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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

March 14, 2014

MEMORANDUM

SUBJECT: Science and Ethics Review of AEATF II Brush and Roller Painting Scenario Design and Protocol for Exposure Monitoring

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

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

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

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

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

Science Review

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

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

    - EPA recommends that the researchers provide the test subjects with a paint edger device and a paint cup and allow the subjects to decide if they want to use them. Also have the subjects use two different colors of paint (e.g., white for ceiling and trim along with a different color for walls).

    - EPA recommends that the researchers provide additional details about how the airflow in the indoor environment is oriented between the painting and air vent (e.g., is the airflow blowing paint in the direction of the test subject as they use the paint roller on the walls? Is the airflow on the ceiling blowing downwards?).

Ethics Review

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

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

    - Add skin conditions of the face or neck to the exclusion criteria listed in the protocol and consent form.

    - Expand the exclusion criteria in the protocol and consent form to exclude subjects with allergies or sensitivities to BIT[1] or other chemical-based products

    - In the section of the consent form titled "Test Product," please describe the test product as a pesticide. The following revision is recommended:

        - *"The test product contains a* ***~~chemical~~*** ***pesticide*** *known as BIT which helps keep bacteria from growing."*

    - In the section of the consent form titled "Risks," please revise the beginning of item #1 as follows:

        - *"Risk of a reaction to the latex paint* ***or the pesticide ingredient (BIT) contained in it****. Direct contact with the paint…."*

    - Expand the discussion of risks in the protocol and consent form to include risks associated with using a ladder to paint ceilings.

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

[1] BIT = 1,2-Benzisothiazol-3(2H)-one

A. 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. 3)
- 40 CFR 26.1125 Checklist (p. 5)
- Latex Paint Application with Brush and Roller Scenario: Rationale for Study Design (pp. 6-19)

Volume 2 of the submitted package includes the following documents:

- SAIRB conditionally-approved draft protocol dated 1/22/14 (pp. 3-53)
- SAIRB Study Status Notification I dated 11/14/13 (pp. 132-3)
- SAIRB Study Status Notification II dated 12/4/13 (p. 134)
- Protocol review by California Department of Pesticide Regulation (CDPR) (pp. 135-141)
- Golden Pacific Laboratories response to protocol review by CDPR (pp. 135-150)
- Informed Consent Form and Experimental Subject's Bill of Rights (draft 1/22/14) (pp. 61-70) – English version provided; will be translated to Spanish after final approval
- Qualification Worksheet (draft 1/22/14) (p. 73) – English version provided; will be translated to Spanish after final approval
- Newspaper Advertisement (draft 1/22/14) (p. 82) – English version provided; will be translated to Spanish after final approval
- Script for receiving phone calls in response to advertisement (draft 1/22/14) (pp. 85-6) – English version provided; will be translated to Spanish after final approval

Volume 3 of the submitted package includes documentation of communications with SAIRB and CDPR, as well as copies of CVs and ethics training records for field investigators..

Volume 4 of the submitted package includes copies of the AEATF II Standard Operating Procedures (SOPs) that are referenced in the AEA09 Brush and Roller Painting Study protocol.

B. Summary Assessment of the Scenario Design

Supporting details are in Attachment 1.

1. **Scenario Design:** The EPA assesses potential occupational and residential (consumer) exposure from various antimicrobial products that are applied by a multitude of application techniques. Most antimicrobial products that are incorporated into latex paints are used as in-can material preservatives. In these instances, the paint is

considered a treated article, and therefore, the paint can itself does not have a pesticide label (http://www.epa.gov/PR_Notices/pr2000-1.pdf). However, exposures to these types of treated articles are considered in the risk assessments conducted by EPA. AEATF II defines the interior latex paint application with brush and roller scenario in this protocol as *"…the hand-held application using a paint brush and/or paint roller of a formulated interior latex paint containing an antimicrobial chemical."* (V1:8)[2] The AEATF II proposes to recruit test subjects from the general population rather than professional painters to monitor consumer applicators. *"This focus on consumer applicators is considered the more conservative approach, given that consumer painters are expected to be less skilled than professional painters. A less skilled painter is more likely to expose themselves to the drips and paint spills."* (V1:9) The test subjects will have their dermal and inhalation exposure to the treated paint monitored while painting only. The tasks of clean-up of the brushes and rollers and removing of the protective barriers will not be included in the scenario. *"Applicator exposure associated with cleaning painting equipment is likely to result in a decrease in residues on the applicator's hands as washing equipment with water will also wash the applicator's hands. Cleaning of equipment may result in increased residues on the applicator's clothing due to splashing, however this may be less than any reduction in hand residues."* (V1:9)

The AEATF II proposes to conducted 18 monitoring events (MEs); 6 MEs for each of 3 chemical concentrations in the paint. The painting activity will be conducted in rooms specifically built within a vacant building for this study.

"Potential dermal exposure to the test substance will be measured externally using whole body inner and outer dosimeters, painter's hats, and hand wipes/washes, and face/neck wipes. Hand exposure will be measured by scrubbing the hands with gauze pads soaked with a solution of 50% isopropyl alcohol/50% distilled water followed by rinsing with the same solvent. The potential total inhalation exposure for each subject will be measured with an OSHA Versatile Sampler (OVS) tube attached to a personal air sampling pump set at a typical sampling rate (2 L/minute). Potential exposure to respirable thoracic and inhalable particles (100, 10 and 2.5 um, respectively) will be characterized with three stage RespiCon Particle Sampler…". (V2:11-12) A separate hand wash removal efficiency study has been submitted to assess the hand wash methodology.

EPA intends to use the data developed by the AEATF II for the brush/roller painting scenario to describe a typical occupational and residential handler's daily exposure to antimicrobial formulated products used in paints. The data must be generic enough to be useful for estimating exposures using various types of paint brushes and rollers as well as areas painted (e.g., rooms). EPA plans to use the data generated from the proposed brush/roller painting study generically to estimate dermal and inhalation exposures, and

[2] This pagination convention is used throughout this review. "V1" refers Volume 1, "V2" refers to Volume 2, etc. Entries after the colon are page references; many page images bear more than one page number. In Volume 1, the cited page number is from the expression "Page n of 19" found at the bottom right-hand corner. Volume 2 page references are from the expression "Page n of 150" found at the bottom right-hand corner. Volume 3 page references are from the expression "Page n of 494" found at the bottom right-hand corner. Volume 4 page references are from the expression "Page n of 105" found at the bottom right-hand corner.

ultimately risks, for other non volatile antimicrobial ingredients that are used in paints. Painting with airless sprayers will be conducted in a separate study at a later time.

EPA believes that the AEATF II brush/roller paint scenario is well defined (some recommendations are provided below), and we expect that the resulting data will meet the needs of EPA and other regulatory agencies. The diversity of daily exposures under the brush/roller paint scenario as defined in this proposal will adequately describe a typical to high-end residential handler's daily exposure to the antimicrobial application. The use of consumers as test subjects will potentially result in higher exposures than commercial painters; but the data could still be used to represent the brush/roller exposure to commercial painters. Note: exposures while painting with an airless sprayer will be monitored at a later date in a separate protocol. The brush/roller exposure data will be used by EPA to extrapolate to the likely exposure expected from future painting events of paint containing antimicrobial products.

2. **Sampling Design:** The AEATF II has described in detail their sampling design for the brush/roller paint scenario and has incorporated random elements where feasible. The AEATF II proposes to monitor dermal and inhalation exposures using passive dosimetry techniques to measure exposure of human subjects during the painting of a room using a brush and roller. The proposed sample size is 18 monitoring events (MEs). The plan is to use 18 individual test subjects (different individuals) recruited from the general population. The test subjects will be segregated into three groups delineated by the concentration of active ingredient in the paint. The volume of treated paint to be used by each ME is ~2 gallons (target range 1.75 to 2.25 gallons). (V1:17) The sample size is believed adequate to provide data to meet EPA's 3-fold relative accuracy goal as per the AEATF II Governing Document (2011). Once the planned studies by the AEATF II have been completed, the adequacy of the sample sizes of completed studies will be revisited.

   The study will be conducted indoors, in rooms constructed specifically for this study, at one geographical location. *"The study will be conducted at a commercial facility in Fresno County, California. The facility must have electricity, water, and a functioning HVAC system. The facility will provide a climate controlled open area sufficient in size to allow the construction of a series of at least 8 painting rooms. In addition the facility will include a subject waiting area, restrooms, changing room, and area for preparation of field fortification samples. Each painting room will measure 10 feet by 10 feet with an 8 foot ceiling height. Each room will contain finished drywall walls and ceiling, an entry door with paintable trim, a simulated window area with paintable trim, baseboards, and a ceiling exhaust fan. Newly constructed rooms will have an initial coat of primer or paint applied prior to the study. Rooms may be re-painted no more than every other day to allow sufficient drying time."* (V2:22)

   The brush/roller paint test subjects will be recruited from the general population. *"Surrogate painters will all be consumers with at least one residential painting experience in the past 5 years, but no professional painting experience, who reside in the Fresno CA metropolitan area. AEATF II intends to require painting experience as an inclusion criterion since a completely inexperienced painter will require instruction.*

Subjects with prior painting experience may have obtained instruction from a variety of sources including friends, paint supply stores, how-to articles, etc. AEATF II feels it important to maintain diversity by requiring subjects have this prior experience, rather than receiving instruction from study personnel." (V1:17-18) The subjects will be instructed to *"…apply the paint as they would in normal practice"* (V2:20). The test substance will be applied by subjects according to typical painting practices as follows: *"The subject will remove the lid from the secondary paint container. Application with the brush will involve dipping the brush into the paint in the secondary paint container, wiping off excess paint on the edges of the secondary paint container, and applying to surfaces. Application with the roller will involve transferring paint from the secondary paint container to a roller pan, pushing the roller through the paint, removing excess paint by rolling on the flat surface of the roller pan, and applying to surfaces. Subjects will be instructed before beginning that the painting goal is to cover the surfaces with an even coat of the minimal thickness that covers the surface completely and does not leave drips or bare spots. Once the subject begins painting they will be allowed to paint using their own techniques and judgment."* (V2:20)

The physical aspects of the tasks include opening the paint can, painting the drywall (walls and ceiling) with the roller and painting the trim (baseboards and window/door molding) with the brush, and at the end of the ME close the lid of the paint can. The researchers will pre-shake the paint to assure uniformity of the active ingredient. The subjects will be provided with a brush, roller, roller pan, extension pole, and step stool or ladder.

Table 1 below summarizes the concentration of the active ingredient as well as the amount of active ingredient handled (AaiH) for the 3 groupings.

Table 1. Range of Concentration and AaiH for the Brush/Roller Paint Scenario.

Group Number	Volume of Paint (gallons)	Concentration of BIT in Paint (ppm)	AaiH (pounds)
Group 1	2 (1.75 to 2.25)	120	0.00261 (0.00228 to 0.00294)
Group 2		400	0.00870 (0.00762 to 0.00979)
Group 3		600	0.0131 (0.0114 to 0.0147)

AaiH (pounds) = gallons paint x paint density 10.88 lb/gal x ppm (mg BIT/kg paint) x 1 kg/1E6 mg conversion.

The AEATF II brush/roller paint study is designed to be representative of the use of antimicrobials in paint in the marketplace; *"…under conditions constructed to broadly represent those expected for the future application of arbitrary antimicrobial pesticides."* (V1:11) The study is designed to capture characteristics that will lead to typical to high end of exposure (and avoid underestimating exposure). The design aspects that tend to over- rather than under-predict exposure include:

- **Test subjects** – Test subjects will be recruited from the general population rather than professional painters. *"This focus on consumer applicators is considered the more conservative approach, given that consumer painters are expected to be less skilled than professional painters. A less skilled painter is more likely to expose themselves to drips and paint spills."* (V1:9)
- **Painting indoors** –*"…an indoor painting environment is likely to increase dermal exposure over an outdoor painting environment due to the painting of ceiling surfaces which represent a significant source for drips and splatter. The AEATF II also feels that an indoor painting environment has a higher potential for inhalation exposure due to the limited air exchanges compared to an outdoor painting environment."* (V1:12)
- **Amount of paint applied** – EPA's assessments use 2 gallons of paint applied by brush/roller when estimating exposures for residential applicators (5 gallons for commercial painters) (http://www.epa.gov/pesticides/science/residential-exposure-sop.html). The EPA's 2011 Exposure Factors Handbook (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252) provides estimates for consumer painting citing a mean of 4 painting events per year, a mean annual volume of 2.9 gallons painted with a 90th percentile annual volume of 6.7 gallons used. The AEATF II proposes to use 2 ± 0.25 gallons of paint per ME and a minimum of 0.5 gallons to keep the ME if the test subject needs to stop for any reason. (V2:24) This amount of paint will require the test subjects to paint 2 rooms. (V2:20)

EPA also notes the following considerations:

- **Exposure Duration** – The protocol anticipates that painting ~2 gallons of paint will take 120 to 180 minutes with a maximum estimate of 3 to 4 hours. Although the exposure data will be normalized by the AaiH rather than time, the amount of time someone takes to paint may have an influence on their potential exposure (e.g., a slow fastidious painter may contact less paint than someone who is careless and sloppy, but a tired painter may be more sloppy). Differences in behaviors (e.g., slow and fastidious versus careless and sloppy) may affect the correlation between exposure and AaiH. However, these types of behaviors that result in variation of exposure are expected and encouraged by randomly selecting test subjects and allowing them to paint as they normally would do without influence by the researchers.
- **Representativeness** – Although EPA accepts the basic scenario design, a few considerations are proposed to allow for more "realism":
    - Different color paint: The AEATF II plans to change the color of paint used in the rooms between MEs to allow for the subject a visual reference while painting. However, to be more realistic, the paint color of the walls, ceiling and trim should be different as would normally (but not always) occur. For example, different color paint would realistically lead one to use a brush along the edges of walls/ceilings.
    - Tape/Edger: When painting different colors along edge of wall/ceiling and/or walls and trim, one typically uses painters tape or some type of

edger to separate the color. To capture this realistic behavior would be difficult with tape as it takes time to dry. Instead of tape, a painting edger maybe more practical.

- Paint Cup: The AEATF II should also provide the test subjects with paint cups and allow them to choose to use the cup or not (as per the paint roller extension and ladder). The use of the cup, or not, may also affect the correlation between exposure and AaiH, but this is realistic and would lead to some expected variation in painting behaviors.

- **Painter's Rag** – The inclusion of a painters rag will influence exposure; and that behavior is realistic. To help aid the interpretation of exposure, it is important to reemphasize the note takers' observations to be collected.

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

- *"The target study design involves construction of 18-24 synthetic antimicrobial paint application with brush and roller days, called monitoring events (or MEs)."* (V2: 21)
- *"Each ME will be randomly assigned to one of the three concentration strata."* (V2:21).
- *"Advertisements soliciting subjects will be posted in the major local newspaper, the Fresno Bee, as well as newspapers circulating in the Spanish speaking community and the African-American community. Individuals who express a desire to participate in the study within a fixed period of time will be contacted and screened in random order. Individuals who meet the study requirements will be recruited until the required number of surrogate painters is obtained. Surrogate painters are randomly assigned to MEs." (V1:18).* As discussed in V1:18, this procedure results in a random sample from those who see the advertisements and volunteer within the time period. This approximates a random sample from the population of future painting days for amateur painters.
- *"The total number of qualified subjects will each be assigned a unique and consecutive number, starting at AE-01 based on the order of their enrollment. The numbers will then be randomized using a research randomizer program accessible at the following internet website: http://randomizer.org. The first 24 numbers in the generated randomized list will determine the participating subjects, while the remaining subjects will be held as replacements, their order for potential entry into the study being determined by the randomization process. The first 18 subjects in the generated randomized list will be assigned to ME01 to ME18. The remaining 6 subjects will be assigned as alternates. At least 2 alternates will be scheduled to be on hand each study day in case any subject is unable, chooses not to participate, or chooses to stop painting before reaching the necessary volume of paint applied."* (V2:23)

3. Choice of Surrogate Material: "*The test substance for these studies is the formulated product, Sherwin-Williams latex paint, containing 1,2-benzisothiazoline-3-one (BIT). The EPA does not require registration of paint containing BIT making no claims of antimicrobial activity; therefore no EPA registration number is available for the paint. A reference EPA registration for Mergal® BIT20, a BIT additive product is 5383-121. … BIT is the active ingredient selected for measurement, based on its stability, abundance in the formulation, and sensitivity of its analytical method."* (V2:17) The vapor pressure of BIT is 4.4E-7 mmHg at 20º C which is considered to be low (not to result in substantial off gassing).

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

Supporting details are in Attachment 2.

1. **Statistical design*:*** As in previous AEATF II studies, 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 for brush/roller painting which was 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.

   "The sample size of this study will be 18 MEs… The number of MEs was determined by EPA in discussion with AEATF II to be appropriate to achieve the benchmark objective in studies of this general design type. For the paint application with brush and roller study, the benchmark objective is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time. … If the benchmark objective is not achieved after completion of the 18 MEs AEATF II will consult with EPA to determine if additional MEs are required." (V1:18)

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

   - **Consideration was given to stratifying the sample based on varying the volume of paint applied instead of active ingredient concentration:**

     Initial discussions among the JRC and AEATF II were to use varying volumes of paint at the same active ingredient concentrations. However, based on previous HSRB meetings that discussed obtaining the range of AaiH by using a range of AI concentrations, along with concerns at lower volumes about what surface areas would be painted (e.g., walls only? Ceiling only, trim?), it was decided to use 2 gallons of paint (as per EPA residential painting assessments) and 3 different concentrations of active ingredient. This approach allows us to test the assumption that the exposure is proportional to the concentration, so that doubling the concentration but using the same volume of paint tends to double the exposure. However this design does not allow us to fully test the assumption that the exposure is proportional to the volume, so that doubling the volume but using the same concentration tends to double the exposure. Since the volumes can vary up to 0.25 gallons from the

nominal 2 gallons, there will be some data to evaluate that second assumption, but the power of such a test will be low. The first assumption is necessary if these results are to be extrapolated to chemicals at different concentrations. The second assumption is necessary if these results are to be applied to painting larger or more rooms that will require more time and more paint. If the results of this study indicate that exposure is not proportional to the concentration, that finding might suggest the need to revisit earlier AEATF II studies for different scenarios that were based on that assumption. If the exposure depends upon the volume of paint used, then that relationship cannot be accurately evaluated in this proposed study.

- **Consideration was given to allowing the test subjects to clean-up at the end of the painting event:**

  The initial design included the test subjects cleaning up after completing the task (e.g., wash paint off of brush and roller). Further reflections on the clean-up portion of the task lead us to believe that the clean-up would wash the paint from the hands prior to the hand wash collection. While this might be representative of some painting events where the brush and roller are washed, not all painting events end with the consumer washing the equipment (e.g., some may save the brush/roller for painting the next day, some may dispose of the brush/roller).

- **Consideration was given to the experience level of the consumers:**

  There was some discussion on whether or not to include criteria for previous painting experience. As concluded in the AEATF II's proposal, consumers learn how to paint from various sources (e.g., friends, paint stores, etc.) and *"…it was important to maintain diversity by requiring subjects have this prior experience, rather than receiving instruction from study personnel."* (V1:18)

2. **Proposed pattern of human exposure:** The AEATF II proposes to select study participants from the general public for the painting scenario from individuals with at least one experience of painting within the last 5 years. The test substance will be applied by subjects according to typical painting practices. *"The subject will remove the lid from the secondary paint container. Application with the brush will involve dipping the brush into the paint in the secondary paint container, wiping off excess paint on the edges of the secondary paint container, and applying to surfaces. Application with the roller will involve transferring paint from the secondary paint container to a roller pan, pushing the roller through the paint, removing excess paint by rolling on the flat surface of the roller pan, and applying to surfaces. Subjects will be instructed before beginning that the painting goal is to cover the surfaces with an even coat of the minimal thickness that covers the surface completely and does not leave drips or bare spots. Once the subject begins painting they will be allowed to paint using their own techniques and judgment."* (V2:20)

The physical aspects of the tasks include opening the paint can, painting the drywall (walls and ceiling) with the roller and painting the trim (baseboards and window/door molding) with the brush, and at the end of the ME close the lid of the paint can. The researchers will pre-shake the paint to assure uniformity of the active ingredient. The subjects will be provided with a brush, roller, roller pan, extension pole, and step stool or ladder. It is anticipated that each room to be painted will require about 1 gallon of paint.

The duration of painting will be based on how long it takes each study participant to paint approximately 2 gallons of paint. The painting time will be recorded. Although there is no prescribed length of time, *"…it is expected that the application of approximately 2 gallons of paint will take multiple hours."* (V1:17) *"…expected to take a maximum of 3 to 4 hours on a single day."* (V2:31) If some subjects take substantially more time than others, it is possible that they are more fastidious painters and may come in less contact with the paint. It is also possible that they will get more tired and be more likely to have a large accidental spill. This may affect one's exposure and thus affect the correlation of exposure and AaiH. However, variation in one's exposure is expected and it is important to capture this variation by allowing the subjects to paint as they normally would do.

The EPA believes that the AEATF II brush and roller paint study will represent typical to high end consumer methods of painting (Note: The painting with an airless sprayer will be conducted at a different time with a separate protocol). The scenario will also be useful to estimate exposure to commercial painters. The selection of consumer subjects, test materials, brush and rollers, indoor rooms with ceilings, window and door trim, and associated activities (e.g., use of an extension for the roller) as described in the protocol is justified. The subjects will be allowed to use the roller extension and/or ladder as they normally would do.

3. **Endpoints and Measures:** The AEATF II proposes to measure dermal and inhalation exposures resulting from painting with a brush and roller. Dermal and inhalation exposure will be measured using whole-body dosimeters (WBD) (inner and outer), a painter's hat, face/neck wipes, hand wipe/washes, and personal air monitors (V2:35-37). For the WBD, the Agencies are most interested in the inner dosimeters to assess potential exposure. The outer dosimeters will add to the existing data base on the development of protection factors for single layer of clothing. The potential for foot exposure is minimal and the feet will not be monitored. The hand and face/neck wipe/wash is an appropriate method to determine exposure to the hands and face/neck. The personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). Both OVS and RespiCon filters will be used to trap and measure particulates 2.5, 10, and 100 um. Flow rates will be approximately 2 L/min for the OVS tubes and 3.1 L/min for the RespiCon (V2:11-12) (SOP AEATF II-8D.1).

"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 intervals appropriate for the duration of the work period per SOP AEATF II-10C.1. Environmental monitoring equipment will be calibrated or standardized according to SOPs. HVAC and room volume will be described in detail and documented in study field notes. Air changes per hour will be experimentally measured for one of the painting rooms." (V2:38)

Although the study researchers plan to measure the air exchange rates, details were not provided. The AEATF II needs to consider the HSRB comments on the previous liquid pour study. The HSRB's written comments on the liquid pour study concerning the ventilation indicated: *"... the focus of interest in ventilation should be on the local air flow between the pouring operation (the source of exposure) and the handler." Further, the Board suggested that "...at the very least, that pattern should be measured before and/or after exposures and the orientation between the source and each handler should be documented for each ME. Alternatively, the room's setup and the orientation between the source and handler could be varied (e.g., rotated 90°) either within or among MEs" (HSRB, October 2011 Meeting Report, 11).*" The Board's comment was made so that users of the data would be able *"…to evaluate the potential for a consistent airflow direction or orientation to have caused the average inhalation route to be either higher or lower than would have been caused by random or variable airflows."*

4. **QA/QC Plan:** The study will be conducted under the FIFRA GLP Standards (40CFR160) (V2:48). The AEATF II QA/QC plan for the brush/roller paint 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.

   Primary components of the field recovery analyses include (V2:39-41): samples to be fortified every day of monitoring; two fortification levels per matrix with the low level 4x the LOQ and high level based on expected levels (V2:40), triplicate samples per fortification level (V2:40), fortified samples exposed to ambient conditions for the maximum duration of exposure, and WBD not covered during exposure duration. Field recovery samples will be fortified in the "field" and stored in the same way as the actual study samples, and will be analyzed concurrently with the actual exposure samples. Correction for loss in field recoveries will correct for all phases of potential losses.

5. **Statistical Analysis Plan:** The results of monitoring data will be provided in the final report. The AEATF II will not statistically analyze the monitoring data. The EPA proposed statistical model for these data is a simple linear regression model for the logarithm of the exposure with an intercept term and with a slope coefficient multiplied by the logarithm of the amount of active ingredient. There are three groups of six MEs at different concentration levels. The MEs in each group will have the same concentration and very similar volumes (approximately 2 gallons). All three groups have the same intercept and slope. The main statistical model will assume a slope of one, which is mathematically equivalent to assuming that the normalized

exposure, defined as the exposure per pound of active ingredient, has the same log-normal distribution for all 18 MEs. 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. We will also investigate alternative models where the three concentration groups can have different intercepts and/or different variances. It will also be important to test the proportionality assumption against independence by fitting models where the slope is not assumed to be one; confidence intervals for the slope will be used to determine if the slope is significantly different from 1 (proportionality) or from 0 (independence). The statistical analysis plan also includes the development of summary tables of the data, and various graphs of the data including exposure plotted against the amount of active ingredient showing the fitted regression models and the different concentration groups, and Q-Q plots of the residuals (to assess the lognormality assumption) and of the studentized residuals (to assess the model performance of the final model).

D. Compliance with Applicable Scientific Standards

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

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

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

Recommendations:

EPA recommends that the study researchers provide additional details about how the airflow is oriented between the painting and the test subject within the indoor environment before the research goes forward.

EPA recommends that the researchers provide the test subjects with a paint edger device, a paint cup, and two different colors of paint (e.g., white for ceiling and trim along with a different color for walls).

The AEATF-II is proposing a hand wash removal efficiency study to allow EPA to correct for incomplete residue removal from the hand sampling. Comments/recommendations on the hand wash removal study are being addressed outside of this protocol.

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 this study is to measure exposure to individuals who apply latex paint containing antimicrobial pesticide products with brush and roller painting equipment. Because many professional and non-professional painters use latex paint containing 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-four adult subjects will be recruited from the Fresno, California area (18 initially assigned for monitoring plus six alternates). Participants will self-identify in response to newspaper advertisements in three different newspapers targeting different demographic groups. Callers responding to the newspaper advertisements will be screened, scheduled for informed consent meetings, and enrolled.

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

   Only individuals who have had at least one experience painting with brush and roller equipment in the past five years, but whom are not professional painters, will be eligible to participate. The protocol proposes to monitor non-professional painters because they are likely to be less skilled and therefore experience higher exposure as compared to professional painters.

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

   No potential subjects are from a vulnerable population. Recruitment materials and interactions with potential subjects will be conducted in English or Spanish,

depending on subject preference. Subjects will be recruited through newspaper advertisements, not through employers, which will minimize the potential for coercion or undue influence.

3. **Risks to Subjects:** The proposed test material, BIT, is an EPA-registered antimicrobial pesticide active ingredient with an essentially complete supporting database. It has been tested extensively in animals and was shown to be moderately toxic by oral and dermal routes, a slight dermal irritant, and a moderate dermal sensitizer. Based on its safety profile, BIT has been approved for use in many household products including paint, laundry detergents, and household cleaners. In this study, BIT would be contained in latex paint consistent with existing EPA approvals and its EPA-approved label.

   Risks to subjects include the risk of a reaction to the test material or irritation due to rubbing alcohol used on the hands, face, and neck; the risk of discomfort and possibly heat-related illness associated with wearing two layers of clothing while doing physically demanding work; the risk of using a ladder to paint ceilings; the risk of discomfort or inconvenience from wearing the air sampling device; the risk of embarrassment from undressing in the presence of a research technician; and the risks associated with pregnancy testing, including an unexpected result or loss of privacy. All identified risks are characterized as of low probability.

   Risks are minimized by exclusion of candidates known to be allergic or sensitive to latex paint, isopropyl alcohol, BIT or other chemical-based products, in poor health, or with broken skin on hands, face, or neck; alerting subjects to signs and symptoms of a skin reaction or heat stress; monitoring heat index with associated stopping rules; allowing subjects to rest whenever they want or need to; medical professional on-site observing the subjects; incorporation of procedures to keep the results of pregnancy testing private and to permit discrete withdrawal; private changing area; provision of personal protective equipment (eye protection).

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 applying latex paints containing antimicrobial products that could be used by EPA and other regulatory agencies to support exposure assessments.

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 conditionally approved by the Schulman Associates IRB. The approval (issued in November 2013) is conditioned on reviews being completed by CDPR and HSRB. CDPR provided comments in December 2013, and the versions of the protocol and consent materials that were reviewed herein incorporate the CDPR's recommended

revisions. EPA anticipates that SAIRB will issue a full approval once the HSRB review process is complete. This research may not be initiated until IRB approval is granted.

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

   All written recruitment, consent, and risk communication materials will be available in both English and Spanish. In order to ensure effective communication and thorough comprehension by anyone preferring Spanish over English, a Spanish-speaking member of the research team will be available to participate in any consent meetings at which a candidate indicates that he or she would prefer to communicate in Spanish.

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

F. Compliance with Applicable Ethical Standards

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

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

EPA Ethics Comments

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

- Revise the first exclusion criteria as follows: ***Skin conditions on the surface of the hands, face, or neck (e.g., psoriasis, eczema, cuts or abrasions)***

- Revise the fourth exclusion criteria as follows: ***Allergies or sensitivities to latex paint, soaps, isopropyl alcohol, BIT, or other chemical-based products***

- In the section of the consent form titled "Test Product," please describe the test product as a pesticide. The following revision is recommended:

    - *"The test product contains a **~~chemical~~** **pesticide** known as BIT which helps keep bacteria from growing."*

- In the section of the consent form titled "Risks," please revise the beginning of item #1 as follows:

    - *"Risk of a reaction to the latex paint **or the pesticide ingredient (BIT) contained in it**. Direct contact with the paint…."*

- Expand the discussion of risks in the protocol and consent form to include risks associated with using a ladder to paint ceilings.

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

EPA Ethics Conclusions

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

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

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

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

Attachments:

1. Summary Review of AEATF II Brush and Roller Painting Study Scenario Design dated February 5, 2014
2. Summary Review of AEATF II Protocol AEA09 dated February 5, 2014
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 Brush and Roller Painting Scenario/Protocol

Title: **INTERIOR LATEX PAINT APPLICATION WITH BRUSH AND ROLLER SCENARIO: RATIONALE FOR STUDY DESIGN** (Volume I)

Date: February 5, 2014

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

1. Scope of Scenario Design

(a) Is the scenario adequately defined?

"The primary purpose of the paint application with brush and roller monitoring study is to develop more accurate information on potential consumer and worker exposures to antimicrobials. These data will consist of dermal and inhalation exposure estimates derived from monitoring subjects under conditions constructed to broadly represent those expected for the future application of arbitrary antimicrobial pesticides. … For the paint application with brush and roller scenario … only a small number of expensive experimentally-obtained monitoring events (MEs) are possible. Each ME represents the exposure possible for a single future handler-day. Although it is only a single task, paint application with a brush and roller still encompasses more handling conditions than any small number of MEs can practically include in a single study. For example, there are many possible active ingredients (ai), different application equipment used, multiple concentrations of active ingredient used, different volumes of product used, different workers and their associated behaviors, and multiple environmental and other handling conditions. All of these are expected to affect exposure to varying degrees. In view of this limitation, a practical goal for this study is that the small sample of paint application with brush and roller MEs be biased towards increased diversity of handling conditions. As a result, the diverse sample of MEs is expected to at least cover the middle portion of the future exposure distribution, cover the upper portion of the future exposure distribution, and capture the range of exposure variation that is expected to exist." (V1:11-12)

"The AEATF II study restricts the paint application with brush and roller scenario to consumer applicators only. This focus on consumer applicators is considered the more conservative approach, given that consumer painters are expected to be less skilled than professional painters. A less skilled painter is more likely to expose themselves to drips and paint spills. It is expected that consumer painter exposure will be above the limits of quantification/detection of the analytical method. The amount of product handled per task, and per day can be used to extrapolate potential exposure to professional painters. Thus, the AEATF II exposure data for brush and roller paint application of antimicrobial pesticides would be 'conservative' (i.e., would over-predict) if used to describe professional application exposure. However, it would be reasonable for regulatory agencies using the data to assume

that exposure levels for professional applicators, when normalized for the amount of active ingredient handled, are not greater than those for consumer applicators." (V1:9)

The AEATF II brush and roller painting scenario design appropriately proposes to diversify the sampling characteristics by selecting test subjects representing consumers from the general public, selecting an indoor painting site (i.e., includes overhead painting on ceilings), as well as varying the active ingredient concentration in the paint (three different concentrations of BIT).

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

"PHED does include one study conducted using paintbrush application methods, but the data does not include paint roller application. …this study has limitations that reduce its value for an antimicrobial- oriented generic database. This study monitors paintbrush application only, but is being used to extrapolate to application with brush and roller combined. It appears that every ME within the study applied an identical amount of product. Thus, there is no variation in amount of a.i. handled within the study. In addition, both the dermal and inhalation exposure data from study 467 have only an analytical quality grade of C. To support the registration of a pesticide, the data should have an analytical grade of A or B. … In addition to PHED, a review of published literature was made to look for studies evaluating exposure to non-volatile paint components. Although numerous studies were available evaluating exposure to paint solvents, only one suitable study was located which studied a non-volatile chemical (Gijsbers et. al., 2004). This study was a comprehensive investigation including dermal exposure from painting with a brush/roller conducted in The Netherlands to provide data to the European risk assessment database (RISKODERM). The study evaluated subject exposure to DEGBE (2-(2-Butoxyethoxy)ethanol) which was a component of the latex paint used at concentrations ranging from 0.4-3.2%. Subjects painted surfaces at construction sites primarily with a brush and sometimes a roller. Dermal and hand exposure were evaluated. However, this study was found to be lacking in several key areas. 1) No mention was made of good laboratory practices, quality assurance reviews, or other regulatory standards being followed. 2) No evaluation was made of potential inhalation exposure to DEGBE. 3) Non-hand dermal samples were only collected from 12 monitoring events. 4) Field recoveries were unacceptable due to background contamination at multiple sites, reducing the number of data points available. 5) The same subject was used for up to four monitoring events with most subjects monitored twice resulting in less than 12 valid and unique monitoring events for hand residues." (V1:9-11)

Based on the PHED and literature study data limitations, the EPA is requiring dermal and inhalation exposure data in many of its assessments to fill this data gap for painting with a brush and roller. The proposed study will fill that data gap.

2. Rationale for Scenario Sampling Design

(a) Are the variables in the brush and roller painting scenario design likely to capture diverse exposures at the high-end?

The design choices in the brush/roller paint scenario include: (1) using different consumers for each monitoring event; (2) selection of the type of brush and roller; (3) use of a painters rag; (4) volume of paint; (5) active ingredient concentration; and (6) different indoor rooms. Additional descriptions of these key variables are provided:

Test Subjects (Consumers). *"Each surrogate painter provides his/her unique set of behaviors to the painting task. Use of the same painter for all monitoring events would over-represent a single type of behavior. As a result, diversification of painter behavior among MEs is accomplished by simply requiring that each ME be based on a different surrogate painter."* (V1:17)

"The AEATF II study restricts the paint application with brush and roller scenario to consumer applicators only. This focus on consumer applicators is considered the more conservative approach, given that consumer painters are expected to be less skilled than professional painters. A less skilled painter is more likely to expose themselves to drips and paint spills." (V1:9)

Brush and Rollers. *" Monitoring events will use a single type of application equipment (brush and roller). Generically speaking the type of equipment used will represent the most commonly used consumer equipment. The "most commonly used" designation was determined by AEATF II from available "top seller" lists on websites of national home improvement stores, and from conversations with paint store personnel. The equipment is defined by materials and techniques used in the construction of the roller and brush. The equipment used will be recommended by the manufacturer for use with indoor latex paint. Common materials used in constructing paint rollers including medium density polyester, high density polyester, microfiber, lambswool, and others including combinations. The roller nap generally ranges from 1/4" to 3/4", but can also be smooth foam. The construction material and nap length determine how much paint the roller holds, how well it spreads, the ability to penetrate rough surfaces, and the smoothness of the applied paint. The 3/8" nap high density polyester is the most commonly used roller cover and is considered appropriate for semi-rough to smooth surfaces such as interior walls. A longer nap would be appropriate for rough surfaces such as exterior stucco. Paintbrushes for home painting are typically 1 to 5" in width and either straight or angled. The most common sizes are 2 to 3" and both straight and angled brushes are commonly sold. Paintbrush materials include various synthetic and natural fibers, with synthetic fibers generally being more common and less expensive. AEATF II has selected a 3" straight polyester brush as a common design which is a Home Depot best seller. AEATF II is not aware of any studies relating roller or paintbrush construction with painter exposure."* (V1:15)

Based on this discussion, the AEATF II selected the Linzer "Better" 3 inch polyester brush from Home Depot (part No. 1170-3) and the Linzer "Better" 9 inch roller cover with 3/8 inch high density polyester from Home Depot (part No. RS1433). (V1:15)

Painters Rag. *"As part of the painting task, painters will be allowed the use of dry "painter's rags." These rags will be used by surrogate painters to wipe excessive liquid paint drips and spills. AEATF II believes that the use of painter's rags represents standard practice for both consumer and professional painters, and is a practical necessity to deal with spills and large drips while painting."* (V1:16)

Volume of Paint. *"The Exposure Factors Handbook (USEPA 2011) provides estimates for consumer painting citing a mean of 4 painting events per year, a mean annual of 2.9 gallons painted with a 90th percentile annual of 6.7 gallons used. The AEATF II proposes to use 2 ± 0.25 gallons of paint per ME and a minimum of 0.5 gallons to keep the ME if the test subject needs to stop for any reason."* (V1:16 and V2:24) *"This amount of paint will require the test subjects to paint 2 rooms."* (V2:20)

Active Ingredient Concentration. *"All MEs in the study will use the same active ingredient, benzisothiazoline-3-one (BIT), at one of three concentrations using pre-formulated latex paint. The target concentrations of BIT in the paint will be 120 ppm (mg/Kg), 400 ppm and 600 ppm. The selected target concentrations are the expected native level of BIT in the manufactured paint, a concentration 5X the lowest concentration, and an intermediate level. The paint concentrations are expected to be sufficient to allow good method sensitivity, but include a safety margin to ensure BIT does not exceed safe levels. AEATF II feels that use of three concentrations of BIT is appropriate since the primary exposure medium is paint. Consequently, AaiH will be directly proportional to the concentration times the total amount of paint applied over the entire workday."* (V1:18)

Indoor Site. *"AEATF II feels that an indoor painting environment is likely to increase dermal exposure over an outdoor painting environment due to the painting of ceiling surfaces which represent a significant source for drips and splatter. The AEATF II also feels that an indoor painting environment has a higher potential for inhalation exposure due to the limited air exchanges compared to an outdoor painting environment."* (V1:12)

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

Random elements have been incorporated into the design as follows:

- *"The target study design involves construction of 18-24 synthetic antimicrobial paint application with brush and roller days, called monitoring events (or MEs)."* (V2: 21)
- *"Each ME will be randomly assigned to one of the three concentration strata."* (V2:17)

- *"Advertisements soliciting subjects will be posted in the major local newspaper, the Fresno Bee, as well as newspapers circulating in the Spanish speaking community and the African-American community. Individuals who express a desire to participate in the study within a fixed period of time will be contacted and screened in random order. Individuals who meet the study requirements will be recruited until the required number of surrogate painters is obtained. Surrogate painters are randomly assigned to MEs."* (V1:18)
- *"The total number of qualified subjects will each be assigned a unique and consecutive number, starting at AE-01 based on the order of their enrollment. The numbers will then be randomized using a research randomizer program accessible at the following internet website: http://randomizer.org. The first 24 numbers in the generated randomized list will determine the participating subjects, while the remaining subjects will be held as replacements, their order for potential entry into the study being determined by the randomization process. The first 18 subjects in the generated randomized list will be assigned to ME01 to ME18. The remaining 6 subjects will be assigned as alternates. At least 2 alternates will be scheduled to be on hand each study day in case any subject is unable, chooses not to participate, or chooses to stop painting before reaching the necessary volume of paint applied."* (V2:23)

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

None.

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

The test substance will be applied by subjects according to typical painting practices. The physical aspects of the tasks include opening the paint can, painting the drywall (walls and ceiling) with the roller and painting the trim (baseboards and window/door molding) with the brush, and at the end of the ME close the lid of the paint can. The researchers will pre-shake the paint to assure uniformity of the active ingredient. The subjects will be provided with a brush, roller, roller pan, extension pole, and step stool or ladder. It is anticipated that each room to be painted will require about 1 gallon of paint. (V1:7)

"The subject will remove the lid from the secondary paint container. Application with the brush will involve dipping the brush into the paint in the secondary paint container, wiping off excess paint on the edges of the secondary paint container, and applying to surfaces. Application with the roller will involve transferring paint from the secondary paint container to a roller pan, pushing the roller through the paint, removing excess paint by rolling on the flat surface of the roller pan, and applying to surfaces. Subjects will be instructed before beginning that the painting goal is to cover the surfaces with an even coat of the minimal thickness that covers the surface completely and does not leave drips or bare spots. Once the subject begins painting they will be allowed to paint using their own techniques and judgment." (V2:20)

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

The proposed study has purposely excluded painting via an airless sprayer. This is an application technique often used by commercial painters. The AEATF II plans to conduct a separate study, under separate protocol, to monitor dermal and inhalation exposures to subjects applying paint with an airless sprayer.

Painting indoors has been selected over painting outdoors. The main rationale is that the indoor sites will include ceilings to be painting which would reasonably be expected to represent the high-end of exposure.

The proposed study has purposely excluded exposures for commercial painters and exposures from large painting tasks.

3. Is the proposed test material an appropriate surrogate?

The proposed test substance, latex paint treated with BIT, is an appropriate surrogate for the brush and roller study. **"***The test substance for these studies is the formulated product, Sherwin-Williams latex paint, containing 1,2-benzisothiazoline-3-one (BIT). The EPA does not require registration of paint containing BIT making no claims of antimicrobial activity, therefore no EPA registration number is available for the paint. A reference EPA registration for Mergal® BIT20, a BIT additive product is 5383-121. … BIT is the active ingredient selected for measurement, based on its stability, abundance in the formulation, and sensitivity of its analytical method."* (V2:17) The vapor pressure for BIT is 4.4E-7 mmHg at 20º C which is considered to be low (i.e., off-gassing expected to be minimal).

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

"The sample size of this study will be 18 MEs, with 6 MEs randomly assigned to each AI concentration strata. The number of MEs was determined by EPA in discussion with AEATF II to be appropriate to achieve the benchmark objective in studies of this general design type. For the paint application with brush and roller study, the benchmark objective is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time. The EPA, in discussion with AEATF II, determined that this benchmark is sufficient for regulatory purposes. If the benchmark objective is not achieved after completion of the 18 MEs AEATF II will consult with EPA to determine if additional MEs are required." (V1:18)

EPA Protocol Review: AEATF II Brush and Roller Scenarios/Protocol

Title: Brush and Roller Painting Study Protocol (Volume 2)

Date: February 5, 2014

Principal Investigator:
Robert J. Testman, M.B.A.

Participating Laboratory:
Golden Pacific Laboratories, LLC
4720 W. Jennifer Ave., Suite 105
Fresno, CA 93722

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

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

1. Societal Value of Proposed Research

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

"The primary objective of this study is to…monitor exposure to consumer painters who apply latex paint containing antimicrobial pesticide products with brush and roller painting equipment." (V2:10)

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

"The data generated from these studies will be used by the EPA in assessing potential exposure and risks to users of antimicrobial products and will be used in developing exposure assessments and human health risk analyses. The primary objective of this study is to use synthetic application-days called monitoring events (MEs) to monitor exposure to consumer painters who apply latex paint containing antimicrobial pesticide products with brush and roller painting equipment." (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 (V2:10)."

"Currently, US EPA relies upon the results from a single study listed in the Pesticide Handler's Exposure Database (PHED) to characterize exposure from the brush and roller application of a paint product (EPA, 1998). That study has a total of 15 MEs [monitoring events] *where paint was applied with a paintbrush only, and with no variation in amount of active ingredient applied. In addition the analytical quality of dermal and inhalation measurements in the PHED study are given a grade of C. This low quality grade limits the study's reliability for regulatory exposure assessment. Increased sensitivity of the analytical methods, exposure dosimetry methods and regulatory needs have changed significantly since the time of the PHED study. EPA has requested confirmatory exposure monitoring data for a number of antimicrobial use scenarios in Registration Eligibility Decision (RED) documents. A study performed for the European risk assessment database, RISKODERM, (Gijsbers et al., 2004) evaluated painter exposure to DEGBE, a non-solvent component of latex paint. However, this study was found to be lacking in several key areas including: no evaluation of potential inhalation exposure, collection of non-hand dermal samples from only 12 MEs, use of same subject for up to four MEs, unacceptable recoveries for many field fortification samples due to contamination, and no description of regulatory standards followed. There appears to be no other publicly available data with which to make a credible estimate of exposure for persons applying paint with a brush and roller. Thus, the rationale for conducting this study is to measure dermal and inhalation exposure in a large enough group of typical users to reasonably characterize central tendency and variability for this use (scenario) of antimicrobial pesticides."* (V2:12)

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

EPA will consider the data from this study in assessing exposures of professional or residential painters who apply latex paint containing an antimicrobial pesticide using brush or roller painting equipment.

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

Due to the limitations of existing data, as discussed in section 1(b) above, 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 be exposed to the test substance when performing painting activities with a brush and roller. There are no acceptable methods or models that could be used to extrapolate subjects' exposure while painting." (V2:13).

"Biological monitoring is not reasonable with BIT, because the primate metabolism of BIT (if any) is not known. The best exposure monitoring data currently available comes from PHED (EPA, 1998), and is inadequate for use with many antimicrobials as described in the Scenario Design document. This is critical information for appropriate risk assessment with some antimicrobials." (V2:17)

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

Yes. The purpose of this research is to measure exposures of individuals who apply antimicrobial-containing latex paint using brush or roller painting equipment. In this study, at least 18 subjects will be monitored in order to capture the expected variation in brush and roller application conditions and techniques. To be able to measure exposure from a full range of conditions and techniques, the study needs to be an intentional exposure study with scripting rather than an observational study.

2. Study Design

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

"The primary objective of this study is to use synthetic application-days called monitoring events (MEs) to monitor exposure [dermal and inhalation] *to consumer painters who apply latex paint containing antimicrobial pesticide products with brush and roller painting equipment."* (V2:13)

"The sample size of this study will be 18 MEs… The number of MEs was determined by EPA in discussion with AEATF II to be appropriate to achieve the benchmark objective in studies of this general design type. For the paint application with brush and roller study, the benchmark objective is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time. … If the benchmark objective is not achieved after completion of the 18 MEs AEATF II will consult with EPA to determine if additional MEs are required." (V1:18)

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 within this review).

2.1 Statistical Design

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

"Advertisements soliciting subjects will be posted in the major local newspaper, the Fresno Bee, as well as newspapers circulating in the Spanish speaking community and the African-American community. Individuals who express a desire to participate in the study within a fixed period of time will be contacted and screened in random order. Individuals who meet the study requirements will be recruited until the required number of surrogate painters is obtained. Surrogate painters are randomly assigned to MEs. As a precaution, more participants are recruited than are expected to be needed. This process results in a simple random sample of qualifying subjects from the volunteer pool. Note, however, that is not the same as a random sample from the existing population of non-professional consumer painters. By definition, volunteers are self-selected and could have different characteristics than non-volunteers. Such distinctions have no relevance in this case, however. There is no particular need to obtain a random sample from the Fresno consumer painter population. This existing population is not the target population for the study. The MEs are synthetic constructs that attempt to predict aspects of a future handler-day population. It is purposive by definition. Thus, a random sample of just one ME component (e.g. subject) from a subpopulation (e.g. Fresno County) provides no statistical advantage. In fact, a random sample of subjects from the volunteer pool is not the only possibility. For example, a more diverse sample of surrogate painters from this pool could also be acceptable if a clear diversifying characteristic were available for all painters. Lacking this, the paint application with brush and roller study uses the reasonable default option of a random sample from the volunteer pool." (V1:18)

"The sample size of this study will be 18 MEs, with 6 MEs randomly assigned to each AI concentration strata. The number of MEs was determined by EPA in discussion with AEATF II to be appropriate to achieve the benchmark objective in studies of this general design type. For the paint application with brush and roller study, the benchmark objective is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time. The EPA, in discussion with AEATF II, determined that this benchmark is sufficient for regulatory purposes. If the benchmark objective is not achieved after completion of the 18 MEs AEATF II will consult with EPA to determine if additional MEs are required." (V1:18)

(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?

The test subjects will be allocated to the treatment group as proposed by the AEATF II below; there is no control group.

"The total number of qualified subjects will each be assigned a unique and consecutive number, starting at AE-01 based on the order of their enrollment. The numbers will then be randomized using a research randomizer program accessible at the following internet website: http://randomizer.org. The first 24 numbers in the generated randomized list will determine the participating subjects, while the remaining subjects will be held as replacements, their order for potential entry into the study being determined by the randomization process. The first 18 subjects in the generated randomized list will be assigned to ME01 to ME18. The remaining 6 subjects will be assigned as alternates. At least 2 alternates will be scheduled to be on hand each study day in case any subject is unable, chooses not to participate, or chooses to stop painting before reaching the necessary volume of paint applied. If the scheduled subjects complete their MEs, the alternates are paid and will not participate that day. Alternates who do not participate will be eligible to participate on another study day. If additional subjects above the 24 initially selected are required, randomized subject 25 will be contacted followed by randomized subject 26 and so on, until all MEs are completed for the study. ME01 to ME18 will be randomly assigned using the research randomizer program to one of the three test substance concentrations. Each test substance concentration will be assigned to 6 total MEs. Once the subjects have been randomized they will be scheduled into the study. No more than two subjects will be monitored in one day." (V2:23-24)

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

Yes, the proposed research includes developing unit exposures for the brush and roller paint scenario for both the occupational and consumer populations and there is adequate justification for selecting test subjects from the general population only (i.e., consumers) to provide the high-end of exposure.

(f) Can the data be statistically analyzed?

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

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

"The AEATF II will not statistically analyze the monitoring data in order to investigate the relationship between exposure and other factors (e.g., environmental conditions including temperature, humidity, air turnover rate, etc.) 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. Two specific types of analyses will be performed (these analyses are discussed in more detail in the AEATF II's Governing Document (AEATF II, 2008)).” (V2:44).

“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 might be considered.“ (V2:45)

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

Yes.

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

Because of its Purposive Diversity Sampling Design, rather than a completely randomized design, the study will support only limited inferences.

The statistical power of the proposed study can be estimated by treating the design as if it were a completely randomized design where the logarithm of the exposure equals the sum of an intercept, the slope multiplied by the logarithm of the amount of active ingredient, and a normally distributed error term. Under the proposed design, the amount of active ingredient is proportional to the product of the paint volume and a concentration of 120, 400, or 600 ppm. The volume can be assumed to equal the nominal 2 gallons for each ME. The error variance is unknown but was estimated from the variance of the logarithms of the data from the PHED study of hand exposures from the use of paint brush only as 0.2846. In this calculation we are ignoring the variance attributable to the actual volume used and other design factors. The statistical power is the probability that complete independence (a log-log slope of zero) is rejected when there is complete proportionality (a log-log slope of one). EPA used a Monte Carlo simulation to demonstrate that if there are 6 MEs for each concentration, then the statistical power was 99.9% using the PHED study variance, and remained above 80% even if the variance is three times larger than found in the PHED study. The variances of the dermal and inhalation exposure for the proposed study are potentially higher due to the fact that the proposed study measures total dermal exposure rather than just exposure to the hands; also measures inhalation exposure; and uses rollers as well as paint brushes.

EPA also used a similar Monte Carlo simulation to estimate the fold relative accuracy of the estimated arithmetic mean and 95th percentile unit exposure. Under the

assumption of complete proportionality (a log-log slope of one) the fold relative accuracies using the PHED study variance are 1.30 for the arithmetic mean and 1.47 for the 95th percentile. The fold relative accuracies are 2.12 and 2.38 if the variance is five times larger than found in the PHED study. This means that the arithmetic mean and 95th percentile can be estimated within a factor of 3 with 95% confidence.

Even though the study is not a completely randomized study, based on these calculations, EPA believes that the proposed study is likely to characterize reliably the high end of exposures that occur while individuals paint with a brush and roller. EPA is confident that this design will provide data on brush and roller exposures more accurately and reliable than currently available data.

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

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

2.2 How and to what will human subjects be exposed?

"The test substance will be applied by subjects according to typical painting practices. The subject will remove the lid from the secondary paint container. Application with the brush will involve dipping the brush into the paint in the secondary paint container, wiping off excess paint on the edges of the secondary paint container, and applying to surfaces. Application with the roller will involve transferring paint from the secondary paint container to a roller pan, pushing the roller through the paint, removing excess paint by rolling on the flat surface of the roller pan, and applying to surfaces. Subjects will be instructed before beginning that the painting goal is to cover the surfaces with an even coat of the minimal thickness that covers the surface completely and does not leave drips or bare spots. Once the subject begins painting they will be allowed to paint using their own techniques and judgment. The subject will be provided an extension pole, step stool and ladder to use as they choose for painting the upper walls and ceiling. If the subject chooses to use a step stool or ladder research staff will remain in close proximity and provide assistance if needed to prevent accidents or spills. If the Principal Investigator determines that a subject's painting technique is outside reasonable consumer practice (e.g. gross over application, under application, or sloppiness) the subject will be re-instructed and then allowed to continue. Subjects will be provided dry cotton rags ("painter's rags") to use in wiping up paint spills on themselves, the equipment, and the floor. The use of painter's rags is considered normal painting practice." (V2:20)

Each test subject will be exposed to latex paint treated with BIT.

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

The choice of the formulation type (i.e., latex paint) is to collect data for painting using an in-can preservative.

"Sherwin-Williams Latex Paint is an end use product used for painting surfaces for protective and beautification purposes. Sherwin-Williams Latex Paint contains BIT. BIT in latex paint is added by the paint manufacturer to inhibit the growth of microbes such as bacteria, and may also be present as an anti-microbial additive in various paint components. BIT was selected as the analyte based primarily upon its abundance in paint products, on its stability, and the sensitivity of its analytical method. BIT has a complete toxicology database with low to moderate mammalian toxicity." (V2:18)

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

Each subject will paint approximately 2 gallons of paint containing 120, 400, or 600 ppm BIT. The AaiH (2 gallons of paint) at concentrations of 120, 400, or 600 ppm are 0.0127, 0.0370, or 0.0635 lbs ai, respectively (see Table 1 above).

"BIT was selected as the analyte based primarily upon its abundance in paint products, on its stability, and the sensitivity of its analytical method. BIT has a complete toxicology database with low to moderate mammalian toxicity." (V2:18)

"All MEs in the study will use the same active ingredient, benzisothiazoline-3-one (BIT), at one of three concentrations using pre-formulated latex paint. The target concentrations of BIT in the paint will be 120 ppm (mg/Kg), 400 ppm and 600 ppm. The selected target concentrations are the expected native level of BIT in the manufactured paint, a concentration 5X the lowest concentration, and an intermediate level. The paint concentrations are expected to be sufficient to allow good method sensitivity, but include a safety margin to ensure BIT does not exceed safe levels. AEATF II feels that use of three concentrations of BIT is appropriate since the primary exposure medium is paint. Consequently, AaiH will be directly proportional to the concentration times the total amount of paint applied over the entire workday." (V1:18)

(c) What duration of exposure is proposed?

Each predefined ME will apply a given amount of paint, not specific time durations. Expected durations are 120 to 180 minutes. (V2:11) The AEATF II anticipates the maximum duration to be 3 to 4 hours. (V2:31)

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 wipe/washes, and face/neck wipes. All monitored subjects will wear the outer dosimeter (representative outer clothing consisting of cotton long pants and cotton long sleeve shirts) directly over the inner dosimeter (consisting of 100% cotton long underwear). Inner and outer dosimeters will be provided by AEATF II. (V2:11) *"Hand exposure will be measured by scrubbing the hands with gauze pads soaked with a solution of 50% isopropyl alcohol/ 50% distilled water followed by rinsing with the same solvent. Face and neck exposure will be measured by wiping the face and neck with gauze pads moistened with 50% isopropyl alcohol / 50% distilled water."* (V2:11)

The amount of test substance handled will be determined from the change in weight of the paint containers used by each subject." (V2:11)

"Sampling for Ambient Pre-existing BIT: Duplicate air samples using personal air sampling pumps and OVS tubes described for worker samples will be collected in the subject dressing area for a fifteen minute period within two hours prior to the start of exposure monitoring on each day of the study. Similarly, duplicate air samples will be collected from each painting room intended for exposure monitoring that day. Duplicate dry gauze wipe samples will be taken by rubbing an approximately 1 foot square area of wall for at least 15 seconds. Air and wall wipe samples will be collected at heights of approximately three and five feet, and analyzed at the discretion of the Study Director." (V2:32)

"The ambient air temperature and humidity during exposure monitoring will be recorded. The air changes per hour (ACH) in the painting rooms will be measured. A description of the HVAC system in use during each ME will also be documented." (V2:11) 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 intervals appropriate for the duration of the work period per SOP AEATF II-10C.1. Environmental monitoring equipment will be calibrated or standardized according to SOPs. HVAC and room volume will be described in detail and documented in study field notes. Air changes per hour will be experimentally measured for one of the painting rooms." (V2:38)

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

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

"This study will be conducted according to FIFRA GLP Standards (40 CFR 160). The field site as well as the analytical facility will be inspected by the quality assurance unit (QAU). The QAU will report to a member of Golden Pacific Laboratory's Board of Directors. The QAU will review the protocol prior to study initiation. Different phases of the field study and the exposure matrix analyses will be inspected. Field and analytical data generated will be audited as the study progresses. The final report will be audited for completeness and accuracy. Results of the audit will be transmitted to both the Principal Investigator and the Sponsor's Representative. QAU organization and responsibilities are summarized in SOPs AEATF II-5A.1 – 5C.1; 5E.1 – 5K.1." (V2:48)

(c) What QA methods are proposed?

"This study will be conducted according to FIFRA GLP Standards (40 CFR 160). The field site as well as the analytical facility will be inspected by the quality assurance unit (QAU). The QAU will report to a member of Golden Pacific Laboratory's Board of Directors. The QAU will review the protocol prior to study initiation. Different phases of the field study and the exposure matrix analyses will be inspected. Field and analytical data generated will be audited as the study progresses. The final report will be audited for completeness and accuracy. Results of the audit will be transmitted to both the Principal Investigator and the Sponsor's Representative. QAU organization and responsibilities are summarized in SOPs AEATF II-5A.1 – 5C.1; 5E.1 – 5K.1." (V2:48)

"Sample matrix fortifications designed to assess the stability of the active ingredient under field, storage and transit conditions in or on the sampling materials (inner and outer dosimeters, hand wipe/wash solutions, face/neck wipes, painter's hats, and air sampling matrices) will take place on each day of the study. … Field fortifications will be conducted at the following levels during the study.

Matrix	***Fortification Level***
Air Sampling Tubes	*100 ng/tube and 2.0 µg/tube*
Hand Wipes/Washes	*4.0 ng/mL and 400 ng/mL*
Face/Neck Wipes	*400 ng/sample and 10 µg/sample*
Painter's Hats	*12 µg/sample and 1.0 mg/sample*
Inner Dosimeter Section	*12 µg/sample and 1.0 mg/sample*
Outer Dosimeter Section	*12 µg/sample and 1.0 mg/sample*
RespiCon Fiberglass Filters	*100 ng/filter and 2.0 µg/filter*

On each study day when field fortifications are conducted, samples of each matrix will be fortified at the two levels shown above. The low fortification represents 4 x LOQ. The high fortification levels are based on expected exposure levels for the

painting tasks being monitored on that day. For each matrix/level combination used during the study, three samples (i.e., triplicates) of that matrix will be fortified and analyzed."(V2:39-*40)*

(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 might be considered." (V2:45)

3. Subject Selection

3.1 Representativeness of Sample

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

The population of concern is professional or non-professional painters who apply latex paint using a brush or roller. *"AEATF II proposes to conduct the brush and roller study using consumer applicators (without experience as professional painters), as use by typical consumer painters is likely to result in higher exposure than would be seen using professional painters as applicators." (V1:8)*

(b) From what populations will subjects be recruited?

"[S]ubjects will be recruited from the population of Fresno County, CA, and the surrounding area." (V2:24)

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

The population of concern is professional and non-professional painters who apply latex paint using a brush or roller. Only non-professional painters will be monitored because their use of the products is likely to result in higher exposure since they are likely to be less skilled compared to professional painters.

Potential subjects will self-identify in response to advertisements placed within the same week in the following three local newspapers in Fresno, California: the Fresno Bee, the California Advocate, and the Fresno edition of Vida en el Valle. "*The Fresno Bee is a large, general circulation daily paper in Fresno County. The California Advocate is the dominant African American community weekly paper in Fresno County, and Vida en el Valle is a weekly Spanish language paper targeting the San*

Joaquin Valley, with separate editions for Fresno and other central valley municipalities." (V2:25)

The placement of advertisements in newspapers targeting different demographic groups should minimize bias and achieve diversity among respondents and subjects. While individuals who express interest in response to a newspaper advertisement about this study may differ in unknowable ways from other individuals who do not step forward, there is no reason to think that respondents in the Fresno area are atypical of similar individuals 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 program, as described in the Governing Document (2008), intends to develop a database of exposure monitoring data that can be used to support practical regulatory decisions about future exposures for different (including currently nonexistent) active ingredients and their associated products. The database needs to address a variety of exposure scenarios for which no or limited data currently exist. The paint application with brush and roller scenario is an important component of the AEATF II program and the focus of this protocol. As noted in the previous section, existing monitoring data for this scenario are considered inadequate. The primary purpose of the paint application with brush and roller monitoring study is to develop more accurate information on potential consumer and worker exposures to antimicrobials. These data will consist of dermal and inhalation exposure estimates derived from monitoring subjects under conditions constructed to broadly represent those expected for the future application of arbitrary antimicrobial pesticides. AEATFII anticipates the resulting database will contain sufficient data to support exposure assessments for paint application with brush and roller." (V1:11-12)

3.2 Equitable Selection of Subjects

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

Inclusion/exclusion criteria are complete and appropriate, except that "skin conditions on the surface of the face or neck" and "sensitivities to BIT or other chemical-based products" should be added to the list of exclusions.

The inclusion/exclusion criteria are listed in Volume 2, page 27-28, and below. The recommended revisions are shown underlined and in red.

"Inclusion Criteria

- *Males or females, at least 18 years of age and able to show a government issued identification*
- *Consider their own health sufficient to conduct the described activities*

- *Willingness to sign the Informed Consent including the Experimental Subject's Bill of Rights Form and Subject Self-Reporting Demographic Form*
- *Speak and read English or Spanish*
- *Resident of Fresno County*
- *At least one brush and roller painting experience in the past 5 years*

"Exclusion Criteria

- *Skin conditions on the surface of the hands,* ***face or neck*** *(e.g., psoriasis, eczema, cuts or abrasions)*
- *Pregnancy, as shown by a urine pregnancy test*
- *Lactation*
- *Allergies* ***or sensitivities*** to *latex paint, soaps,* ~~*or*~~ *isopropyl alcohol,* ***BIT or other chemical-based products***
- *Severe respiratory disorders (e.g., moderate or severe asthma, emphysema)*
- *Cardiovascular disease (e.g., history of myocardial infarcts, stroke, congestive heart failure or uncontrolled high blood pressure)*
- *Severe diabetes*
- *Immunologically suppressed (e.g. undergoing chemotherapy, transplant patients)*
- *Has worked as a professional painter in the past 10 years*
- *Is an employee or spouse of an employee of any company represented by AEATF, GPL, other contract organization involved with the study, paint manufacturer, or the American Chemistry Council."* (V2:27-28)

(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. (V2:27-28)

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

No.

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

The recruiting process is described in V2:24-28.

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

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

3.3 Remuneration of Subjects

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

"If with help from the interviewer, a subject fills out Part I of the demographic form (the Health Questionnaire), information that disqualifies them from participation may become evident. If this occurs, the disqualified subject will be paid $20 for their time and inconvenience. All individuals that show up for the informed consent interview will be compensated $20 in cash at completion of the interview for their time and inconvenience. All individuals who are qualified, sign the informed consent form, and report to their assigned study site, will receive $100 in cash for their time and inconvenience when they leave the study site, whether they are monitored or not." (V2:29)

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

Yes. The proposed payment amount is fair and reasonable compensation for the subjects' time and inconvenience. *"The value for compensation 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."* (V2:29)

(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 paid in cash when subjects leave the study site. (V2:29)

4. Risks to Subjects

4.1 Risk characterization

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

The proposed test material is EPA-registered, with an essentially complete supporting database. Additional discussion is provided below on the comparison of the hazard and anticipated exposures for the test subjects in this study.

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

Risks are of a reaction to the active ingredient BIT, to the latex paint, and/or to the alcohol wash and wipes; 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, and the potential for a breach of confidentiality. (V2:66-67) An additional risk related to the use of a ladder to paint a ceiling is not discussed in the protocol or consent form.

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

Anticipated exposure levels to the test subject are based on the brush painting data in EPA's Pesticide Handler's Exposure Database (PHED). Based on the PHED data, the unit exposure for inhalation is 0.28 mg/lb ai. The dermal unit exposure for single layer and no gloves is 180 mg/lb ai (note: 175 mg/lb ai was measured on the hands). The number of dermal samples range from 14 to 15 for the body (a range is reported because of the incomplete body part measurements; forearms not measured), 15 hand samples for subjects wearing no gloves. Within the PHED brush scenario, all of the MEs handled the same amount of ai (i.e., 0.051 lbs ai).

The AEATF II cited the EPA BIT RED (2005) to indicate that the potential inhalation and dermal risk were not of concern for painting. The dermal endpoint in the BIT RED (2005) was based on an oral toxicity study and a 41% dermal absorption (after 72 hours). Subsequent to the RED, the EPA revised the dermal endpoint for BIT and the dermal endpoint is now based on a 90-day dermal toxicity study in rats (MRID 45184601). In the dermal toxicity study, rats were dosed with 10 to 50 micro liters of test substance onto an unknown area (area reported in raw data that was not supplied with the report). EPA has proposed to use the LOAEL of 100 mg/kg/day as the point of departure, where the effects seen were macroscopic and microscopic changes to the stomach mucosa. A NOAEL was not established for this study. The dermal Target MOE is 1000 based on 10x for the interspecies extrapolation, 10x for intraspecies variation, and 10x for lack of a NOAEL. However, there are many uncertainties in the 90-day dermal toxicity study, such as how did the stomach

irritation effects result from a dermally applied dose? The dermal toxicity study report indicates:

- *"The treated site of each rat was covered with a 4-ply gauze patch (Abco #052123) and further covered with Zonas non-irritating tape to retain the gauze dressing and to ensure that the animal could not ingest the test article.*
- *…at which time the wrappings were removed and the residual test article was gently wiped in order to prevent ingestion."*

Even though the researchers took these precautions to avoid ingestion by the rats, the report also indicates:

- *"Also, epidermal hyperplasia/hyperkeratosis, sebaceous gland hyperplasia and some dermal inflammation was seen in the untreated skin sites of a few rats of all compound-treated groups. This change at the untreated sites was also likely the result of the taping and wrapping procedures and/or migration of the test substance onto the adjacent skin.*
- *Although the test material was wiped from the treatment sites after the removal of the wrapping, it is very possible that some residual compound was still present. These changes in the stomach are consistent with those caused by ingestion of an irritating substance and are likely the result of ingestion of some of the compound. These changes are considered to be the result of local superficial irritation of the gastric mucosa and not a systemic effect."*

EPA notes in the oral (gavage) rat toxicity study (MRID 46346201), macroscopic and microscopic lesions were seen in the stomach at the LOAEL of 25 mg/kg/day (NOAEL of 8 mg/kg/day). Given the precautions taken in the dermal toxicity study to preclude incidental ingestion during grooming, the fact that a dose of 8 to 25 mg/kg/day would be needed to observe stomach irritation, coupled with no direct observations noted in the dermal toxicity study report of incidental ingestion, EPA is proposing to use the LOAEL of 100 mg/kg/day as the point of departure to represent the dermal route as a conservative (protective) approach. The acute dermal irritation of BIT is classified as a category IV (slight irritant) and as a moderate dermal sensitizer. The 90-day dermal toxicity study in rats indicated some dermal reactions at the dose of 100, 300, and 1000 mg/kg/day dose at the 3, 2, and 1 week timeframes, respectively.

The inhalation endpoint for BIT has been derived from co-critical oral (dog and rat) toxicity studies. The inhalation POD is based on a NOAEL of 5 mg/kg/day from the subchronic dog study, where the effects were an increased incidence of emesis and clinical chemistry alterations at the lowest dose tested of 20 mg/kg/day. The subchronic rat study provides support for the dog study (rat study NOAEL of ~8 mg/kg/day is based on macroscopic and microscopic lesions in the non-glandular and glandular regions of the stomach). For inhalation, the Target MOE is 1000 based on 10x interspecies extrapolation, 10x intraspecies variation, and 10x for route-to-route extrapolation from an oral to inhalation route.

Table 2 provides a comparison of the anticipated dermal paint brush exposures to the point of departure (POD) from the 90-day dermal rat study (LOAEL = 100 mg/kg/day). The dermal MOE is presented at the maximum AaiH based on the following equation: LOAEL 100 mg/kg/day / 180 mg/lb ai unit exposure x maximum 0.0714 lbs ai (which is 2.25 gal of paint treated at 600 ppm) x (1/80 kg BW). The MOE is the unitless ratio of the POD/dose where the target MOE is 1000.

Table 2 also provides a comparison of the anticipated inhalation paint brush exposures to the point of departure (POD) from the subchronic dog study (NOAEL = 5 mg/kg/day). The inhalation MOEs is presented at the maximum AaiH using the following equation: NOAEL 5 mg/kg/day / 0.28 mg/lb ai unit exposure x maximum 0.0714 lbs ai (which is 2.25 gal of paint treated at 600 ppm) x (1/80 kg BW). The MOE is the unitless ratio of the POD/dose where the target MOE is 1000.

Based on the comparisons of the anticipated exposures and subchronic endpoints selected, there are minimal inhalation and dermal risks of concern at the maximum AaiH.

Table 2. Dermal and Inhalation MOE Estimates at Varying AaiH for Brush/Roller.

Route	UE (mg/lb ai)	BIT (ppm)	Paint (gallons)	AaiH (lbs)	Dose (mg/kg/day)	MOE
Inhalation	0.28	600 (max)	2.25 (max)	0.0147	0.000051	97,000
Dermal	180				0.033	3,000

Dose (mg/kg/day) = UE (mg/lb ai) x AaiH (lbs ai) x (1/80 kg BW)
MOE = NOAEL or LOAEL (mg/kg/day) / Dose (mg/kg/day). Where inhalation NOAEL is 5 mg/kg/day (oral toxicity study) and dermal LOAEL is 100 mg/kg/day (dermal toxicity study). Target MOEs for inhalation and dermal are 1000.

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

The potential dermal and inhalation risks have been evaluated by EPA through a comparison between the POD and the anticipated dermal and inhalation exposure. The comparison indicates minimal dermal and inhalation risks. Please see part 4.1(c) (above) for details. The AEATF II references the EPA for the MOEs (V2:15).

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

Individuals who may be at an increased risk for adverse effects are not eligible to become subjects in this study, including individuals known to be allergic to latex paint, soaps, or isopropyl alcohol, subjects in poor health, or with broken skin.

4.2 Risk Minimization

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

Subjects will wear protective eye wear; paint label safety precautions will be explained to subjects; skin reaction and heat stress signs and symptoms will be explained to subjects; and researchers will closely observe subjects for possible signs of early heat illness and will immediately contact an on-site health professional if a subject develops signs or reports symptoms of heat illness or other forms of distress or reactions.

"Safety precautions:

A copy of the Materials Safety Data Sheet (MSDS) and the product label (English and Spanish versions) will be included in the study file, and provided to the study team (professional observers and researchers). A copy of the product label (English or Spanish, as requested) will be provided to each subject, and each subject will be made aware of the MSDS and a copy in their preferred language will be provided upon request. Label safety cautions will be explained to the subjects involved in the study….For this study PPE (protective eyewear) will be provided and use directions will be followed by the subjects and ensured by the study research personnel. If a subject does not use required PPE or does not follow use directions within reason, or does so in a manner that presents safety issues in the judgment of the study research personnel, the study research personnel may terminate the subject's participation."

"Heat stress signs and symptoms will be explained to the subjects. A copy of the poster entitled "Controlling Heat Stress Made Simple" in English and Spanish will be posted in the dressing area at the site.

"Test substance which may get on the skin will be removed through one or more hand wipes/washes and the face/neck wipe procedure (sample collection events) during the ME. Following completion of each ME, each subject will wash their hands thoroughly with soap and water. The Principal Investigator or on-site health professional will examine their hands and note any irritation to the skin at termination of each participant's monitoring. Section 9D includes additional details regarding stop criteria and medical management." (V2:19)

"Stop Criteria and Medical Management

It is not expected that test subjects will experience any adverse effects from participation in this study. In the unlikely event adverse effects are experienced, they will likely be related to skin reactions during or following the study, or heat stress or odor aversion during the study. The Principal Investigator or on-site health professional will discuss the symptoms of heat stress, odor aversion and eye and skin

reactions with the subjects prior to participation in the study. Subjects will be instructed to inform the Principal Investigator or research staff (or personnel) immediately if they feel ill, suffer an eye or skin reaction or experience any other unanticipated adverse effects they feel may be related to the study during or following conduct of the study. The Principal Investigator or on-site health professional will also examine the hands immediately prior to the monitoring period to ensure there are no existing abrasions, cuts or skin conditions that increase the risk of skin problems during the monitoring period. A Spanish-speaking member of the research team will be present during monitoring events involving subjects whose preferred language is Spanish.

"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 notify the on-site health professional and follow instructions from that health professional. If instructed, research staff will assist the subject in gently washing exposed skin with clean water and mild soap. After drying the area with a clean towel, the Principal Investigator will be contacted for further instructions.

"The extra layer of clothing worn by subjects may increase the risk of heat related illness. To minimize the possibility of heat stress, the study will be conducted indoors in an environment where the heat index (HI) is expected to be less than 85. If the temperature at the study site exceeds 82 degrees Fahrenheit research personnel shall monitor the heat index, and stop subjects' work if the heat index exceeds 95. The SOP AEATF II-11B.1 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 on-site health professional will be immediately contacted for further medical management instructions. If they answer negatively, they will be permitted to continue working, and frequently thereafter asked whether they would like to rest for a moment. Any affirmative answer will be handled as described above.

"If subjects develop visible signs or report symptoms of distress such as pronounced fatigue, headache, cramps, feeling faint, increased pulse, muscle spasms, heavy sweating (or dry skin if previously sweating), extreme thirst, or rapid breathing, the subjects will be required to stop working immediately, and given their choice of water or a sports drink.

"The on-site health professional will immediately be contacted for further medical management instructions. If the worker's condition appears to be serious, a member

of the study team will call 911 and allow emergency medical personnel to respond and treat the subject. The AEATF will pay for reasonable and appropriate medical treatment for a study-related injury or illness that is not paid for by the subject's own insurance or the insurance of a third party under which the subject is covered.

"Study personnel will be instructed to inform the Principal Investigator 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.1 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 Principal Investigator to determine whether further medical management is appropriate.

"The Principal Investigator will maintain a record of adverse health observations and reports, and follow Sponsor, SAIRB, Inc., EPA and California DPR policies for medical event reporting per SOP AEATF II-11F.0. 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." (V2:29-31)

Other protections include:

- Candidates with skin conditions on the surface of the hands (e.g., psoriasis, eczema, cuts or abrasions) are excluded (V2:28)
    - *EPA recommends that the sponsors add "skin conditions of the face or neck" to the list of exclusions*
- Candidates known to be allergic to latex paint, soaps, or isopropyl alcohol are excluded (V2:28)
    - *EPA recommends that the sponsors expand this exclusion to also exclude individuals who have allergies <u>or sensitivities to BIT or other chemical-based products</u>*
- Candidates who are pregnant, nursing, or in poor health are excluded (V2:28)
- The consent form alerts subjects to signs and symptoms of eye and skin reactions and advises them to stop the painting if they experience a reaction to the paint, or if they feel faint or too hot (V2:66)
- The ambient temperature will be monitored, and subjects will be observed for signs of heat stress. There are appropriate stopping rules if the heat index becomes unsafe (SOP 11B.1, Heat Stress). (V4:88-99)
- A medical professional (a registered nurse) will be hired for this study and will be present during the monitoring events. (V2:29, and confirmed via email between K. Sherman, EPA, and R. Testman, GPL)

- The protocol minimizes the risk of psychological harm related to the pregnancy tests by providing a private place for women to take the test and following procedures designed to protect the confidentiality of any test result (SOP 11A.1, Pregnancy Testing and Nursing Status). (V4:85-86)

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

Heat stress index above 95 (V2:30)

Other medical reasons (V2:31)

"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." (V2:31)

(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 (V4:88-99)
SOP 11.C.2 for Emergency Procedures (V4:100-103)

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

"It is not expected that test subjects will experience any adverse effects from participation in this study. In the unlikely event adverse effects are experienced, they will likely be related to skin reactions during or following the study, or heat stress or odor aversion during the study. The Principal Investigator or on-site health professional will discuss the symptoms of heat stress, odor aversion and eye and skin reactions with the subjects prior to participation in the study. Subjects will be instructed to inform the Principal Investigator or research staff (or personnel) immediately if they feel ill, suffer an eye or skin reaction or experience any other unanticipated adverse effects they feel may be related to the study during or following conduct of the study. The Principal Investigator or on-site health professional will also examine the hands immediately prior to the monitoring period to ensure there are no existing abrasions, cuts or skin conditions that increase the risk of skin problems during the monitoring period. A Spanish-speaking member of the research team will be present during monitoring events involving subjects whose preferred language is Spanish.

"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 notify the on-site health professional and follow instructions from that health professional. If instructed, research staff will assist the subject in gently washing exposed skin with clean water and mild soap. After drying the area with a clean towel, the Principal Investigator will be contacted for further instructions.

"The extra layer of clothing worn by subjects may increase the risk of heat related illness. To minimize the possibility of heat stress, the study will be conducted indoors in an environment where the heat index (HI) is expected to be less than 85. If the temperature at the study site exceeds 82 degrees Fahrenheit research personnel shall monitor the heat index, and stop subjects' work if the heat index exceeds 95. The SOP AEATF II-11B.1 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 on-site health professional will be immediately contacted for further medical management instructions. If they answer negatively, they will be permitted to continue working, and frequently thereafter asked whether they would like to rest for a moment. Any affirmative answer will be handled as described above.

"If subjects develop visible signs or report symptoms of distress such as pronounced fatigue, headache, cramps, feeling faint, increased pulse, muscle spasms, heavy sweating (or dry skin if previously sweating), extreme thirst, or rapid breathing, the subjects will be required to stop working immediately, and given their choice of water or a sports drink.

"The on-site health professional will immediately be contacted for further medical management instructions. If the worker's condition appears to be serious, a member of the study team will call 911 and allow emergency medical personnel to respond and treat the subject. The AEATF will pay for reasonable and appropriate medical treatment for a study-related injury or illness that is not paid for by the subject's own insurance or the insurance of a third party under which the subject is covered.

"Study personnel will be instructed to inform the Principal Investigator 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.1 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 Principal Investigator to determine whether further medical management is appropriate.

"The Principal Investigator will maintain a record of adverse health observations and reports, and follow Sponsor, SAIRB, Inc., EPA and California DPR policies for medical event reporting per SOP AEATF II-11F.0. 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: 29-31)

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

The consent form states: *"If within 24 hours of your participation in the study you experience a skin reaction or other adverse effect that you believe is related to your participation in the study you should seek medical treatment and call the Principal Investigator, Robert Testman, at Golden Pacific Laboratories (559 275-9091) as soon as possible."* (V2:67)

"The medical management procedures set forth in SOP AEATF II-11C.1 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 Principal Investigator to determine whether further medical management is appropriate. (V2:31) (SOP 11C.2 is located in Volume 4, pages 100-103)

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

The informed consent form states: *"If you are hurt or sick while you are participating in this study, a nearby medical facility will provide care. If necessary, we will take you there. The AEATF 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 the insurance of a third party under which you are covered. The Principal Investigator in consultation with the on-site medical professional will decide if you have an injury or illness that is due to your participation in the study. If within 24 hours of your participation in the study you experience a skin reaction or other adverse effect that you believe is related to your participation in the study you should seek medical treatment and call the Principal Investigator, Robert Testman, at Golden Pacific Laboratories (559 275-9091) as soon as possible."* (V2:67)

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?

"While there are no direct benefits to the subjects participating in this research study, there are indirect benefits to both the subjects and society. Paint products containing antimicrobial chemicals are used extensively in homes, schools, businesses, etc. to control mold and other microbes with potential to produce illness in humans, domestic animals and pets. Society may benefit from continued ability to use antimicrobials that improve the quality of life. Measuring exposure of subjects in this research study will produce reliable data about the 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 to these chemicals. The ability to accurately predict risk may allow other chemical classes of antimicrobials to also be registered based on exposure estimates generated from the data to be produced by this study." (V2:16)

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

"Results from the study may benefit EPA and painters by reducing uncertainty about the range of exposure experienced by consumers and workers handling paint containing 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." (V2:16)

(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 to people who use latex paint, with resulting societal benefits in the form of more accurate and confident assessments of exposure and risk.

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

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

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Schulman Associates IRB

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

Yes

(c) Is this IRB registered with OHRP?

Yes

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

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

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

Yes.

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

Yes.

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

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

8. Informed Consent

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

Yes.

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

Yes. See Attachment 5.

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

Yes. See Attachment 4.

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

Ability to speak and read English or Spanish is specified as a criterion for inclusion in the study. (V2:28)

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

"A Spanish-speaking member of the research team will be available at recruitment meetings to assist and ensure communication with anyone preferring Spanish over English. The subjects will be asked if they would like to have the meeting conducted in English or Spanish." (V2:27)

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

(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 paint and BIT labels, paint MSDS, recruiting materials, flyers, and poster entitled "Controlling Heat Stress Made Simple"). (V2:19)

During the private consent meeting, the researcher will provide each volunteer with a full overview of the study, participation requirements, any potential risks and benefits, alternatives to participation, etc. To make sure that the potential subjects understand what is being asked of them, a short list of standardized questions requiring a response will be asked of each potential subject (SOP AEATF II-11J.1). (SOP 11-J.1 was not submitted in Volume 4 of the Brush and Roller Study; however, it is provided in Volume 4 of the AEATF II's Solid Pour Study submission)

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

"3.0 Ensuring Comprehension

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

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

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

"3.4 The Study Director (or designee) obtaining the consent will not sign the Consent Form unless he/she believes that the process has been free of coercion or undue influence and that the candidate fully understands the information presented." (SOP 11-J.1 was not submitted in Volume 4 of the Brush and Roller Study; however, it was submitted as part of the Solid Pour Study submission)

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

Please see the text quoted from SOP AEATFII-11J.1, above

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

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

SOP AEATF II-11J.1 states: *"The Study Director (or designee) obtaining the consent will not sign the Consent Form unless he/she believes that the process has been free of coercion or undue influence and that the candidate fully understands the information presented."* (SOP 11-J.1 was not submitted in Volume 4 of the Brush and Roller Study; however, it was submitted as part of the Solid Pour Study submission)

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."* (V2:67)

9. Respect for Subjects

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

"All subjects' names and personal identifiers provided will be kept confidential to ensure their privacy.

"Records relating individual names to their AE number will be retained separately from the study file in an area clearly marked "CONFIDENTIAL". Golden Pacific Laboratories will retain subject's records indefinitely. Subjects may obtain copies of their own records from the Principal Investigator on request."(V2:29)

"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. After the subject has taken the pregnancy test she will be asked if she still wants to participate in the study. If she declines, she will be paid $100 for her inconvenience and will be free to go. If she wants to continue, a female member of the research team familiar with interpretation of the test will confirm the results of the pregnancy test. 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. A note indicating that the pregnancy test was performed in accordance with SOP AEATF II-11A.1 will be made in the raw data." (V2:32)

(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 be in this study it will be because you want to. There will be no direct benefit to you if you do decide to participate and no harm to you if you decide not to. The choice is up to you." (V2:67)

"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, you will not be penalized in any way or lose any benefits." (V2:68)

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

All individuals that participate in an informed consent interview will be compensated $20 in cash at completion of the interview, regardless of whether they decide to participate. All individuals who are qualified, sign the informed consent form, and report to their assigned study site, will receive $100 in cash for their time and inconvenience when they leave the study site, whether they are monitored or not. (V2:29)

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. (V2:68)

§ 26.1111 Criteria for IRB approval of research
AEATF II Brush and Roller Painting Scenario/Protocol AEA09: February 5, 2014

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 Brush and Roller Painting Scenario/Protocol AEA09: February 5, 2014

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 Brush and Roller Painting Scenario/Protocol AEA09: February 5, 2014

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 Brush and Roller Painting Scenario/Protocol AEA09: February 5, 2014

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	V3: 23-146, 242-329 V1: 6-19 V3: 299-309 Reviewed ICF and conditionally approved
	(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.+		N Y Y n/a Y	V3:233-234, V2:132-134 V3:234, Unanimous V3:195-223
	(3) Records of continuing review activities.		n/a	None
	(4) Copies of all correspondence between the IRB and the investigators.		Y	V3:5-239
	(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 N	V3:238-239
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		Y	Previously provided to EPA by Schulman Associates
	(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	V2:14-16, 66-67
		(2) The measures proposed to minimize risks to the human subjects;	Y	V2:29-34, 63-67
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	V2:16
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	V2:17
		(5) The balance of risks and benefits of the proposed research.	Y	V2:16
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Orig. V3:161-171 Approved: N//a
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	V2:24-28, 82-86
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	V2:25-27, 85-86
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	V3:5-239
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.		N	Conditionally approved