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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

*March 18, 2014*

**MEMORANDUM**

**SUBJECT:** Science and Ethics Review of AEATF II Paint Hand Wash Removal Efficiency Protocol

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**TO:** Steven Weiss, Chief
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We have reviewed the referenced proposal from both scientific and ethics perspectives. Scientific aspects of the proposed research are assessed in terms of the recommendations of Brouwer et al (2000) 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 EPA recommends that the AEATF II video this hand wash procedure so that researchers that use this same procedure in future studies can better gauge and mimic this procedure.

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:

    - 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…."*

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

**Completeness of Protocol Submission**

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

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

- Transmittal Letter (p. 2)
- 40 CFR 26.1125 Checklist (pp. 7-8)

Volume 2 of the submitted package includes the following documents:

- SAIRB conditionally-approved draft protocol dated 1/23/14 (pp. 3-38)
- SAIRB Study Status Notification I dated 11/14/13 (pp. 132-3)
- SAIRB Study Status Notification II dated 12/4/13 (p. 134)

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

- 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 1/23/14) (pp. 44-53) – English version provided; will be translated to Spanish after final approval
- Qualification Worksheet (draft 1/23/14) (p. 56) – English version provided; will be translated to Spanish after final approval
- Newspaper Advertisement (draft 1/23/14) (p. 71) – English version provided; will be translated to Spanish after final approval
- Script for receiving phone calls in response to advertisement (draft 1/23/14) (pp. 74-5) – 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 AEA08 Removal Efficiency Study protocol.

## A. Summary Assessment of the Scenario Design

Supporting details are in Attachment 1.

**1. Scenario Design:** This proposal is to measure the hand wash removal methodology to determine its efficiency to support the AEATF II's protocol to monitor exposure of test subjects while they paint with brush/rollers. The AEATF II defines the objective of this efficiency study as: *"This study is being conducted to determine the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint containing BIT."* (V2:7)[2] *"The primary objective of this study is to determine the removal efficiency of BIT in latex paint, and in isopropyl alcohol (IPA) from human hands."* (V2:9) The AEATF II proposes to recruit test subjects from the general population. *"Adult subjects will be recruited from the population of Fresno County, CA and the surrounding area"* (V2:20) In summary, the test subjects will have their right and left palm surfaces fortified with BIT-treated paint or BIT-treated isopropyl alcohol (IPA). The test substance will be allowed to dry on the subject's hands for 45 minutes and then the researchers will perform a hand wash procedure to mimic the hand wash procedure in the actual painting study. The results of the paint portion of the efficiency study will be used to correct for any losses on the test subject's hands in the paint brush/roller exposure study. The results of the IPA portion of the efficiency study will be

[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 5" found at the bottom right-hand corner. Volume 2 page references are from the expression "Page n of 105" found at the bottom right-hand corner. Volume 3 page references are from the expression "Page n of 318" found at the bottom right-hand corner. Volume 4 page references are from the expression "Page n of 74" found at the bottom right-hand corner.

used to compare the differences in the efficiency between paint and a non-paint liquid. The IPA portion will also be available for future studies using non-paint liquids for hand wash sampling method corrections.

The following are the basic procedures to be performed by the researchers in this hand wash efficiency study:

- Prior to fortification the hands will be washed with Ivory soap and water and dried with paper towels. (V2:18)
- *"BIT in paint or solvent will be applied to hands using positive displacement micropipettes…."* (V2:16)
- *"The test substance will be applied to the palmar surfaces of each hand using a positive displacement micropipette. … A glass capillary tube will be used to spread the test substance across the center of the palmar surface, but test substance will not be spread closer than 2 cm from any edge of the palmar surface. The capillary tube from each subject will be placed into a glass test tube and stored frozen prior to analysis."* (V2:18-19)
- *"After 45 minutes* [of drying time] *the subjects will hold their hands over a stainless steel bowl while researchers scrub the hands with a gauze sponges (J&J Mirasorb 4-ply each)* [stacked together]. *The gauze sponge will be soaked with 50% IPA I 50% distilled water and used for scrubbing until all dried paint is loosened or removed. The researchers will then rinse the hand with the same solvent by pouring the solvent over the hand and having the subject rub their fingers and palm together. The total volume of IPA/water solution used will be 250 mL. The used gauze sponges will be added to the hand wash solution collected in the stainless steel bowl and saved with the rinse solution for analysis. The procedure will then be repeated for the second hand producing a second sample."* (V2:19)

The AEATF II proposes to use a total of 20 test subjects to measure hand wash efficiency. The subjects will be randomly assigned to either paint or IPA solutions at two concentrations of BIT per solution as depicted in Table 1. The proposal reports the fortifications as 78.5 µg/hand and 390 µg/hand (same as calculated in Table 1). (V2:17) Based on the conversion of the solution concentrations to a loading on the palmar surface area, it is estimated that the loadings on the hands are 1.6 and 7.8 µg/cm$^2$ for Groups 1/3 and 2/4, respectively.

In comparison, the paint brush scenario in the Pesticide Handlers Exposure Database (PHED) indicates the loading on the subjects ranged from 4.8 to 19.7 µg/cm$^2$ with an arithmetic mean of 10.5 µg/cm$^2$. The proposed loadings are within the range of anticipated hand wash residue from the proposed brush/roller painting scenario. Note: A glass capillary tube will be used to spread the test substance across the palm. The amount remaining on the tube will be accounted for in the efficiency calculations; and this amount will be subtracted from the loading estimate provided in Table 1 (i.e., the loading in Table 1 is the nominal amount and the actual will be a little less).

**Table 1. Summary of Hand Wash Efficiency Proposal.**

| Group | No. Test Subjects | Solution (per hand) | Concentration of BIT | AaiH (per hand) | | Loading (µg/cm$^2$)[c] |
|---|---|---|---|---|---|---|
| | | | | Pounds[a] | µg[b] | |
| 1 | 5 | 500 µL Latex Paint | 120 ppm | 1.73E-7 | 78.2 | ~1.6 |
| 2 | 5 | | 600 ppm | 8.63E-7 | 391 | ~7.8 |
| 3 | 5 | 100 µL IPA | 0.786 mg BIT/mL IPA | -- | 78.5 | ~1.6 |
| 4 | 5 | | 3.9 mg BIT/mL IPA | -- | 390 | ~7.8 |

[a]AaiH (pounds) for paint = mg/kg BIT conc x µL solution x 1 kg/1E6 mg conversion x 1 L/1E6 µL conversion x 10.88 lb/gal paint density x 1 gal/3.785 L conversion

[b]AaiH (µg) for the IPA solution is based on the values reported in the protocol (V2:17). EPA estimate of AaiH is similar but differences in the IPA density used in the calculation may account for rounding differences (therefore, EPA's estimate is not provided for IPA). The paint estimates are based on EPA's calculations.

[c]Loading (µg/cm$^2$) = AaiH (mg) x (1000 µg/mg conversion) / (50 cm$^2$ palm surface area; EPA reviewer's estimate).

EPA intends to use the paint portion of the hand wash removal efficiency study results to correct for potential loses during the hand wash sampling to be conducted in the AEATF II's brush/roller painting exposure study (and the future airless paint sprayer exposure study if performed with BIT as the surrogate chemical). The AEATF II indicates that the IPA portion of the results *"…will better enable extrapolation of the paint data to other antimicrobial active ingredients."* (V2:11) This means that the IPA results can be used (1) in future exposure studies to correct for hand wash removal efficiencies where a non-paint liquid solution is used; and (2) to make comparisons of removal efficiency differences between paint versus liquids (non-paint).

EPA believes that the AEATF II hand wash removal efficiency study is well defined, and we expect that the resulting data will meet the needs of EPA and other regulatory agencies (e.g., hand wash removal efficiency data corrections).

**2. Sampling Design:** *"This study is being conducted to determine the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint containing BIT."* (V2:7) The study will also measure the removal efficiency of BIT from an isopropyl alcohol (IPA) solution.

*"The test substances in this study are latex paint containing two concentrations of 1,2-benzisothiazoline-3-one (BIT), CAS No. 2634-33-5, and IPA containing BIT at two concentrations. The BIT in IPA will be tested with concentrations of approximately 786 ug/ml and 3.9 mg/ml. The latex paint will be tested with BIT concentrations of approximately 120 ppm and 600 ppm (mg/kg). The EPA does not require registration of paint making no claim of surface protection; therefore no EPA registration number is available for the paint. The BIT is added commercially using registered products such as Mergal® BIT20 (EPA Reg. No 5383-121). … The paint test substance will be supplied in commercially available 1 gallon to 5 gallon paint cans, and is expected to have a BIT concentration of approximately 120 ppm as manufactured. Additional BIT in a minimal volume of dipropylene glycol will be added by the testing facility to achieve a higher BIT concentration of approximately 600 ppm. … All study participants will be adult subjects*

*capable of performing the functions described in the protocol. Subjects will be required to provide their signed Informed Consent using a form approved by an Institutional Review Board (IRB) prior to participation in the study. Twenty eight (28) qualified subjects will be recruited to participate in the study; twenty will participate in the study while eight will serve as alternates. Both the left hand and the right hand of each subject will be used during the study. The subjects will first wash their hands with liquid Ivory soap, rinse their hands with water and dry their hands with clean paper towels. The subjects will be seated around a table with their hands resting on a padded surface. Latex paint containing BIT will be applied to the palmar surfaces of each hand of 10 subjects at one of two concentrations (5 subjects each). A small volume of solvent (IPA) containing BIT will be applied to the palmar surfaces of each hand of 10 other subjects at one of two concentrations (5 subjects each). After forty-five (45) minutes the surface of the hands will be cleaned using the hand wipe and wash procedure. Hand exposure will be measured by scrubbing the hands with gauze sponges soaked with a solution of 50% isopropyl alcohol/50% distilled water until all dried paint is loosened or removed, then rinsing with the same solvent while the subject rubs fingers to their palm. The gauze pads will be added to the rinse solvent for extraction. The results from these subjects will allow accurate calculation of removal efficiency from the skin for BIT in IPA or latex paint, and correction of data from monitoring events (MEs) for this factor."* (V2:10)

*"Each subject will be placed into one of four groups. Subjects assigned to group one will have each hand fortified with a 500 ~L volume of paint containing approximately 120 ppm BIT. Subjects assigned to group two will have each hand fortified with a 500 uL volume of paint containing approximately 600 ppm BIT. Subjects assigned to group three will have each hand fortified with a 100 uL of a fortification solution of BIT targeted to be at a concentration of 786 ug/ml in isopropyl alcohol (IPA). Subjects assigned to group four will have each hand fortified with a 100 uL of a fortification solution of BIT targeted to be at a concentration of 3.9 mg/ml in isopropyl alcohol (IPA). Subject hands will thus be fortified at concentrations of approximately 78.5 ug per hand or 390 ug per hand.*

*The subjects will be seated during application and drying periods with their hands placed on a padded surface on a table. The appropriate volume of the assigned carrier and test substance will be aliquoted onto the palmar side of the hand using a positive displacement pipette and spread over the palmar surface with a glass capillary tube. The glass capillary tube will be placed into a glass test tube and retained for analysis. The paint or solution will be left on the hands to dry for 45 minutes. Each hand will then be washed by scrubbing with a gauze sponge soaked in 50% IPA/50% distilled water solution and rinsed with the same solution. The solution and gauze sponge will be collected as a single sample for each hand, extracted and analyzed."* (V2:17)

**3. Choice of Surrogate Material:** The test substance for this study is the formulated product, Sherwin-Williams latex paint, containing 1, 2-benzisothiazoline-3-one (BIT). This is the same substance that is being monitored in the brush/roller exposure study for which the results of the hand wash efficiency study will be used to correct loses of BIT during the hand exposure monitoring/sampling. In addition, the AEATF II plans to also

use IPA treated with BIT to determine the hand wash efficiency in a solvent other than paint. The CAS number for BIT is 2634-33-5. The *EPA registration for Mergal® BIT20 is 5383-121. BIT has been selected as the surrogate compound in the brush/roller exposure study because of "… its stability, abundance in the formulation, and sensitivity of its analytical method."* (Volume 2 of the separate Brush/Roller Protocol on page 17) The vapor pressure of BIT is 4.4E-7 mmHg at 20º C which is considered to be low.

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

Supporting details are in Attachment 2.

1. **Statistical design:** The sample size for this proposal is for 20 test subjects to be placed in 4 groups, 5 subjects per group, each subject will have their left and right hand sampled (see Table 1 above). The protocol does not mention a rationale for the sample size. There are no guidelines for the hand wash removal efficiency study. In fact, this is the first removal efficiency study being conducted for the Office of Pesticide Programs (OPP) since the Human Studies Rule in 2006. Brouwer et al (2000) reviewed the literature and reported the sample size for 10 different chemicals. Typically researchers conducting these types of studies used a sample size of 4 for each different hand loading tested. AEATF II proposes to use 5 test subjects per different loading and both the left and right hands per subject will be tested (n=10 per loading). As detailed in Subsection 2.1a of Attachment 2, the proposed sample sizes will give an estimated precision of within plus or minus 10% for the mean percentage removal efficiency for each of the four groups.

2. **Proposed pattern of human exposure:** The proposal is an experiment to measure the hand wash removal efficiency rather than to capture a specific pattern of exposure such as potential exposure from painting with a brush/roller. EPA is basing our assessment of the proposal based on the findings in the review of the literature by Brouwer et al (2000). Brouwer et al (2000) did not identify a standard approach for hand wash efficiency sampling. However, the authors did list two approaches they reviewed in the literature: (1) mass balance and (2) direct spiking. The mass balance approach is based on transferring residues from surfaces and the direct spiking approach is for exposure to liquids. The direct spiking approach is proposed in this protocol and is appropriate to support the proposed AEATF II study for monitoring exposure during painting with brush/rollers (in a separate study). The AEATF II's proposed study is assessed by EPA based on the various variables suggested by Brouwer et al (2000):

    - **Residence time** – Residence time is the duration of exposure of the test substance on the subject's hand prior to the wash procedure. Various citations are provided suggesting that the sampling efficiency over time is reduced for some compounds. This is *"of major importance"* for chemicals that are absorbed or adsorbed to the skin. The dermal absorption of BIT in rats is ~40% over 72 hours (MRID 46327901). The AEATF II's proposes to use a 45 minute residence time. The

painting study, for which this efficiency study is being conducted, anticipates the exposure time to be from 120 to 180 minutes (maximum of 3 to 4 hours). Subjects will be exposed throughout this anticipated sampling time; not all of the exposure occurs at time zero. Given the dermal absorption over time in this rat study of 1.7% after 4 hours, 3.2% after 8 hours, 19.1% after 24 hours, 35.3% after 48 hours, and 40.6% after 72 hours, the absorption at the proposed residence time of 45 minutes should not be too different than the absorption at the maximum of 4 hours anticipated in the painting exposure study. This would imply that the 45 minute residence time proposed would be sufficiently long to allow the paint to dry yet not be substantially affected by dermal absorption over the anticipated 2 to 3 hour exposure time in the painting study. Note: Absorbable material remained on the rat skin after washing; these values were as follows: 15.1% after 4 hours, 23.9% after 8 hours, 36.8% after 24 hours, 48.7% after 48 hours, and 47.6% after 72 hours. A substantial amount remained on the skin indicating a vigorous wash procedure is necessary and an efficiency study is warranted.

- **Skin loading (mass)** – *"…shows some, but not consistent, evidence for the assumption of decrease of removal efficiencies for low skin loadings."* While the total mass (µg) of a surrogate chemical reported in PHED for the paint brush scenario is greater than the AEATF II's proposed efficiency study, the two are not a good comparison because PHED is based on the entire hand and the efficiency study is based on only the palmer surface area only. A better comparison is the loading (µg/cm$^2$) of BIT and the loading observed in the PHED paint brush scenario (µg/cm$^2$); and the two are very similar. PHED reports a range of loadings from 4.8 to 19.7 with a mean of 10.5 µg/cm$^2$ compared to the hand loadings of 1.6 and 7.8 µg/cm$^2$ in this BIT proposal. The loading (µg/cm$^2$) in the BIT proposal is based on EPA's estimate (see Table 1) assuming a 50 cm$^2$ palm surface area (estimated by EPA as a palm surface area minus the 2 cm edge not proposed to be treated, and then rounded). The actual surface area to be fortified in the BIT proposal is not provided. If Brouwer's observation is correct (decreased removal efficiencies for low skin loadings), this would lead to a more conservative (protective) correction factor rather than less. This research will also provide some data to answer Brouwer's question of *"…no data are available to evaluate the influence on sampling performance for … similar surface area exposed for different mass of the contaminant, i.e., different amounts of contaminant per surface area contaminated (µg/cm$^2$)."*
- **Method of contamination and chemical/physical state** – The hand exposure in the painting study will be to the BIT-treated latex paint. The efficiency study is also using the same BIT-treated latex paint matrix, plus the IPA-treated solution. The actual method of contamination in the painting study results from splashes/drips/physical contact resulting in paint exposure to various parts of the hand. A controlled efficiency study is based on application of the test substance with a pipette and spread on palm with a glass tube. Although there are differences in the exposure/application, it is the nature of the studies.
- **Number of consecutive washes** – The same wash procedure used in this efficiency study will be used in the brush/roller exposure study (i.e., scrubbing

hand with gauze sponge with a follow-up 250 mL rinse while subject rubs their fingers to their palm).

- **Wash time** -- The same wash procedure used in this efficiency study will be used in the brush/roller exposure study. The wash time will be similar if the same procedures are followed. EPA recommends that the AEATF II video the procedure so that researchers in future studies can gauge and mimic this hand wash procedure.
- **Washing fashion/time and rinsing time** -- The same wash procedure used in this efficiency study will be used in the brush/roller exposure study (i.e., *"…scrubbing the hands with gauze sponges soaked with a solution of 50% isopropyl alcohol/50% distilled water until all dried paint is loosened or removed, then rinsing with the same solvent while the subject rubs their fingers to their palms. The gauze pads will be added to the rinse solvent for extraction."* (V2:10) ). The researchers will need to be sure they use the same vigor/pressure/time for this wash procedure in the paint brush/roller study as in this efficiency study.
- **Solvent rinsing** – The gauze sponges used for scrubbing the hand to loosen or remove the dry paint will be soaked with a 50/50 solution of IPA/distilled water and then the hand subsequently rinsed with 250 mL of the 50/50 IPA/distilled water.
- **Water/soap methods** – not applicable to the proposed procedure.
- **Water hardness** – the hand wash solution is a 50/50 solution of IPA/distilled water. Therefore, the water hardness is not applicable.
- **Pre-wash** – The test subjects will have their hands washed with Ivory liquid soap prior to being fortified with the test substance.

The EPA believes that the AEATF II hand wash efficiency study will be useful in correcting the potential losses during the sampling of test subject's hands in the painting exposure study.

3. **Endpoints and Measures:** The AEATF II proposes to measure the hand wash removal efficiency for BIT-treated paint and BIT-treated IPA solution.

   *"Air temperature and relative humidity of the room for the duration of the 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."* (V2:27)

4. **QA/QC Plan:** The study will be conducted under the FIFRA GLP Standards (40CFR160) (V2:8). The AEATF II QA/QC plan for the efficiency study is described in sufficient detail and is adequate to ensure that the measurements are accurate and reliable. The QA/QC plan includes: *"Sample matrix fortifications designed to assess the stability of the active ingredient under field, storage and transit conditions in or on the sampling materials (hand wipe/wash solutions containing gauze sponges) will take place on each day of the study. Field fortification solutions of BIT in latex paint or in solvent will be prepared at the appropriate concentrations."* (V2:27) *"Field*

*fortification samples will be fortified and will remain at ambient temperature for at least 1 hour before being placed into frozen storage. Samples will then be maintained in frozen storage until analyzed."* (V2:28)

5. **Statistical Analysis Plan:** The results of monitoring data will be provided in the final report. *"At the end of the study, a complete report will be prepared. The results of the study will include (1) the application amount of the test substance and BIT on the palm of the hand, (2) the amount of BIT found in the wipe solution samples and (3) the percent of BIT that can be removed from the surface of the skin. Residues of BIT found on the capillary tubes used during application will be subtracted from the amount applied to determine a corrected amount applied. Percent removal efficiency will be calculated as the amount of compound removed from the skin by the wipe/wash procedure, divided by the corrected total amount of compound applied to the skin times 100. Statistical procedures planned for use in this study include the calculation of means of replicate analyses and the standard deviations. Linear regression may be used in generation of calibration curves. All statistical techniques used will be fully described in the final report."* (V2:31-32)

## 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 (Although the protocol itself does not adequately justify the sample size used, EPA's calculations using the literature review by Brouwer et al (2000) provide that justification.)
- Fortification levels and number of samples for laboratory, field, and storage stability samples

Additionally, the AEATF II is conducting the study under the Good Laboratory Practices (GLPs).

**Recommendations:**

EPA recommends that the AEATF II video tapes the hand wash procedure so that it can be duplicated in future BIT studies.

## 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 the removal efficiency of the antimicrobial active ingredient BIT in latex paint and in isopropyl alcohol from human hands. The data produced by this study will allow the interpretation of results from a separate study measuring exposure of consumer painters who apply latex paint containing BIT. 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-eight adult subjects will be recruited from the Fresno, California area (20 initially assigned for monitoring plus eight 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.

   The inclusion/exclusion criteria are complete and appropriate except that "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 the latex paint or the risk irritation due to rubbing alcohol used on the hands; 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; alerting subjects to signs and symptoms of a skin reaction; medical professional on-site observing the subjects; and incorporation of procedures to keep the results of pregnancy testing private and to permit discrete withdrawal.

4. **Benefits:** This research offers no direct benefits to the subjects. The principal benefit of this research is to allow accurate interpretation of results from a separate study measuring exposure of individuals who apply latex paint containing BIT. This information 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 present at the meetings at which candidates are qualified and sign consent forms.

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

## F. Compliance with Applicable Ethical Standards

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

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

### EPA Ethics Comments

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

- 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…."*

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 Removal Efficiency Study protocol dated February 5, 2014
2. Summary Review of AEATF Removal Efficiency Study protocol 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 Hand Wash Removal Efficiency Protocol**

**Title:** **REMOVAL EFFICIENCY STUDY** (Volume II)

**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?

*"This study is being conducted to determine the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint containing BIT."* (V2:7) The study will also determine the removal efficiency for an IPA-BIT treated solution.

*"The test substances in this study are latex paint containing two concentrations of 1,2-benzisothiazoline-3-one (BIT), CAS No. 2634-33-5, and IPA containing BIT at two concentrations. The BIT in IPA will be tested with concentrations of approximately 786 ug/ml and 3.9 mg/ml. The latex paint will be tested with BIT concentrations of approximately 120 ppm and 600 ppm (mg/kg). The EPA does not require registration of paint making no claim of surface protection; therefore no EPA registration number is available for the paint. The BIT is added commercially using registered products such as Mergal® BIT20 (EPA Reg. No 5383-121). … The paint test substance will be supplied in commercially available 1 gallon to 5 gallon paint cans, and is expected to have a BIT concentration of approximately 120 ppm as manufactured. Additional BIT in a minimal volume of dipropylene glycol will be added by the testing facility to achieve a higher BIT concentration of approximately 600 ppm. … All study participants will be adult subjects capable of performing the functions described in the protocol. Subjects will be required to provide their signed Informed Consent using a form approved by an Institutional Review Board (IRB) prior to participation in the study. Twenty eight (28) qualified subjects will be recruited to participate in the study; twenty will participate in the study while eight will serve as alternates. Both the left hand and the right hand of each subject will be used during the study. The subjects will first wash their hands with liquid Ivory soap, rinse their hands with water and dry their hands with clean paper towels. The subjects will be seated around a table with their hands resting on a padded surface. Latex paint containing BIT will be applied to the palmar surfaces of each hand of 10 subjects at one of two concentrations (5 subjects each). A small volume of solvent (IPA) containing BIT will be applied to the palmar surfaces of each hand of 10 other subjects at one of two concentrations (5 subjects each). After forty-five (45) minutes the surface of the hands will be cleaned using the hand wipe and wash procedure. Hand exposure will be*

*measured by scrubbing the hands with gauze sponges soaked with a solution of 50% isopropyl alcohol/50% distilled water until all dried paint is loosened or removed, then rinsing with the same solvent while the subject rubs fingers to their palm. The gauze sponges will be added to the rinse solvent for extraction. The results from these subjects will allow accurate calculation of removal efficiency from the skin for BIT in IPA or latex paint, and correction of data from monitoring events (MEs) for this factor."* (V2:10)

*"Each subject will be placed into one of four groups. Subjects assigned to group one will have each hand fortified with a 500 ~L volume of paint containing approximately 120 ppm BIT. Subjects assigned to group two will have each hand fortified with a 500 uL volume of paint containing approximately 600 ppm BIT. Subjects assigned to group three will have each hand fortified with a 100 uL of a fortification solution of BIT targeted to be at a concentration of 786 ug/ml in isopropyl alcohol (IPA). Subjects assigned to group four will have each hand fortified with a 100 uL of a fortification solution of BIT targeted to be at a concentration of 3.9 mg/ml in isopropyl alcohol (IPA). Subject hands will thus be fortified at concentrations of approximately 78.5 ug per hand or 390 ug per hand.*

*The subjects will be seated during application and drying periods with their hands placed on a padded surface on a table. The appropriate volume of the assigned carrier and test substance will be aliquoted onto the palmar side of the hand using a positive displacement pipette and spread over the palmar surface with a glass capillary tube. The glass capillary tube will be placed into a glass test tube and retained for analysis. The paint or solution will be left on the hands to dry for 45 minutes. Each hand will then be washed by scrubbing with a gauze sponge soaked in 50% IPA/50% distilled water solution and rinsed with the same solution. The solution and gauze sponge will be collected as a single sample for each hand, extracted and analyzed."* (V2:17)

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

In a separate study, the AEATF II plans to conduct dermal exposure monitoring for test subjects using treated paint. The hand exposure in the AEATF II's other study on painting will use the same hand wash approach as proposed in this protocol's hand wash efficiency study. As noted in Brouwer et al (2000), "*when removal techniques are used to assess dermal exposure monitoring for risk assessment purposes, it is recommended to conduct sampling efficiency studies as a key issue for method performance."* 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 important variables in a hand wash efficiency study are discussed in Brouwer et al (2000) and described above in this review. The hand wash methodology proposed in this protocol is the same hand wash approach/procedure being proposed in the AEATF II's

painting exposure study. The hand wash procedures in the efficiency study need to be very similar, if not identical, to the hand wash procedures in the exposure study to be able to use the efficiency results to correct for loses (i.e., incomplete residue removal from subject's hands).

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

Random elements have been incorporated into the design as follows: *"The total number of qualified subjects will each be assigned a unique and consecutive number, starting at RE-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 28 numbers in the generated randomized list will determine the participating subjects, while the remaining subjects will be held as alternates, their order for potential entry into the study being determined by the randomization process. The 28 subjects for the groups will be split into four groups, each corresponding to one of the four test substance/concentration combinations. The first set of seven subjects will be placed into Group 1, the second set of seven subjects will be placed into Group 2, the third set of seven subjects will be placed into Group 3, and the fourth set of seven subjects will be placed into Group 4.*

*Within each group of seven, the first five subjects will be the primary subjects to have their hands treated per the scenario assignment. The last two subjects in the group of seven will be considered as alternates and will be on hand if any subject is unable, chooses not to participate, or chooses to stop before reaching the end. If the first five subjects complete the assignment, the alternates are paid and will not participate in that group. Alternates who do not participate will be placed back in the pool of subjects. If additional subjects above the 28 initially selected are required, randomized subject 29 will be contacted followed by randomized subject 30 and so on, until all assignments are completed for the study.*

*Once the subjects have been randomized into four groups, subjects from the first group will be scheduled into the study. No more than two groups will be monitored in one day. The randomization process will prevent bias."* (V2:19-20)

**(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?**

This protocol is a controlled exposure experiment (i.e., test subject's hands will be fortified with a BIT-treated substance by the researchers). The procedures that the researchers will use to fortify the subject's hands are described above.

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

The sampling design uses the palmar surfaces of the hands to measure hand wash removal efficiency. Fortifying the tops of the hands and the fingers will be excluded in the design.

**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 second test solution to be tested, BIT in an IPA solution, will provide hand wash efficiency results for future studies conducted with BIT. The IPA solution will also provide differences in hand wash efficiency between paint and IPA.

***"****The test substances for this study are the formulated product, Sherwin-Williams latex paint (referred to as SW latex paint in this protocol), containing 1, 2-benzisothiazoline-3-one (BIT) and BIT prepared in isopropyl alcohol (IPA). BIT is the active ingredient selected for measurement in the proposed paint applicator exposure studies, based on its stability, abundance in the formulation, and sensitivity of its analytical method. GLP purity analysis (content of active ingredient in each test substance concentration) will be performed by the testing facility prior to its use in the study."* (V2:14-15) 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?**

A rationale for the proposed sample size was not provided. There are no guidelines available to suggest a sample size. The sample size for this proposal is for 20 test subjects to be placed in 4 groups, 5 subjects per group (see Table 1 above). Brouwer et al (2000) reviewed the literature and reported the sample size for 10 different chemicals. Typically researchers used a sample size of 4 for each different hand loading tested. AEATF II proposes to use 5 subjects per different loading and both the left and right hand per subject (n=10 hands per loading). A statistical rationale for the proposed sample size based on data from Brouwer et al (2000) is provided in Subsection 2.1 (a) of Attachment 2.

**EPA Protocol Review: AEATF II Hand Wash Removal Efficiency Study Protocol**

**Title:** Removal Efficiency Study

**Date:** February 5, 2014

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**1. Societal Value of Proposed Research**

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

*"The primary objective of this study is to determine the removal efficiency of BIT in latex paint, and in isopropyl alcohol (IPA) from human hands."* (V2:9)

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

This proposed study will address the removal efficiency of the hand wash sampling procedure. In a separate study, the AEATF II plans to conduct dermal exposure monitoring for test subjects using treated paint. The hand exposure in the AEATF II's other study on painting will use the same hand wash approach as proposed in this protocol's hand wash efficiency study. The hand wash removal efficiency is important to know so that users of the exposure data can quantify the hand wash method's performance. As noted in Brouwer et al (2000), *"when removal techniques are used to assess dermal exposure monitoring for risk assessment purposes, it is recommended to conduct sampling efficiency studies as a key issue for method performance."* The proposed study will fill that data gap.

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

EPA will use these data to correct any loses measured for the hand wash procedure to be used in the AEATF II painting exposure studies. The IPA portion of this study can be used in future exposure studies using BIT as a test compound that use the identical hand wash procedure.

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

Although there are some hand wash removal efficiency studies in the literature and some conducted by pesticide registrants, none of the studies used BIT or a paint matrix. *"Data is not available from other studies to allow accurate estimation of the dermal removal efficiency of BIT using the study techniques."* (V2:11).

**(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 antimicrobial chemicals when performing painting activities. In-vitro models are unlikely to capture the variability of performing the wipe/wash procedure on human subjects, and will reduce the ability to extrapolate data from existing human hand removal efficiency studies. In this study, at least 20 subjects (5 for each scenario) will be monitored in order to capture the expected variation in skin differences, concentration, and paint or solvent as a carrier of the BIT."* (V2:11).

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

Yes. The purpose of monitoring test subject's hands to measure hand wash removal efficiency will allow the researchers to correct for loses of BIT residue from the hand wash methodology in the AEATF II paint exposure studies.

**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 determine the removal efficiency of BIT in latex paint, and in isopropyl alcohol (IPA) from human hands." (V2:9)*

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.

## 2.1 Statistical Design

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

A rationale for the sample size was not reported in the protocol. In the literature review by Brouwer et al (2000), sample sizes for various hand wash sampling studies using direct spiking of different compounds and different loadings ranged from 3 to 12. The corresponding standard deviations of the percentage removal efficiency ranged from 3 to 14 percent. To estimate the precision of the estimated mean percentage removal efficiencies, we can assume that the removal efficiencies for BIT in latex paint have similar distributions to the efficiencies for the compounds studied by Brouwer et al and that the measurements are independent, even though both hands of the same test subject are tested. On that basis the mean percentage removal efficiency at each concentration level can be estimated from the ten measurements with 95% confidence to be within plus or minus 2.1% using the lowest reported standard deviation, and to be within plus or minus 10.0% using the highest reported standard deviation. (These numbers were calculated assuming the efficiencies are approximately normally distributed. The 10.0% means that the unsigned error in the estimated mean percentage removal efficiency is no more than 10). If the study results indicate that the BIT removal efficiencies are the same at both BIT in latex paint concentration levels (120 and 600 ppm), so that the data can be combined, then the estimated precision improves to 1.4% and 6.6%, respectively. The same calculations apply to the BIT in IPA data. These statistical calculations suggest that the proposed study sample sizes should be adequate. However, if the proposed study finds much higher standard deviations than those summarized in Brouwer et al (2000) using different compounds and carriers, then additional hand wash removal efficiency testing may be necessary to obtain sufficiently accurate estimates of the mean hand wash removal efficiency.

### (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 RE-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 28 numbers in the generated randomized list will determine the participating subjects, while the remaining subjects will be held as alternates, their order for potential entry into the study being determined by the randomization process. The 28 subjects for the groups will be split into four groups, each corresponding to one of the four test substance/concentration combinations. The first set of seven subjects will be placed into Group 1, the second set of seven subjects will be placed into Group 2, the third set of seven subjects will be placed into Group 3, and the fourth set of seven subjects will be placed into Group 4. Within each group of seven, the first five subjects will be the primary subjects to have their hands treated per the scenario assignment. The last two subjects in the group of seven will be considered as alternates and will be on hand if any subject is unable, chooses not to participate, or chooses to stop before reaching the end. If the first five subjects complete the assignment, the alternates are paid and will not participate in that group. Alternates who do not participate will be placed back in the pool of subjects. If additional subjects above the 28 initially selected are required, randomized subject 29 will be contacted followed by randomized subject 30 and so on, until all assignments are completed for the study. Once the subjects have been randomized into four groups, subjects from the first group will be scheduled into the study. No more than two groups will be monitored in one day. The randomization process will prevent bias.* (V2:19-20)

**(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 the key parameters suggested by Brouwer et al (2000). Test subjects will be drawn from the same populations as the painting exposure study.

**(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. See response below for the analysis (Subsection (g)).

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

*"At the end of the study, a complete report will be prepared. The results of the study will include (1) the application amount of the test substance and BIT on the palm of the hand, (2) the amount of BIT found in the wipe solution samples and (3) the percent of BIT that can be removed from the surface of the skin. Residues of BIT found on the capillary tubes used during application will be subtracted from the amount applied to determine a corrected amount applied. Percent removal efficiency will be calculated as the amount of compound removed from the skin by the wipe/wash procedure, divided by the corrected total amount of compound applied to*

*the skin times 100. Statistical procedures planned for use in this study include the calculation of means of replicate analyses and the standard deviations. Linear regression may be used in generation of calibration curves. All statistical techniques used will be fully described in the final report."* (V2:31-32)

**(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?**

Since the proposed design is intended to develop estimates of the hand removal efficiency, rather than applying a statistical test, calculations of statistical power are not relevant for this study. See item (a) in this section for estimates of the precision of the estimated mean hand removal efficiencies.

**(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?**

Each test subject will be exposed to latex paint or an IPA solution treated with BIT.

*"Prior to applying a test substance to the hand and performing the hand wipe and wash, a standard procedure will be used to clean the hands. All subjects will wash their hands with liquid Ivory soap, rinse their hands with water and dry their hands using clean paper towels at least 5 minutes before the test substance application. The palmar surface of subject's hands will not come in contact with any surface between washing and completion of the monitoring event. Each subject will sit in the climate controlled room prior to the application and until the hand-wiping procedure is completed."* (V2:27)

*"The test substance will be applied to the palmar surfaces of each hand using a positive displacement micropipette. On each hand, either a 500 uL volume of the appropriate paint concentration or a 100 uL volume of the appropriate solvent concentration will be applied. A glass capillary tube will be used to spread the test substance across the center of the palmar surface, but test substance will not be spread closer than 2 cm from any edge of the palmar surface. The capillary tube from each subject will be placed into a glass test tube and stored frozen prior to analysis.*

*The subjects will be asked to sit quietly with their hands resting on a padded surface on a table for 45 minutes. A television or similar entertainment will be provided. Study personnel will continuously be present to monitor and respond to any subject requests. On-site medical personnel will be available to assist with any subject concerns.*

*After 45 minutes the subjects will hold their hands over a stainless steel bowl while researchers scrub the hands with a gauze sponge (J&J Mirasorb 4-ply each). The gauze sponge will be soaked with 50% IPA/50% distilled water and used for scrubbing until all dried paint is loosened or removed. The researchers will then rinse the hand with the same solvent by pouring the solvent over the hand and having the subject rub their fingers and palm together. The total volume of IPA/water solution used will be 250 mL. The used gauze sponge will be added to the hand wash solution collected in the stainless steel bowl and saved with the rinse solution for analysis. The procedure will then be repeated for the second hand producing a second sample. The subjects will be asked to again wash their hands with soap and water, and dry them with paper towels."* (V2:18-19)

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

The choice of the formulation types (i.e., latex paint and an IPA solution) is to determine hand wash efficiencies for future exposure studies using either paint or a non-paint liquid in the exposure scenarios. The addition of the IPA solution will also allow for a comparison between the efficiencies of paint and a non-paint liquid. BIT is the choice for the test substance to be able to use the results of this efficiency study for other studies using BIT as the chemical/surrogate.

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

Two concentrations are proposed, 120 and 600 ppm BIT. Based on these solution concentrations, it is estimated that the loading on the hands are 1.6 and 7.8 $\mu g/cm^2$ for treatment Groups 1/3 and 2/4, respectively. In comparison, the paint brush scenario in the Pesticide Handlers Exposure Database (PHED) indicates the loading on the subject's hands ranged from 4.8 to 19.7 $\mu g/cm^2$ with an arithmetic mean of 10.5 $\mu g/cm^2$. The proposed loadings are within the range of anticipated hand wash residue from the proposed brush/roller painting scenario.

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

The entire monitoring event is expected to be no more than 1.5 to 2 hours, of which, 45 minutes of exposure to the test substance is proposed. (V2:18-19)

## 2.3 Endpoints and Measures

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

The AEATF II proposes to measure the hand wash removal efficiency for BIT-treated paint and BIT-treated IPA solution.

*"Air temperature and relative humidity of the room for the duration of the 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."* (V2:27)

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

*"This study will be conducted in compliance with the US EPA FIFRA Good Laboratory Practice (GLP) Standards (40 CFR 160). The study will adhere to applicable SOPs of the Antimicrobial Exposure Assessment Task Force II (AEATF II)* … [20 SOPs listed]*."* (V2:8)

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

The study will be conducted according to FIFRA GLP Standards (40 CFR 160).

Field recoveries will be used to correct for any losses due to field, storage and transport. *"Sample matrix fortifications designed to assess the stability of the active ingredient under field, storage and transit conditions in or on the sampling materials (hand wipe/wash solutions containing gauze sponges) will take place on each day of the study. Field fortification solutions of BIT in latex paint or in solvent will be prepared at the appropriate concentrations, or aliquots of the study test substances may be used. Storage conditions of the solutions used for fortifications will be specified by the analytical laboratory and the actual storage details will be recorded in the study file."* (V2:27)

*"BIT in paint or solvent will be applied to hands using positive displacement micropipettes, which are sent out annually to the factory for calibration. The testing facility will verify the amount of test substance delivered by the micropipettes by weighing at least 5 aliquots to determine accuracy and precision of delivery. The Study Director will be informed of the verification results prior to use of the micropipettes with the subjects."* (V2:16)

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

The study report will include means and standard deviations of the replicate measurements of the hand wash recovery percentages in each group. It is

recommended that these data are also used to calculate 95% confidence intervals for the mean hand wash recovery percentage. In addition it is recommended that a t test is used to compare the mean hand wash recovery percentages for the two concentrations, and thus evaluate whether it is appropriate to combine all of the BIT in latex paint data or all of the BIT in solvent data to reduce the uncertainty in the mean hand wash recovery percentage.

## 3. Subject Selection

### 3.1 Representativeness of Sample

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

The population of concern is people who use latex paint that contains an antimicrobial ingredient.

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

"*Adult subjects will be recruited from the population of Fresno County, CA, and the surrounding area." (V2:20)*

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

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."* (V2:21)

Expected participants will self-identify in response to advertisements placed in local newspapers. The placement of advertisements in newspapers targeting different demographic groups should minimize bias and achieve diversity among respondents and subjects. While individuals who express interest in response to a newspaper advertisement about this study may differ in unknowable ways from other individuals who do not step forward, there is no reason to think that respondents in the Fresno, California 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 results of this hand wash efficiency study for BIT in paint or BIT in an IPA solution may be used in conjunction with exposure studies that employ the same hand wash procedures for exposures to BIT in paint or liquid solutions.

**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 "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 as verified by a government issued photo ID*
- *Consider their self to be in good health*
- *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*

*Exclusion Criteria*

- *Skin conditions on the surface of the hands (e.g., psoriasis, eczema, cuts or abrasions)*
- *Pregnancy, as shown by a urine pregnancy test*
- *Lactation*
- *Allergies* ***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)*
- *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."* (V2:23-24)

**(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. (V2:24)

**(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 V2:21-23.

**(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?**

*"After 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." (V2:25)*

**(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."* (V2:25)

**(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. (V2:25)

## 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 an unexpected result of pregnancy testing; and the potential for a break of confidentiality. (V2:49-50)

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

The dosing levels for the hands in this protocol are 1.6 and 7.8 µg BIT/$cm^2$ of hand surface area.

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.

Table 2 provides a comparison of the anticipated hand doses to the point of departure (POD) from the 90-day dermal rat study (LOAEL = 100 mg/kg/day). The dermal MOEs are based on the following equation: LOAEL 100 mg/kg/day / dose level mg/kg/day. The maximum dose (mg/kg/day) to the hands is 0.39 mg/hand x 2 hands x (1/80 kg BW) = 0.0098 mg/kg/day. The dermal MOE at the highest dose is 10,000 (i.e., LOAEL 100 mg/kg/day / 2 hand dose 0.0098 mg/kg/day). The MOE is the unitless ratio of the POD/dose where the target MOE is 1000. Based on this estimate, there is minimal dermal risk of concern.

**(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 risks have been evaluated by EPA through a comparison between the dermal LOAEL and the dermal dose. The comparison indicates minimal dermal risks. Please see part 4.1(c) (above) for details.

**(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?**

Skin reaction symptoms will be explained to subjects; and researchers will closely observe subjects for possible signs or symptoms of a reaction. Subjects with cuts or abrasions or other skin conditions on their hands, subjects with a history of allergies or sensitivities to materials similar to those in this study, and subjects in poor health will be excluded.

*"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. The Principal Investigator or on-site health professional will discuss the symptoms of skin reactions with the subjects prior to participation in the study. Subjects will be instructed to inform the Principal Investigator or research staff immediately if they feel ill, suffer a 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 research personnel 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 skin reaction during the study period, research staff will immediately request the on-site health professional to evaluate the skin reaction. If appropriate, 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 or on-site health professional will be contacted for further 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. Research staff will assist the subject in gently washing exposed skin with clean water and mild soap.*

*"If a monitoring event is terminated early due to medical reasons or the subject withdraws for any reason, samples from the subject will not be collected. Research staff will assist the subject in gently washing exposed skin with clean water and mild soap.*

*"Study personnel will be instructed to inform the Principal Investigator immediately of any skin reactions, 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 is treated for medical reasons, 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." (V2:25-27)*

Other protections include:

- Candidates with skin conditions on the surface of the hands (e.g., psoriasis, eczema, cuts or abrasions) are excluded (V2:24)
- Candidates known to be allergic to latex paint, soaps, or isopropyl alcohol are excluded (V2:24)
    - *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 (V2:24)
- The consent form alerts subjects to signs and symptoms of skin reactions and advises them to alert one of the researchers if they experience a reaction or any discomfort (V2:66)
- 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?**

"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." (V2:26)

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

SOP 11.C.2 for Emergency Procedures (V4:69-72)

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

*"Study personnel will be instructed to inform the Principal Investigator immediately of any skin reactions, 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 is treated for medical reasons, 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. (V2:26-27)*

**(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, Megan Boatwright, at Golden Pacific Laboratories (559 275-9091) as soon as possible."* (V2:50)

*"If two or more subjects develop an adverse skin reaction after they leave the study site, all subjects will be contacted by the Study Director to determine whether further medical management is appropriate." (V2:26)*

**(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, Megan Boatwright, at Golden Pacific Laboratories (559 275-9091) as soon as possible."* (V2:50)

**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. Society may benefit from continued ability to use antimicrobials that improve the quality of life. Measuring removal efficiency in this research study will produce reliable data about the dermal exposure of workers and the general population performing these tasks."* (V2:14)

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

*"The resulting data will improve the completeness and accuracy of the database used by the EPA to assess exposure to these chemicals. 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." (V2:14)*

**(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 the 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. (V2:24)

**(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."* (V2:23)

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.

**(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 label, paint MSDS, recruiting materials, and flyers).

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 Removal Efficiency 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." (V2:50)

**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."(V2:25)*

*"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. In the case of a positive test the subject will not participate in the study, but will be paid $100 for her inconvenience and will be free to go. A note indicating that the pregnancy test was performed in accordance with SOP AEATF II-11A.1 will be made in the raw data for each female subject."* (V2:18)

**(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."* (V2:50)

*"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."* (V2:51)

**(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. (V2:25)

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. (V2:51)

## § 26.1111 Criteria for IRB approval of research
## AEATF II Removal Efficiency Study AEA08: 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 Removal Efficiency Study AEA08: 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 Removal Efficiency Study AEA08: 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 Removal Efficiency Study AEA08: 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<br>• all research proposals reviewed by the IRB,<br>• scientific evaluations, if any, that accompanied the proposals reviewed by the IRB,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | Y<br>n/a<br>Y<br>n/a | V3:37-113<br><br>V3:184-191, conditionally approved |
| | | (2) Minutes of IRB meetings . . . in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution.+ | <br>N<br>Y<br>Y<br>n/a<br>Y | <br><br>V3:86-88<br>V3:134, Unanimous<br><br>V3:116-130 |
| | | (3) Records of continuing review activities. | n/a | None |
| | | (4) Copies of all correspondence between the IRB and the investigators. | Y | V3:5-140 |
| | | (5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations;<br>• any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant. | Y<br><br><br><br>N | V3:139-140 |
| | | (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 | V2:12-14, 49-50 |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | V2:11-12, 17-20, 25 |
| | | (3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue | Y | V2:14 |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | V2:14 |
| | | (5) The balance of risks and benefits of the proposed research. | Y | V2:14 |
| | | §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. V3:29-36<br>Approved: N//a |
| | | §1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used. | Y | V2:20-24, 71 |
| | | §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 | V2:74-75 |
| | | §1125(e): All correspondence between the IRB and the investigators or sponsors. | Y | V3:5-140 |
| | | §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 |