the ME and randomize the use of the measuring cup.
- **Receiving container height/location** – for the receiving containers to be placed on either the floor or the table the selection will be made randomly. The height of the 10+ gallon basin in Group 3 will always be on the floor (because of the weight of the 5 gallon source containers in Group 3). Once this height selection is made for a particular ME it will remain constant throughout that particular ME.
- **Scenario order** – the order in which the conventional source containers versus the reduced splash source containers are poured will be randomly selected.

- **Study participant assignment by size group** – study participants will be randomly assigned to group size source containers for both of the scenarios.

"The study will be conducted at one testing site. Since the study will be conducted indoors in a temperature controlled facility under simulated test conditions the activity of pouring is unaffected by the physical location of the room. As such, there is no need to conduct the monitoring in multiple geographic locations (V2:27)."

The study will be conducted in two rooms within a laboratory located in Concord, Ohio. "The use of a single geographic location for the field phase of the study is based on the premise that the type and variety of indoor liquid pouring activities being performed will not differ substantially from a similar array of tasks being performed at other indoor locations (V1:25)." "The purpose in conducting these studies in an environmental chamber or room is to be able to control and measure environmental conditions such as temperature, relative humidity and air exchange rates and air flow (V1:25)."

In order to make the most effective use of a limited number of monitoring events, the overall sampling design is purposive. No feasible opportunities to incorporate random elements in the sampling design have been overlooked except that EPA recommends randomizing the order in which the source containers are poured and the assignment of the use of the measuring cup in Group 2 for 3 of the 6 subjects.

3. **Choice of Surrogate Material:** The choice of n-alkyl dimethyl benzyl ammonium chloride (ADBAC) and didecyl dimethyl ammonium chloride (DDAC) as the antimicrobial materials for these scenarios are appropriate. The C14 portion of ADBAC is the active ingredient to be measured on the dosimeters. The AEATF II has experience with these two materials from prior studies, they are widely used, readily available, and there are reliable and sensitive analytical methods available for them.

   "The selected products are Maquat WP (EPA Reg. No.10324-91) and Maquat DS 1412-10% (EPA Reg. No. 10324-25). The active ingredient in Maquat WP is DDAC (CAS# 7173-51-5) while the active ingredient in Maquat DS 1412-10% is ADBAC (CAS# 68424-85-1). Diluted Maquat WP (DDAC) will be the test substance used in the conventional pour events while diluted Maquat DS 1412-10% (ADBAC) will be the test substance used in the reduced-splash pour events (V1:26)."

   "The formulated products will be diluted and dispensed into the various containers either at a manufacturing site or laboratory prior to their use in the study by a chemist who is not involved in the conduct of this study. The target concentrations to be used in this study are 0.2% total ADBAC and 0.2% DDAC. These concentrations were chosen as they represent what can be purchased by consumers and do not trigger the need for protective gloves or any other PPE. These concentrations are higher than what was used in the AEATF Mop Study (0.027% ADBAC and 0.04% DDAC) to help maximize the potential for detectable residues (V1:26-27)."

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

Supporting details are in Attachment 2.

1. **Statistical design:** "…existing data are either of poor quality or only marginally relevant to the pouring of antimicrobial containing liquids. 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." (V1:18).

   "For this particular scenario the AEATF II is creating three groups to increase diversity based on source container size, container pouring characteristics, and amount of active ingredient handled. There will be three groups of source container sizes, with 6 MEs per group, resulting in a total of 18 MEs for conventional pour and 18 MEs for reduced splash pour (V1:18-19)."

   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 alternative considerations that were made during the review of this final protocol are discussed below:

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

     Although the JRC has selected AaiH as the normalization variable for the unit exposure, the discussion at the April 2011 HSRB meeting for the wipe study briefly inquired about switching from stratifying the sample based on duration (and hence approximately AaiH) to concentration. EPA considered stratifying the sample by varying the ADBAC and DDAC concentrations. To incorporate concentration into the design process of AEATF II liquid pour scenario, we would need to ensure sufficient diversity in the normalizing factor (i.e., concentration) to permit users of the data some ability to examine the reasonableness of this particular choice. More specifically the sample size for the alternative study design should be determined in such a way that there should be at least 80% statistical power to distinguish complete proportionality from complete independence between exposure and

concentration for a given reference model. The practical range of concentration for the alternative design should be from 0.02 to 0.20 percent. Higher concentrations could not be selected or the workers would need to wear chemical resistant gloves (which would change the scenario by including personal protective equipment (PPE)). In this proposed analysis, either equal numbers of tests are made at the concentrations of 0.02 and 0.2 percent, or equal numbers of tests are made at the four logarithmically spaced concentrations of 0.02, 0.043, 0.093, and 0.2 percent.

Since these statistical power calculations are intended to evaluate the effects of concentration changes, the assumption is also made here that the variances attributable to the chemical used, source container size, receiving container size, volume poured, and other potential factors are also zero, so that the exposure can depend only upon the concentration. In particular this assumption implies that the grouping by source container size has no effect on the normalized exposure and that the effect of amount of active ingredient handled on exposure depends only on the concentration and not on the volume. In reality it is plausible that the exposure depends on one or more these factors including the concentration, but a simplified set of assumptions is used to simplify the statistical analysis by focusing solely on concentration effects.

For each simulated new configuration of MEs, exposure data are simulated for the MEs assuming proportionality with the concentration levels, which implies that the slope of the true regression between log exposure and log concentration is 1. For each simulated set of data, a regression analysis is then performed and the significance of the log-log slope determined (using a 2-sided test). The power is the proportion of the simulation configurations for which the slope was significant at $p < 0.05$. From the simulation study (10,000 simulations) the following results were found (Table 2):

Table 2. Summary of Simulation Results

N (Total number of MEs)	Concentrations (Number of MEs per concentration)	Power
14	0.02 (7), 0.2 (7)	0.81
18	0.02 (9), 0.2 (9)	0.91
18	0.02 (5), 0.043 (4), 0.093 (4), 0.2 (5)	0.73
22	0.02 (6), 0.043 (5), 0.093 (5), 0.2 (6)	0.82

Thus if the two most widely spread concentrations are used, then the proportionality to concentration can be detected with a power of 0.8 or more using only 14 MEs, and the power increases to 0.9 if 18 MEs are used (as in the current liquid pour experimental design). If the four logarithmically spread concentrations are used, then the proportionality to concentration can be detected with a power of 0.8 or more using 22 MEs, but the power is only 0.7 if 18 MEs are used (as in the current liquid pour experimental design). These designs have higher power than the CEB analyses using designs with

randomly selected concentrations that required a total of 39 MEs to achieve 80% power because of the lower variability of the concentrations.

A crucial assumption in these analyses is that the exposures to a concentration as low as 0.02 % ai can be detected. Otherwise it would be necessary to increase the concentration levels to maintain the same order-of-magnitude differences and thus the same power, which might require the highly undesirable need for personal protective equipment (PPE).

EPA did not recommend this modification to the study design for several reasons including: (1) lowering the percent of active ingredient by perhaps an order of magnitude would increase the risk of obtaining non detect samples; (2) a higher percent ai would require the need for personal protective equipment (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; container size is not regulated. It is important to include various size source containers in the sampling design. Therefore, the diversity of the variables selected by the AEATF II (e.g., range of source container sizes from 24 fluid ounces to 5 gallon buckets; size and type of receiving container such as spray bottles versus 10+ gallon basins; use of measuring cups or not; height of pouring) can be reasonably assumed by the JRC to provide a rough estimate of the high end of exposure.

- **Consideration was given to the MEs in Group 2 that will make 2 measuring cup pours into the receiving bucket and subsequently pour the remaining contents from the source container into the receiving bucket:**

  By pouring the remaining product from the source container after making 2 measuring cup pours the effect could be to dilute the normalized exposure for that ME. The dilution to the normalized unit exposure (e.g., mg ai/pound of ai handled) may occur if the act of using the measuring cup increases the likelihood of exposure. Thereby the greatest exposure observed over the ME is based only a small portion of the total active ingredient in the source container. In other words, if the bulk of the exposure is due to the pouring into a measuring cup, then the normalized exposure ought to be calculated as the exposure divided by the amount of active ingredient poured into the measuring cup(s), rather than the much lower ratio of the exposure divided by the total amount of active ingredient poured. Typically if a person using a pesticide needs to measure only a portion of the volume in the source container (such as using a mop bucket), they would not then pour the remaining contents of the container into the receiving container. EPA did not recommend modifying this aspect of the study design because only 3 of the 6

MEs will be using the measuring cups in Group 2 (the other 3 MEs in Group 2 will pour the entire contents of the source container directly into the receiving container). Additionally, the use of the measuring cup for the spray bottles will capture the effect the measuring cup has on exposure in the final distribution of the scenario. However, EPA remains open to comment on this issue (e.g., either do not use the measuring cup in Group 2 at all or do not pour the remaining source container for the Group 2 MEs that use the measuring cup).

2. **Proposed pattern of human exposure:** The AEATF II proposes to select professional janitors and property maintenance workers as the study participants for the liquid pour scenarios. The study participants will manually pour two different products that have been diluted to 0.2 percent active ingredients. The diluted product rather than the originally packaged concentrates will be prepared prior to the study and will not be monitored. This is necessary to have a concentrated product that will not result in the need for chemical resistant gloves (concentrated DDAC and ADBAC are dermal irritants) and to have each active ingredient in its own source container (many existing products are a combination of both DDAC and ADBAC). Depending upon which Group the study participant is randomly assigned to they will pour the entire contents from 4, 6, 10, or 15 source containers which range from 24 fluid ounces to 5 gallons. The duration of pouring will be based on how long it takes each study participant to pour the prescribed amount as they *would normally do*. There is no prescribed duration; the AEATF II estimates the expected range of duration to be 10 to 60 minutes (V2:14). The physical aspects of pouring include manually picking up the source container, opening the top, and pouring the contents into either measuring cups and then into receiving containers or directly into various types of empty receiving containers placed at either floor or table height. The study participants, who will be randomly selected to measure the product in measuring cups prior to adding to spray bottles, will also fill the spray bottles with water. EPA is recommending that the study participant be allowed to make the selection of filling the empty spray bottle from the source container either before or after filling it with water (i.e., let them fill the bottle as they *normally would do*). The study participants will not apply the mixed solutions generated from this study. The various types of applications (e.g., spray & wipe, mop, etc) will be monitored in separate AEATF II studies.

   The EPA believes that the AEATF II liquid pour study will represent typical worker and/or consumer methods of open pouring from source containers. The selection of janitorial and property maintenance subjects, test materials, source container sizes, receiving containers, pouring heights and associated activities (e.g., use of a measuring cup) as described in the protocol is justified.

3. **Endpoints and Measures:** The AEATF II proposes to measure dermal and inhalation exposures resulting from manually open pouring a liquid antimicrobial product. Dermal and inhalation exposure will be measured using whole-body dosimeters (inner and outer), hand and face washes, and personal air monitors. 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). The sampling train will consist of OSHA Versatile Sampler (OVS) tubes with glass filters backed by XAD2 sorbent (AEATF II-SOP 8D.1; V4:105-108). Because the air sampling will not size particles, the Agencies will assume conservatively that all of the residues are inhalable and/or respirable, which will tend to overestimate inhalation exposure. The sampling pumps will be calibrated prior to use.

Environmental parameters of the work area such as air temperature, and relative humidity will also be documented at 5 minute intervals per SOP 10C. "A facilities maintenance engineer with HVAC training or an industrial hygienist will be retained to document the HVAC system and measure the air exchange rate. The dimensions of the rooms will be measured and documented in study field notes. It will be noted whether the HVAC and/or vent fans are operating during each ME (V2:48)."

4. **QA/QC Plan:** The AEATF II QA/QC plan for the liquid 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: samples to be simultaneously fortified with both ADBAC and DDAC (V2:49); two fortification levels per matrix with the low level 3 to 4x the LOQ (V2:50), triplicate samples per fortification level (V2:50), 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 proposed statistical model for these data differs from the mixed effects modeling used for the earlier mop and wipe studies 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 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 95th 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. If the groups have different intercepts, then additional summary statistics (and confidence intervals) will be calculated to summarize the overall distribution, either by using the group with the highest summary statistics as a worse-case scenario, or by using the fitted models to estimate the exposure distribution assuming each container size group is equally likely to be used in the population. 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). Note however, that some preliminary statistical modeling suggests that the sample sizes may not be large enough to detect proportionality from independence with sufficient statistical power (e.g., above 80%). In light of the sample size needed to achieve statistical power we do not plan to test for proportionality; but rather use a conservative approach (protective of human health) when we select the unit exposure. 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.

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:

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

- Allow random selection for two additional items: (1) randomize the order in which the randomly-selected source container sizes are poured; and (2) randomize the selection of which three subjects will use a measuring cup in Group 2.

- Allow the study participants to fill the spray bottles from the source container and with water in the order they *would normally do* as opposed to the researchers directing them to fill with water after pouring the concentrate from the measuring cup.

- Provide a description of how the different size source containers will be randomly assigned to each ME.

- Provide details about how the airflow in the laboratory room will be measured and what the target airflow will be (e.g., will the airflow be minimized?).

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 liquid antimicrobial products. This activity involves open pouring from various sizes of containers both with and without engineering to reduce splash. Because many consumers and workers pour 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:** Twenty-two adult subjects will be recruited among professional janitorial workers in Concord, Ohio and Lake County, Ohio. Participants will self-identify in response to newspaper advertisements. The protocol does not identify the newspapers in which the 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.

   Callers responding to the newspaper advertisements will be screened, scheduled for informed consent meetings, and enrolled at the volunteer's convenience. Although additional randomization could be obtained if candidates for informed consent meetings and enrollment were randomly selected from a pool of respondents, the AEATF II has concluded that it is necessary to enroll subjects as they are processed. The AEATF II learned in recruiting for previous studies that delaying enrollment in

order to compile and randomize a list of potential subjects is infeasible because it results in significant attrition among potential participants and delays in the recruiting process.

Participants will be screened from among respondents to newspaper advertisements, and in that sense they will be representative of the population of janitorial service workers in the Concord, Ohio and Lake County, Ohio area. There is no reason to think that janitorial service workers in these areas are not typical of janitorial service workers in any other area of the United States.

The inclusion/exclusion criteria are complete and appropriate. Pregnant or nursing women are excluded from participation. Employees or relatives of employees of the investigators and of cleaning product manufacturers 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 materials are EPA-registered for the use proposed, are of low toxicity to mammals, and will be used in full compliance with the approved labels. Risks to subjects include risks of a reaction to the test material or the solvents used to obtain residues from hands and face/neck; of discomfort and possibly heat-related illness associated with wearing two layers of clothing while doing physically demanding work; 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. All identified risks are characterized as of low probability.

   Risks are minimized by exclusion of candidates known to be sensitive to quaternary ammonium compounds or in poor health or with broken skin on hands, face, or neck; testing in a controlled-temperature environment; 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; close observation of subjects; training of experienced technicians to minimize embarrassment; incorporation of procedures to keep results of pregnancy testing private and to permit discrete withdrawal; provision of appropriate work clothing and PPE.

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 liquid antimicrobial products from conventional and reduced-splash containers. 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 Independent Investigational Review Board, Inc., (IIRB) of Plantation Florida. The submitted materials include a full record of correspondence between the investigators and the IIRB.

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.

   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 protocol and/or consent form should be revised as follows and resubmitted for review by the approving IRB:

- 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.

- Remove all generic references to "second alternate language" or "alternate language as appropriate to the area/population" and replace with "Spanish."

In addition, the AEATF should incorporate the forthcoming guidance from the HSRB's working group about how to provide personal exposure results to subjects.

Before submitting future protocols, the AEATF-II should develop a process for improving and verifying the accuracy of the Spanish translations, and articulate that process in an SOP or the protocol.

EPA Ethics Conclusions

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

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

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 Liquid Pour Scenario Design dated July 28, 2011
2. Summary Review of AEATF II Protocol AEA05 dated July 28, 2011
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 Liquid Pour Scenario/Protocol

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

Date: July 28, 2011

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 liquid 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 liquid pouring task characteristics (V1:21)." The AEATF II liquid pour design appropriately proposes to diversify the sampling characteristics by selecting various source container types and sizes; receiving container types, sizes, and contents; height of pouring; pouring volume and number of pours; and the use or non-use of a pre-measuring cup (V1:21).

Preliminary versions of the AEATF II liquid 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. Many varied antimicrobial products can be formulated as a liquid and packaged in different size containers. Liquid formulations packaged such that they can be manually poured (i.e., containers up to ~ 5 gallons) are common in residential (consumer) settings as well as in commercial/occupational settings such as cleaning-type products with antimicrobial claims (e.g., mopped onto floors or sprayed onto hard surfaces), swimming pools and spas, pulp and paper mills, cooling towers, metal working fluids, etc.

Product containers include various sizes as well as conventional pour containers and reduced splash containers designed to reduce splashing of the liquid. Most liquid formulations have the viscosity of water. From this array of choices, the consensus among the AEATF II and the three regulatory agencies was to separately monitor the

conventional versus reduced splash containers as the results can be translated to the label as a type of engineering control (i.e., restrict packaging to reduced splash containers).

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

"Some pour liquid data does 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 open pour liquid scenario currently available comes from PHED (EPA, 1998). However, these data are based on the mixing and loading of agricultural pesticides and do not necessarily represent how antimicrobials are typically used. As such, these data poorly reflect current pouring methods and containers used for antimicrobial pesticides (V1:15)."

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 open pouring of liquid products.

2. Rationale for Scenario Sampling Design

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

The design choices in the two liquid 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 volume and number of pours; (6) use or non-use of a measuring cup; and (7) using different workers for each monitoring event within a scenario (the same worker will complete a ME for both conventional and reduced splash container by using a separate active ingredient in each of the containers).

Source Containers. Source containers are grouped into three sizes: small, medium, and large. The sizes of the containers cover close to the range that one could feasibly find in the market place and manually pick up to pour. These sizes include 24, 32, 64, 96, 128, and 180 fluid ounces as well as 5 gallon buckets for the conventional containers. The range of sizes is similar for the reduced splash with a minimum size of 60 fluid ounces.

Receiving Containers. Four different receiving containers are proposed: (1) 32 fluid ounce spray bottles; (2) 2 gallon buckets; (3) 4 gallon buckets; and (4) 10+ gallon basins. The receiving containers will be empty to maximize the splash-back effect to capture the high end of exposure conditions. The workers that fill the spray bottles and 2 gallon buckets will first pre-measure the concentrate from the source container before adding it to the receiving container. The spray bottles will then be filled with water by the worker and shaken. Study participants should be allowed to

work as they *normally would do* and decide for themselves which order to fill the spray bottles with concentrate and water.

Height of Pouring. The height at which the workers hold the spray bottles will be left up to the discretion of the worker. The 2 and 4 gallon buckets and 10+ gallon basins will be placed either on the floor or on a table to vary the height. The pouring height of the 5 gallon buckets into the 10+ gallon basins will always be on the floor level.

Pouring Volume. The amount of liquid poured and number of pours will depend upon the size of the source containers used. For the conventional scenario, each ME will consist of pouring 10 containers in the small (Group 1) and medium (Group 2) size containers. There are three different size source containers in these groupings and the sizes will be randomly selected (some more than once because a total of 10 containers will be poured in each ME). Each ME in the large (Group 3) container grouping will pour four 5 gallon buckets. For the reduced splash scenario, each ME in Groups 1 and 2 will pour 15 source containers of the various sizes and six of the 5 gallon buckets in the Group 3 (V1:26-27) and (V2:33). The amount of active ingredient handled (AaiH) will be determined by the total volume poured and the percent active ingredient. For example, for the reduced splash scenario Group 3, the worker will pour 6 source containers that are 5 gallons each for a total of 30 gallons. The amount of active ingredient in 30 gallons is as follows: 30 gallons product from source containers x density (assume density of water 8.34 lb/gal) x 0.002 ai by weight = 0.5 lb ai.

Measuring Cup. Some antimicrobial products are pre-measured using a measuring device and then poured into, for example, spray bottles or mop buckets. The workers will be pouring first into a measuring cup and then pouring that measured portion into the spray bottles and 2 gallon buckets. The spray bottles pours will consist of single measuring cup while the bucket receiving container will receive two measured pours. Afterwards the entire contents of the source container will also be poured into the bucket.

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

"A total of 22 subjects will be recruited for this study. Each subject will be assigned a unique identification number starting at AEA05-01 and ending with AEA05-22. The subject numbers 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 will determine the participating subjects, while the remaining subjects will be held as alternates, their order for potential entry into the study being determined by the randomization process. The 4 alternate subjects will be on-call for the duration of the study. Alternates will get compensated as if they participated in the study (V2:34)."

"Containers within each source container group: the number and size of containers used by each test subject will be randomly assigned within each group. For example in the

PL/C – Group 1, two 24 oz. containers, six 32 oz. container and two 64 oz. containers for a total of 10 containers may be selected. Depending on availability of the containers it is possible that the appearance and opening of the two 24 oz. containers may be different. The actual selection will depend on what is available for the study. A description of the containers used in each ME will be entered into the field trial notebook." (V1:24)

"For each monitoring event the location of the receiving container (floor or table) will be randomly assigned. This location will be constant for the entire monitoring event. The exceptions to this will be for the trigger spray bottle and the pouring of the 5 gallon pails. The location of the trigger spray bottle during filling will not be specified; the test subject will be allowed to hold or place it as they normally would. The 10 gallon receiving container for the 5 gallon source containers (Group 3) will always be placed on the floor to avoid potential ergonomic injury to study participants during the lifting and pouring of the 5 gallon pails (V1:24)."

"The order of the PL/C and PL/RS scenario (i.e. which one is done first) will also be selected randomly to avoid a potential systematic bias of someone becoming more proficient with pouring. Modifications in this assignment scheme may be made if questions concerning potential ergonomic injury arise (V1:25)."

"The final randomization will be to assign each study participant to a set of PL/C and PL/RS scenarios. Because this is a random process, it may be possible that the same person will not handle the same size containers for his two monitoring events. 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 (V1:25)."

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

Two additional random elements should be added: (1) randomize the order in which the randomly-selected source container sizes are poured; and (2) randomize the selection of which three subjects will use a measuring cup in Group 2.

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

"The AEATF II Monitoring Program defines an antimicrobial pouring liquids scenario as the manual transfer of a product that contains an antimicrobial active from a source container into a receiving container. Each transfer of a volume of liquid from a source container to a receiving container is considered a pour. In some situations (e.g. use of an antimicrobial concentrate) the product is poured into a measuring container before it is transferred into another, secondary container (e.g. a bucket). In some occupations (e.g. cleaning professionals) workers may pour from same or various containers multiple times per day. Generally, pouring of a liquid containing a biocide is only a small part of a larger task where other potential exposures to the biocide may occur. In this study only the exposure from the actual pouring task will be measured. Information about the potential

exposure resulting from pouring liquids can then be used in combination with analogous information for other scenarios to estimate total exposure to antimicrobial products for larger task. Two specific liquid pouring scenarios are of interest to AEATF II. These are:

- Pouring liquids from conventional containers (PL/C), and
- Pouring liquids from reduced-splash containers (PL/RS)

Reduced-splash containers, also called "no-glug" containers, can encompass a range of different container types and sizes. In general they possess an air bypass or other design feature that prevents or reduces splashing that could cause exposure. Conventional containers do not have design features intended to reduce splashing. Both conventional and reduced-splash containers are commonly used for antimicrobial products and are expected to have different exposure potentials (V1:13)."

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

The study will monitor only professional janitors and property maintenance workers, so any differences in behavior that a consumer may exhibit while pouring a liquid product will not be monitored. However, given that pouring a liquid product from a container is not a specialized task, the exclusion of consumers from the sampling design is not considered to be a limiting factor. "In this study, the subjects will be recruited from janitorial service and property maintenance companies. Since pouring is a generic activity, no differences in pouring techniques are expected as a function of the industry, occupation, or worker population being evaluated. No special techniques or training is needed to pour a liquid from one container into another. The janitorial and professional maintenance populations were chosen because they use antimicrobial products frequently and this is a readily identifiable group who handle antimicrobial products compared to other occupations. Additionally the AEATF II has experience at recruiting from this population. Subjects will be recruited from the surrounding geographic area." (V1:26)

The liquid pouring scenarios exclude the task of application of the pour product. 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 substances, ADBAC and DDAC, are appropriate choices for the development of surrogate exposure data because they are both stable, characterized by low vapor pressures (estimated to be 2E-11 mmHg for both ADBAC and DDAC), low concentrated solutions are not dermally irritating, no systemic toxicities were seen in 90-day dermal rat studies, and they have been demonstrated to have low analytical limits of detection.

"To leverage analytical work which has already been conducted as part of the AEATF II program and avoid the need to conduct hand rinse efficiency recovery studies with other active ingredients, the active ingredients DDAC (didecyl dimethyl ammonium chloride)

and ADBAC (n-alkyl dimethyl benzyl ammonium chloride) have been selected for the pour liquid study. The products to be used in this study are registered formulated products that will be diluted prior to use. The selected products are Maquat WP (EPA Reg. No.10324-91) and Maquat DS 1412-10% (EPA Reg. No. 10324-25). The active ingredient in Maquat WP is DDAC (CAS# 7173-51-5) while the active ingredient in Maquat DS 1412-10% is ADBAC (CAS# 68424-85-1). Diluted Maquat WP (DDAC) will be the test substance used in the conventional pour events while diluted Maquat DS 1412-10% (ADBAC) will be the test substance used in the reduced-splash pour events (V1:26)."

"The target concentrations to be used in this study are 0.2% total ADBAC and 0.2% DDAC. These concentrations were chosen as they represent what can be purchased by consumers and do not trigger the need for protective gloves or any other PPE (V1:27)."

ADBAC and DDAC have been approved for use in many formulations, and are extensively used in many janitorial and consumer products. The EPA has recently re-registered both DDAC and ADBAC and issued Reregistration Eligibility Decision (RED) documents for both (EPA, 2006a,b).

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 liquids. 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 (V1:18)."

EPA Protocol Review: AEATF II Liquid Pour Scenarios/Protocol

Title: A Study For Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of a Liquid Containing an Antimicrobial

Date: July 28, 2011

Principal Investigator:
Leah Rosenheck

Participating Laboratories:
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Sponsor: American Chemistry Council
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Reviewing IRB: Independent Investigational Review Board
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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 pouring of liquid antimicrobial products. ….. The data generated from this biocides pouring use pattern should be sufficient to complete the data set for this pouring scenario (V2:10)."

"The purpose of this research project is to find out how much chemical people are exposed to when pouring liquid disinfectants from different size containers. We will do this by measuring how much of the disinfectant gets onto the clothing you wear and on your hands and face while you pour. We will also measure how much chemical gets into the air while you are pouring the disinfectants (V2:99)."

(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 pouring of liquid

antimicrobial products. ….. The data generated from this biocides pouring use pattern should be sufficient to complete the data set for this pouring scenario (V2:10)."

"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 (V2:11)."

"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 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 (V2:14-15)."

(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 liquid formulations and poured into other containers prior to applications.

(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 (V2:16)."

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 pouring of liquid

antimicrobial products. ….. The data generated from this biocides pouring use pattern should be sufficient to complete the data set for this pouring scenario (V2:10)."

"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 (V2:61)."

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 22 subjects will be recruited for this study. Each subject will be assigned a unique identification number starting at AEA05-01 and ending with AEA05-22. The subject numbers 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 will determine the participating subjects, while the remaining subjects will be held as alternates, their order for potential entry into the study being determined by the randomization process. The 4 alternate subjects will be on-call for the duration of the study. Alternates will get compensated as if they participated in the study.

The 18 subjects selected to participate in the study will be randomly assigned to one of the three container size groups for conventional pour and to one of the three container size groups for reduced splash pour. Randomly assigning subjects to each group means that they may not necessarily be handling the same size containers and amount of chemical for both the conventional pour ME and the reduced splash pour ME.

For purposes of assigning subject numbers to container 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 container size groups for each type of container. Note that that each participant will be assigned to two randomly selected subject identification numbers, one to determine the group for conventional pour and one to determine the group for reduced splash pour. The randomly selected subject identification numbers will correspond to a ME (V2:34)."

(e) 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.

(f) 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 (V2:61)."

"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 (V2:61)."

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

Yes.

(h) 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 liquid product. EPA is confident that this design will provide data on liquid pour exposures more accurately and reliable than currently available data. See Section A.3.C.5 above for additional discussion of the statistical plan.

2.2 How and to what will human subjects be exposed?

"Subjects will be brought to the monitoring area containing all the containers they are expected to pour and the appropriate receptacle containers. They will be informed as to when and how many times to use the measuring cup and when to just pour from the container directly into the receiving receptacle(s). ... Subjects will be asked to begin pouring the way they normally do on the job (V2:43)."

Test subjects will be exposed during liquid pouring according to typical practices. Pouring will include the study participants manually picking up the source container, opening the top or lid, and pouring the contents into either measuring cups and then into receiving containers or directly from the source container into various types of empty receiving containers which will be placed at either floor or table height. The study participants which are randomly selected to measure the product in measuring cups prior to adding to spray bottles will also fill the spray bottles with water and shake. The study participants will not apply the mixed solutions generated from this study. The various types of applications (e.g., spray and wipe, mop, etc.) will be monitored in separate AEATF II studies.

Each test subject will be exposed to two chemicals. "Both are registered formulated products designed to be diluted prior to use. The products are Maquat WP (EPA Reg. No.10324-91) and Maquat DS 1412-10% (EPA Reg. No. 10324-25). The active ingredient in Maquat WP is DDAC, didecyl dimethyl ammonium chloride (CAS# 7173-51-5) while the active ingredient in Maquat DS 1412-10% is ADBAC, n-Alkyl dimethyl benzyl ammonium chloride (CAS# 68424-85-1) (V2:22)."

"Diluted Maquat WP (DDAC) will be the test substance used in the conventional pour events while diluted Maquat DS 1412-10% (ADBAC) will be the test substance used in the reduced-splash pour events (V2:22)."

"Both Maquat WP and Maquat DS 1412-10% will be diluted to a 0.2% active ingredient solution for use in this study. This concentration was chosen because products containing 0.2% DDAC and ADBAC are available for consumer purchase and do not require the use of protective equipment including gloves. Examples of such consumer products include EPA Registration Number 4822-554 (SC Johnson), EPA Registration Numbers 5813-55, 62, 73, and 96 (The Clorox Company), EPA Registration Number 6836-195 (Lonza Inc.), and EPA Registration Number 1839-83 (Stepan Company) (V2:22-23)."

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

The choice of the formulation type (i.e., liquid) is to collect data for liquid formulations. The AEATF II will collect exposure data for other types of formulations (e.g., solid) at a later date.

"To leverage the analytical and field experience gained in the previously conducted AEATF studies, the task force has decided to use DDAC, didecyl dimethyl ammonium chloride (CAS# 7173-51-5) and ADBAC, nalkyl dimethyl benzyl ammonium chloride (CAS# 68424-85-1) as the active ingredients in the pour liquid scenario. This decision is further reinforced by the stability of these two products and the sensitivity of the analytical methods. Additionally ADBAC and DDAC have complete toxicology databases with low mammalian toxicity. Analytical techniques

can distinguish between these two quats on the same dosimeters, thus allowing the use of the same dosimeters (i.e., whole-body dosimeter, hand wash, and air sampler) to monitor both conventional and reduced-splash containers (V2:24)."

"In a search of the existing registered products, no low concentration product containing only DDAC or only ADBAC could be located. Therefore, it was decided to select high concentration formulated products as the test materials and dilute them to 0.2% prior to their use in the study. Using the diluted single active ingredient products will allow monitoring to be done without the need to wear protective gloves or a second layer of clothing (V2:24)."

The limits of quantification (LOQs) for both ADBAC and DDAC are sensitive: air samples 10 ng/tube, hand wash 2 ng/mL, face/neck 50 ng/sample, dosimeters 3 ug/sample.

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

In this study, all MEs will apply both ADBAC and DDAC.

"The total amount of product poured by each subject per ME will range from 240 fl oz to 3,840 fl oz (30 gallons) depending on the size of the container being used and the number of containers handled. In order to achieve diversity in the pouring conditions with respect to the source containers, subjects will be placed into one of three groups based on the source container size. There will be 6 subjects randomly assigned to each of the three groups. This will ensure a range of container sizes are used to generate a distribution of exposure data for this open pour liquid scenario. The exposure data from all three groups will be combined to generate one unit exposure number to use in risk assessments for liquid formulation products that are poured manually.

Each subject will conduct two sets of monitoring events, one with the conventional containers and one with the reduced splash containers. This will generate 18 data points for conventional pouring and 18 data points for pouring from reduced splash containers. The three groups will be defined as follows:

Group 1: Small size container group:
a. Conventional 16, 24 or 32 oz ―necked container; and
b. Reduced splash 60 - 64 oz containers

Group 2: Medium size container group:
a. Conventional 96, 128 (1 gallon) or 180 oz "handled" container; and
b. 96, 128 (1 gallon) or 180 oz reduced splash handled container (vent system)

Group 3: Large size container group:
a. Conventional 640 oz (5 gallon) open container (pail); and

b. Reduced splash 640 oz (5 gallon) closed container (pail with lid, vent & pour spout)

Within these groupings other characteristics such as the use of a measuring cup and the size, type, and location of the receiving containers will also be varied to the extent feasible to provide for diversity in the data set (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 10 to 60 minutes (V2:14).

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. Subjects will wear their own socks and shoes. Hand exposure will be measured by rinsing the hands with a solution of 50% isopropyl alcohol/ 50% distilled water. Face and neck exposure will be measured by wiping the face and neck with gauze pads moistened with 50% isopropyl alcohol / 50% distilled water. Dosimetry SOPs are provided in SOPs 8A through 8D (V4:85-108).

"The amount of product poured will be determined by gravimetric analysis of the full, partially empty, and empty containers used by each subject (V2:14)."

"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. 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 be retained to document the HVAC system and measure the air exchange rate. The dimensions of the rooms will be measured and documented in study field notes. It will be noted whether the HVAC and/or vent fans are operating during each ME (V2:48)." EPA notes that SOP AEATF II-10C does not provide much detail for the automated instrumentation (see V4:132).

(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 (V2:61)."

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 substances) will be performed on both of the formulated products prior to use in the study and a Certificate of Analysis will be kept in the raw data file. Samples of the diluted product used in the study will be collected and analyzed to verify the concentration (V2:23)."

(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 (V2:61)."

(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 (V2:61)."

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 liquid antimicrobial products into mop buckets or spray bottles for dilution; pouring liquid antimicrobial products into washing machines, swimming pools, spas, cooling towers, pulp & paper mills; and pouring liquid antimicrobial products in other industrial situations, including metal working applications and paint manufacturing.

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

(b) From what populations will subjects be recruited?

"In order to obtain a subject pool who is familiar with handling and pouring containers of antimicrobial products, adult subjects will be recruited from the janitorial/cleaning service population from Concord, Ohio and the surrounding Lake County where the test site is located. The monitoring of janitorial and professional maintenance workers provides a larger pool to recruit from compared to other occupations that involve the handling and pouring of antimicrobial products. Additionally the AEATF has previous experience at recruiting from this population. To adequately capture the ethnic diversity in the area, recruitment materials and all communications with potential subjects will be available in English and a second alternate language appropriate for this region and population of concern." (V2:32)

Subjects will be recruited through advertisements in local newspapers. The IRB-approved advertisement provides a telephone number for individuals to call if they are interested in participating in the study. (V2:32)

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

Expected participants will self-identify in response to advertisements placed in local newspapers. The AEATF has yet to 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.

Individuals who express interest in response to a newspaper advertisement about this study may differ in unknowable ways from other workers who do not step forward. However, there is no reason to think that janitorial service workers in Concord, Ohio and/or Lake County, Ohio are atypical of janitorial service workers in any other area of the United States.

(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.

"The AEATF II Monitoring Program defines an antimicrobial pouring of liquids scenario as the manual transfer of a product that contains an antimicrobial substance from a source container into a receiving container. Each transfer of a volume of liquid from a source container to a receiving container is considered to be a pour. In some situations (e.g. use of an antimicrobial concentrate) the product is poured into a measuring container before it is transferred into another, secondary container (e.g. a bucket). In some occupations (e.g. cleaning professionals) workers may pour from the same or various containers multiple times during their work day. In this study only the exposure from the actual pouring task will be measured. Information about the potential exposure resulting from pouring liquids can then be used in combination with analogous information for other use scenarios to estimate total exposure to antimicrobial products for combined daily work activities. The primary objective of this study is to monitor exposure to professional workers who manually pour liquid products containing antimicrobials.

"The basic element in this simulated-condition study involves the pouring of a liquid formulation or diluted formulation which is defined as a monitoring event (ME). Each

ME will consist of measuring potential dermal exposure (through use of inner and outer dosimeters) and inhalation exposure (through air sampling tubes collecting breathing zone air concentrations) for a single subject working within a specified set of conditions…These MEs will be done using diluted test substance that does not require the use of PPE. These data will be used to generate baseline unit exposures for use in occupational risk assessments involving the pouring of liquid formulations to support the registration of antimicrobial products….The generation of a new, relevant, high quality base set of data will fill a data gap identified by the US 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." (V2:11-13)

The two proposed test chemicals, ADBAC and DDAC, have very low vapor pressures allowing them to be good candidates for use as surrogate compounds. These same two test chemicals have been used by the AEATF II in previous exposure studies.

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. They are listed in Volume 2, page 18, 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 Subject Self Reporting Demographic Form
- Speak and read English or [alternate language as appropriate to the area/population]
- Experience in providing janitorial or property maintenance services
- Job duties include the pouring of biocides and/or antimicrobial products
- Physical ability to lift and pour 5 gallon containers of liquid product (approximately 50 pounds each) up to 10 times consecutively

"Exclusion Criteria:

- Skin conditions on the surface of the hands (e.g., psoriasis, eczema, cuts or abrasions)
- Pregnancy, as shown by a urine pregnancy test
- Lactation
- Allergies to household chemical-based products, including quaternary ammonium compounds, soaps or isopropyl alcohol

- Is an employee or spouse of an employee of any company represented by the AEATF, the contract research organizations conducting the study, or the American Chemistry Council." (V2:18)

(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. (V2:18)

(c) If any potential subjects are from a vulnerable population, what is the justification for including them?

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 V2:35-37.

(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.

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for 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.

"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." (V2:38-39)

(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." (V2:38)

4. Risks to Subjects

4.1 Risk characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?

The proposed test materials are EPA-registered, with an essentially complete supporting database. The test materials are of low toxicity to mammals.

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

Risks are of a reaction to the test materials or the solvents used to obtain residues from hands and face/neck; 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 form include risk of a reaction to the test materials, risk of stinging from alcohol wash and wipes, risk of physical stress, a small possibility of heat stress, risk of discomfort, risk of embarrassment, and possible surprise at the results of a pregnancy test. (V2:80)

(c) What is the probability of each risk associated with the research? How was this probability estimated?

All identified risks are characterized as of low probability. No quantitative estimates are reported.

4.2 Risk Minimization

(a) What specific steps are proposed to minimize risks to subjects?

Use of test materials shown to be of low toxicity to mammals; use in strict accord with approved labeling; exclusion of candidates known to be sensitive to quaternary ammonium compounds; exclusion of candidates in poor health or with broken skin on hands, face, or neck; provision of safety glasses; testing in a controlled-temperature environment; short duration of monitoring event (no more than 1 hour per ME/no more than 2 hours total per subject); alerting subjects to signs and symptoms of muscle strain, eye and skin reactions, and heat stress; monitoring heat index with associated stopping rules; close observation of subjects by researchers and a medical professional (nurse, EMT, or Physician Assistant); training of experienced technicians to minimize embarrassment; incorporation of procedures to keep results of pregnancy testing private and to permit discrete withdrawal; provision of appropriate work clothing and PPE. (V2:24, 26, 39-40)

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

Two test substances will be used in this study. Both are registered formulated products designed to be diluted prior to use. The products are Maquat WP (EPA Reg. No.10324-91) and Maquat DS 1412-10% (EPA Reg. No. 10324-25). The active ingredient in Maquat WP is DDAC and the active ingredient in Maquat DS 1412-10% is ADBAC. Diluted Maquat WP (DDAC) will be the test substance used in the conventional pour events. Maquat WP will be diluted to a 0.2% DDAC concentration. For the reduced-splash pour events, Maquat DS 1412-10% will be diluted to a 0.2% ADBAC concentration. The established NOAELs for both ADBAC and DDAC are provided below.

The ADBAC risk assessment developed to support the Reregistration Eligibility Decision (RED) document provides for the selection of the toxicological endpoints for risk assessment purposes. The dermal toxicological endpoints indicate no systemic toxicity. However, dermal irritation has been observed in 21- and 90-day dermal toxicity studies in guinea pigs and rats, respectively (MRIDs 41105801 and 41499601, respectively). The short-term dermal endpoint selected from the 21-day study is 333 ug/cm^2 and 80 ug/cm^2 in the 90-day study. The possible exposure of subjects in this proposed study to a formulated product containing 0.2% concentration of ADBAC will not trigger a risk of concern. The inhalation toxicological endpoint identified for ADBAC for all exposure durations is based on a developmental toxicity study in rabbits (MRID 42392801) with a NOAEL of 3 mg/kg/day. The inhalation risk assessment in the ADBAC RED document indicates that no inhalation risks are anticipated at this low concentration.

The DDAC risk assessment developed to support the RED document provides for the selection of the toxicological endpoints for risk assessment purposes. The dermal

toxicological endpoints indicate that low concentrations of DDAC (0.13% ai tested in a 21-day dermal toxicity study, MRID 45656601) display no dermal irritation effects and no systemic effects up to and including the limit dose of 1000 mg/kg/day. The possible exposure of subjects in this proposed study to a formulated product containing 0.2% concentration of DDAC will not trigger a risk of concern. The inhalation toxicological endpoint identified for DDAC for all exposure durations is based on two oral toxicity studies (prenatal developmental toxicity in rats, MRID 41886701, and a chronic toxicity study in dogs, MRID 41970401). The selected NOAEL from both studies is 10 mg/kg/day. The inhalation risk assessment in the DDAC RED document indicates that no inhalation risks are anticipated at this low concentration.

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

Heat stress index above 95 (V2:39)

Other medical reasons (V2:39-40)

"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." (V2:40)

(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.2 for Emergency Procedures (V4:158-161)

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

"If a subject reports an adverse eye or skin reaction during the work period, they will be asked to immediately stop working. Research staff will then assist the subject in gently washing exposed skin with clean water and mild soap. After drying the area with a clean towel, the medical professional will determine if medical treatment is necessary.

"The extra layer of clothing (inner dosimeter) worn by subjects may increase the risk of heat-related illness. The possibility of heat stress will be minimal since the study will be conducted indoors in a controlled environment where the heat index (HI) is expected to be less than 85. Research personnel shall monitor the heat index, and stop subjects' work if the heat index exceeds 95. The SOP AEATF 11.B 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, especially if the worker has been working for a while. 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 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 asked 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 skin reactions, 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, skin 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 Study Sponsor, IIRB, Inc., and EPA policies for medical event reporting per 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." (V2:39-40)

(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?

"Study personnel will be instructed to inform the Study Director and medical professional immediately of any skin reactions, heat stress, or other unanticipated adverse effects observed or reported during conduct of the study. The medical management procedures set forth in SOP 11-C.2 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, skin 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 Study Sponsor, IIRB, Inc., and EPA policies for medical event reporting per 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." (V2:40)

The following revision should be made to the consent form before the study is initiated:

- Add a section that explains to subjects that if, within 24 hours of completion of their participation in the study, they experience a skin or eye reaction or other adverse effect that they believe is related to their participation in the study, they should contact the Study Director immediately. A telephone number should be provided.

The AEATF should develop procedures for handling such a call and document those procedures in a new or existing SOP.

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

The informed consent form states: "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. Medical records will not be part of the study. To find out more, or if you think you may have been hurt during the study, you can call (202) 249-6724 between 8 am and 5 pm Monday through Friday." (V2:81)

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 are used extensively in hospitals, schools, homes, etc. to control pathogenic 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." (V2:21)

(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 liquid 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 janitorial/cleaning service workers as a whole and 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 janitorial workers and the general public. Exposure data for this liquid 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?

Independent Investigational Review Board, Inc., Plantation, Florida (IIRB)

(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?

IIRB, Inc. earned "Full Accreditation" from the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) in December of 2009.

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

No.

(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… The protocol will be reviewed by an Institutional Review Board (IRB)." (V2:10)

8. Informed Consent

(a) Will 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?

Literacy in English or an "alternate language as appropriate to the area/population" is specified as a criterion for inclusion in the study. (V2:18)

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

At least one member of the research team will be fluent in both English and Spanish. A Spanish-speaking member of the research team will be present during monitoring events involving subjects whose preferred language is Spanish. (V2:39)

Recruitment materials and all communications with potential subjects will be available in English and Spanish, as preferred by the subject. In addition, a copy of the poster entitled "Controlling Heat Stress Made Simple" in English and Spanish will be posted in the dressing area at each site.

(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.0)." (V2:36-7)

SOP AEATFII-11J.0 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." (V4:171-3)

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

Please see SOP AEATFII-11J.0 (V4:169-173)

(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.O 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: 172)

The consent form states:

> "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. Your alternative is to not participate in this study." (V2:133)
>
> "I have reviewed this Informed Consent Form with the volunteer named above, and answered all his/her questions. I have made every effort to ensure the volunteer understands the purpose, risks and benefits of the research, what will happen on the day of the test, and his/her freedom to withdraw at any time and for any reason. I have done this in circumstances that minimize the possibility of coercion or undue influence, and I believe the volunteer has made an informed and free choice to participate." (V2:136)

9. Respect for Subjects

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

"Subjects' names will not be revealed in the final report; instead information relating to each subject will be done using the identification code only. All subjects' names and personal identifiers provided will be kept confidential to ensure their privacy.

"Records correlating subject names to their identification codes and SISN will be retained separately from the study file in an area clearly marked "CONFIDENTIAL." (V2:38)

"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…Results of the pregnancy test will be kept in confidence, they will not be recorded, and they will be discussed only with the subject that provided the urine sample." (V2:41-42)

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

The informed consent form states:

"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. Your alternative is to not participate in the study." (V2:133)

"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." (V2:134-5)

(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." (V2:38-9)

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. (V2:135)

§ 26.1111 Criteria for IRB approval of research
AEATF II Liquid Pour Scenario/Protocol AEA05: July 28, 2011

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 Liquid Pour Scenario/Protocol AEA05: July 28, 2011

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 Liquid Pour Scenario/Protocol AEA05: July 28, 2011

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 Liquid Pour Scenario/Protocol AEA05: July 28, 2011

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 • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	V2: 117-177, V3 V2:125
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	V2:121
	(3) Records of continuing review activities.		n/a	
	(4) Copies of all correspondence between the IRB and the investigators.		Y	V2:4-317, V3
	(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y Y	Provided separately to EPA V2:122
	(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	V2:18-21
		(2) The measures proposed to minimize risks to the human subjects;	Y	V2:18-21
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	V2:21
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	V2:14-16
		(5) The balance of risks and benefits of the proposed research.	Y	V2:21
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Original V3:142-159 Approved V2:125-177
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	V2:35-39;148;168;174
	§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	V4:169-173
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	V3:6-224
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.		Y	V2:119-120