



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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

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MEMORANDUM

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

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We have reviewed the referenced protocol titled “A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer” (Airless Sprayer Study or AEA10) submitted by the Antimicrobial Exposure Assessment Task Force II (AEATF II) from both scientific and ethics perspectives. This protocol proposes to evaluate potential dermal and inhalation exposure to commercial painters during the application of paint containing an antimicrobial using an airless sprayer. Scientific aspects of the proposed research are assessed in terms of the recommendations of the EPA Guidelines Series 875 and of the EPA Human Studies Review Board. Ethical aspects of the

proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board.

A. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 6. All elements of required documentation are provided in the submitted protocol package and supplementary documentation of review by Schulman Institutional Review Board (IRB).

B. Summary Assessment of the Scenario Design

Supporting details are in Attachment 1.

1. **Scenario Design:** The EPA assesses potential occupational and residential (consumer) exposure from various antimicrobial products that are applied by a multitude of application techniques. Most antimicrobial products that are incorporated into latex paints are used as in-can material preservatives. In these instances, the paint is considered a treated article, and therefore, the paint can itself does not have a pesticide label (http://www.epa.gov/PR_Notices/pr2000-1.pdf). However, exposures to these types of treated articles are considered in the risk assessments conducted by EPA. In a previous AEATF II protocol, the task force proposed to monitor the brush/roller scenario. In this current AEATF II protocol, the task force proposes to monitor the airless sprayer scenario. The AEATF II defines the interior latex paint application with an airless sprayer scenario in this protocol as “*...the application by a professional painter of a formulated interior latex paint containing an antimicrobial chemical using a professional grade airless paint sprayer.*” (V1:14)¹ The AEATF II proposes to recruit professional painters as test subjects rather than from the consumer applicators. “*Although airless sprayers can be used by non-professional painters (consumers) as an alternative to using a brush and roller, it is not as common nor would a consumer cover as much surface area or use as much paint in a day as a professional painter. For these reasons, this study will be done with professional painters with a range of experience.*” (V1:14) The test subjects will have their dermal and inhalation exposure to the treated paint monitored while painting only. The tasks of clean-up will also be monitored except for activities requiring the use of water which might wash residues off of dosimeters, the hands, or the face/neck.

The AEATF II proposes to conduct a total of 18 monitoring events (MEs) assigned to 3 volumes of paint applied using 2 active ingredient concentrations (i.e., propiconazole) as illustrated in Table 1 below.

¹ 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 42” found at the bottom right-hand corner. Volume 2 page references are from the expression “Page n of 159” found at the bottom right-hand corner. Volume 3 page references are from the expression “Page n of 227” found at the bottom right-hand corner. Volume 4 page references are from the expression “Page n of 159” found at the bottom right-hand corner.

Table 1. Summary of Airless Sprayer Study Groupings and Monitoring Events.

	Volume of Paint Sprayed	Propiconazole Concentration	Amount of Propiconazole Handled	Number of MEs
Group 1	10 gallons	1,200 ppm	0.144 lb	3
		12,000 ppm	1.44 lb	3
Group 2	15 gallons	1,200 ppm	0.216 lb	3
		12,000 ppm	2.16 lb	3
Group 3	30 gallons	1,200 ppm	0.432 lb	3
		12,000 ppm	4.32 lb	3

The painting activity will include: “*Activities associated with and/or preceding spraying paint such as sprayer setup (positioning, hose and cord, spray gun setup, priming the spray line, stirring the paint, etc.) and paint preparation and staging (opening cans, portioning paint into buckets as needed) will be monitored in addition to spraying the paint. Masking and placement of drop cloths and tarps will not be monitored; these tasks will be done beforehand by study researchers. Spray painting will consist of painting walls, doors, door frames, built-in features such as shelves and closets, as well as ceilings. The test subjects will be experienced professional painters who will be told which rooms and surfaces to paint, but will not be instructed on how to paint. After spraying is completed, associated clean-up activities such as dealing with the remaining paint and cleaning and stowing the paint sprayer will be monitored, as these are typical work tasks for painters.*” (V1:22). Additional details on the paint sprayers (e.g., model numbers, nozzles, etc) are provided in the review below.

“*The study will be conducted indoors, in rooms constructed specifically for this study, at one geographical location. “Monitoring will be conducted using existing and/or purposefully built test rooms within a vacant commercial building to create a simulated work site. The simulated work site will mimic a typical home or office environment, with a mixture of large and small rooms, hallways, closets, storage shelves, and doorways. Fixtures such as ceiling fans, interior doors, and simulated windows will also be present. There will be sufficient rooms and surfaces so that sequential subjects will not paint the exact same rooms. The use of a controlled simulated work site allows for freedom from personal interferences with non-subjects, easier scheduling logistics, and eliminates the potential contamination from other sources of propiconazole. It also makes it easier to design monitoring events that focus only on paint application with an airless sprayer as opposed to the broad range of painting tasks a subject and his or her crew might engage in during the painting of an actual job site. Using vacant buildings/areas and simulated work sites also offers greater control of the scheduling of monitoring events. However, the repeated use of simulated work sites reduces exposure diversity that might come from painting different structures and with a range of sizes and layouts. For this reason, the test site will either consist of multiple rooms and hallways and surfaces so that different*

combinations of rooms and hallways will be used by different test subjects or several different buildings^s will be leased for the study.” (V2:30)

EPA intends to use these data developed by the AEATF II for the airless sprayer painting scenario to describe typical occupational and residential handlers’ daily exposure to antimicrobial formulated products used in paints. The data must be generic enough to be useful for estimating exposures using various types of sprayers, nozzles, etc as well as areas painted (e.g., ceilings, walls, rooms). EPA plans to use the data generated from the proposed airless sprayer painting study generically to estimate dermal and inhalation exposures, and ultimately risks, for other nonvolatile antimicrobial ingredients that are used in paints. Painting with brush/rollers has already been conducted in a separate study by the AEATF II and is thus outside of the scope of this effort.

EPA believes that the AEATF II airless sprayer paint scenario is well defined (some recommendations are provided below), and expects that the resulting data will meet the needs of regulatory agencies. The diversity of daily exposures under the airless sprayer scenario as defined in this proposal will adequately describe a typical to high-end commercial painter’s daily exposure to the antimicrobial application. The use of commercial painters as test subjects will potentially result in overall higher exposures than residential painters based on the amount of paint sprayed; but perhaps lower unit exposures because the commercial painters are more experienced. EPA’s regulatory approval process for paint includes assessment of commercial painters applying 50 gallons of paint with an airless sprayer and residential painters spraying 15 gallons of paint using an airless sprayer. Thus the risk driver for regulatory decisions is the higher risks from the commercial painter scenario who apply more paint per day and who paint more frequently than residential painters. The airless sprayer exposure data will be used by EPA to extrapolate to the likely exposure expected from future painting events of paint containing antimicrobial products.

2. **Sampling Design:** The AEATF II has described in detail their sampling design for the airless sprayer paint scenario and has incorporated random elements where feasible. The AEATF II proposes to monitor dermal and inhalation exposures using passive dosimetry techniques to measure exposure of human subjects during the painting of rooms using an airless sprayer. The proposed sample size is 18 monitoring events (MEs). The plan is to use 18 individual test subjects (different individuals) recruited from a population of commercial painters with a least 3 months of prior experience. The test subjects will be segregated into three groups delineated by the amount of paint to be sprayed. The volume of treated paint to be used by the three groups is 10, 15, and 30 gallons. The sample size is believed adequate to provide data to meet EPA’s 3-fold relative accuracy goal as per the AEATF II Governing Document (2011). Once the planned studies by the AEATF II have been completed, the adequacy of the sample sizes of completed studies will be revisited.

The study will be conducted indoors at one geographical location – Orlando, Florida. *“The test site will consist of one or more leased buildings which will have individual rooms, either existing or constructed specifically for this study, within the structure to provide 10,000 to 15,000 square feet of surface area for painting.” (V1:17) “The test site*

will mimic a typical home or office environment, with large and small rooms, hallways, closets, storage shelves, and doorways. Each test room will measure at a minimum 10 feet by 10 feet with an 8 to 9 foot ceiling height. Subjects will be instructed to paint horizontal and vertical surfaces as well as ceilings in specified rooms. Fixtures such as ceiling fans, interior doors, and simulated windows will also be installed. The purpose of conducting this study in vacant buildings/areas is to be free from interferences from non-subjects.” (V1:19)

The airless sprayer selected for the study is the Graco Ultra Max II 695 PC Pro. This airless sprayer “*...represents a typical professional grade airless paint sprayer, capable of delivering 0.95 gallons (water) per minute, and up to 3,300 psi (typical operating pressure is 2,000 psi). Since all airless sprayers basically operate the same way by atomizing fluid into small droplets, the differences in exposure are a function of the worker technique, spray pressure, nozzle type/size, and structure or surfaces being painted as opposed to the sprayer itself. As such, all subjects painting in the simulated work-site will use the same airless sprayer. The airless paint sprayer will be a mid- to high-grade professional equipment that is commonly used by mid-size commercial paint companies. The “most commonly used” designation was determined by AEATF II from conversations with paint store personnel, and the equipment is defined by capability and grade.*” (V1:19) “*A selection of five different nozzles based on recommendations from paint and paint equipment suppliers will be provided during the study: Graco Reverse-AClean-+ (RAC) IV with SwitchTips 415, 417, 517, 619, and 521 that have fan swaths ranging from 8 to 12 inches and tip orifices from 0.015” to 0.021”. This will allow the subjects to use the tip that they are most familiar with. New tips will be provided for each monitoring event and extras will be available should one clog. In addition to having a selection of nozzles to choose from, there will be three different tip extensions (10, 15, and 20 inches) available. The subjects will be allowed to select which they want to use, if any. The spray pressure will be adjusted by each subject and will be recorded along with their nozzle selection and whether they use a tip extension.”* (V2:32)

The airless sprayer paint test subjects will be recruited from the population of commercial painters based on the following: “*Surrogate painters will all be professional painters with at least 3 months of experience using airless sprayers for architectural painting (painting of residential, commercial, and/or industrial buildings) within the last 5 years. The type of training on the use of an airless sprayer such as from a trade school, journeyman program, or on-the-job will be recorded for each subject. Advertisements soliciting subjects will be posted in both English and Spanish local newspapers as well as on local radio stations. Additionally, postings will be placed in local retail and professional paint stores as allowed by store management.*” (V1:22)

The physical aspects of the painting scenario includes: “*Activities associated with and/or preceding spraying paint such as sprayer setup (positioning, hose and cord, spray gun setup, priming the spray line, stirring the paint, etc.) and paint preparation and staging (opening cans, portioning paint into buckets as needed) will be monitored in addition to spraying the paint. Masking and placement of drop cloths and tarps will not be monitored; these tasks will be done beforehand by study researchers. Spray painting will*

consist of painting walls, doors, door frames, built-in features such as shelves and closets, as well as ceilings. The test subjects will be experienced professional painters who will be told which rooms and surfaces to paint, but will not be instructed on how to paint. After spraying is completed, associated clean-up activities such as dealing with the remaining paint and cleaning and stowing the paint sprayer will be monitored, as these are typical work tasks for painters. However sprayer cleaning will only be included up to the point where water is introduced to the cleanup activities. Since water would likely remove residue from the subject's hands, the monitoring will terminate just prior to the point that the subject would normally rinse the spray line and nozzle with water."

(V1:22) EPA notes additional consideration of the logistics is needed for the "stowing" of the paint sprayer if the test subject is not going to clean it with water.

The design aspects that tend to either over- or under-predict exposure include:

- **Test subjects** – Test subjects will be recruited from commercial painters rather than residential populations. *"The one potential noteworthy source of underestimation is that the population being monitored will consist entirely of professional painters with at a minimum of 3 months of experience. The rationale for the selection of professional painters over consumers is two-fold: (1) it is not as common for consumers to use airless sprayers, and (2) consumers would paint less surface area. While these two rationales hold true, the data generated from this study will also be used to assess consumers who use airless sprayers; however, the antimicrobial regulatory approval process is based on the highest exposure scenario, which is commercial painters because of the higher amount of paint they handle in a day in comparison to consumers. As such, the subjects in this study will paint for a longer period of time and use higher volume spray equipment than what is typical for consumers which may tend to bias exposure to the higher end."* (V1:14)
- **Painting indoors** – *"...source of overestimation bias in the study design is the use of an indoor site. AEATF II believes that an indoor painting environment is likely to increase dermal exposure over an outdoor painting environment due to painting in restricted spaces which provides a significant source for overspray fallout, drips, and bounce-back. The AEATF II also believes that an indoor painting environment has a higher potential for inhalation exposure due to the limited space and restricted air movement compared to an outdoor painting environment."* (V1:14)
- **Reuse of rooms** -- *"...potential source of inherent overestimation bias in the study design...is the use of a simulated work site and the need to reuse the same test rooms for multiple subjects. The residue remaining from prior uses represents a potential source of contamination for subsequent users. This will be minimized by allowing adequate drying time to mitigate the possibility for cross contamination (ambient air-sampling and wall-wipe samples will be collected prior to re-use)."* (V1:14)
- **Cleaning the paint sprayer** -- *"However sprayer cleaning will only be included up to the point where water is introduced to the cleanup activities. Since water would likely remove residue from the subject's hands, the monitoring will*

terminate just prior to the point that the subject would normally rinse the spray line and nozzle with water.” (V1:22).

- **Hand wash removal efficiency** – The AEATF II intends to use the results of the hand wash removal efficiency study previously conducted using BIT for the brush/roller study as a surrogate for this airless sprayer study. Not correcting the hand wash samples would tend to underestimate exposures. The final determination in the use of the BIT study results as a surrogate to correct the hand sampling for loss of propiconazole during this study will be made after the study’s final report is submitted and subsequently reviewed by the EPA and the Human Studies Review Board (HSRB). The AEATF II has provided a rationale to bridge the BIT hand wash study to propiconazole (V1:36). The rationale includes several skin wash removal results from various dermal absorption studies and the water solubility of the two chemicals; BIT is slightly soluble in water at 1100 mg/L and propiconazole is less soluble in water at 100 mg/L (V1:41). Table 2 summarizes the average skin wash removal percentages. Although none of the existing data are an exact match to a hand wash sampling method, the overall data indicate that propiconazole will wash off of skin at least as well as BIT and that use of the skin wash removal data for BIT as a surrogate will not underestimate exposure to propiconazole. Therefore, EPA does not believe exposing human test subjects in a new study is warranted.

Table 2. Summary of Skin Wash Removal Percentages.

AI	Matrix	Loading ($\mu\text{g ai/cm}^2$)	Anticipated Airless Sprayer Hand Loading ($\mu\text{g/cm}^2$) ^d	Skin exposure time & Skin Wash Method	Avg Skin Wash Removal
BIT	Paint	0.44 to 1.5 (a)	6.6 to 200	45 minutes; 50/50 IPA/Water sponge	60-73% (human hands)
Propiconazole	Formulated Product	0.6 (b)		6 hrs; wash 5x mild soap (40 g/L) cotton swabs	73% (in-vivo rat)
		0.56 (b)		6 hrs; 50/50 ethanol/water rinse	73% (in-vitro human)
	Paint	10 (c)		10 hrs; 3% Ivory soap/water sponge, water/sponge, dry/sponge.	92% (in-vivo rat)

(a) AEATF II BIT hand wash removal study (brush/roller study).

(b) MRID 46250701.

(c) MRID 47736503.

(d) Anticipated hand loading from the airless sprayer study based on current PHED 0467 and Formella (1995).

Range of loading is the average unit exposure for the hand values (37,700 $\mu\text{g/lb ai}$), the hand surface area

of 820 cm², and the minimum and maximum pounds propiconazole to be handled in this proposed study (i.e., 0.144 and 4.32 lb ai from Table 1 above).

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

- “*The primary objective of this study is to use synthetic application-days called monitoring events (MEs) to monitor exposure to professional painters who apply paint containing antimicrobial pesticide products with airless spraying equipment.*” (V2: 17).
- “*Subjects will be randomly assigned into three groups, each group applying a different volume of paint. Within those groups half of the subjects will apply paint containing approximately 1,200 ppm propiconazole; the other half will apply paint containing approximately 12,000 ppm propiconazole.*” (V2:28).
- “*A total of 22 test subjects will be recruited for this study; 18 will be monitored while four will serve as extras in case a scheduled subject withdraws from the study or is terminated. Surrogate painters will all be professional painters with at least 3 months of experience using airless sprayers for architectural painting (painting of residential, commercial, and/or industrial buildings) within the last 5 years. The type of training on the use of an airless sprayer such as from a trade school, journeyman program, or on-the-job will be recorded for each subject. Advertisements soliciting subjects will be posted in both English and Spanish local newspapers as well as on local radio stations. Additionally, postings will be placed in local retail and professional paint stores as allowed by store management.*” (V1:22).
- “*The recruitment ads will run for at least one week; if it appears that less than 22 potential test subjects will be signed up for consent meetings by the end of the week, the ads will be extended and will continue until at least 22 prequalified people will have signed up for consent meetings.*” (V2:37). As discussed in V1:22 and V2:37, this procedure results in a random sample from those professional painters who see the advertisements and volunteer within the time period. This approximates a random sample from the population of future painting days for professional painters using airless sprayers.
- “*A total of 22 subjects will be recruited for this study. Each subject will be assigned a unique identification number called a subject ID which will start at AEA10-W01 and ending with AEA10-W22. The subject numbers will be assigned to each test subject by having them randomly draw an ID code number out of a bowl. The first 18 numbers (AEA10-W1 through AEA10-W18) identify the subjects who will be scheduled for monitoring, while the four remaining subjects (AEA10-W19 to 22) will be held as alternates. The alternate subjects will be on-call for the duration of the study. Alternates will get compensated even if they do not get monitored in the study. Each subject will be randomly assigned to one of the three spray volume groups based on the ME number that they pull out of a second bowl. ME numbers (1 through 18) will be written on individual pieces of paper, folded, and placed into a bowl. Subjects W1 through W18 will draw one number from the bowl to obtain*

his/her ME number. The Subject ID number and the associated ME number for each subject will be recorded in the raw data.” (V2:36)

- 3. Choice of Surrogate Material:** “*The test substance to be used in this study is the formulated paint, Sherwin-Williams SuperPaint® Interior Acrylic Latex Paint (Product Number A86W00151), containing propiconazole. The EPA does not require registration of paint containing propiconazole making no claims of antimicrobial activity; therefore no EPA registration number is available for the paint. Propiconazole was selected for use in this study based on its low mammalian toxicity, stability, presence as a preservative in paints at relatively high rates, and it not being a biocide used in clothing textiles or cleaning detergents. Wocosen® 500 SL which is a preservative containing propiconazole used during the manufacturing of materials will be added to each 5 gallon container of Sherwin-Williams paint before any test subject is monitored.*” (V2:25) This is a flat latex paint. According to the AEATF II, the paint is not expected to be diluted with water; however, if a subject feels the paint needs to be thinned in order to spray, he/she will do so and it will be documented by the observer. Wocosen 500 SL is EPA Reg. No. 43813-37 and the CAS number for propiconazole is 60207-90-1. The vapor pressure of propiconazole is 4.2E-7 mmHg at 25° C (MRID 41720301) which is considered to be low (not to result in substantial off gassing).

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

Supporting details are in Attachment 2.

- 1. Statistical design:** As in previous AEATF II studies, the AEATF II is employing a base case design (Governing Document, 2011) that was agreed upon with the US EPA at the initiation of this study program. The generation of a new, relevant, high quality “base set” of data will fill this data gap for airless sprayer painting which was identified by the EPA. It is anticipated in some cases that after the base case is collected no additional data collection will be necessary as the data will be sufficient to meet regulatory needs. In other situations, the task force, in consultation with regulatory agencies, may determine that additional data are required. At that point, more rigorous statistical methods outlined in the Governing Document may be applied.

The benchmark objective in the AEATF II exposure studies is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure is accurate to within 3-fold 95% of the time (i.e., 3-fold relative accuracy goal or “k=3”). “*If the benchmark accuracy goal (i.e., k=3) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional monitoring events might be considered.*” (V2:60)

- 2. Proposed pattern of human exposure:** The test substance will be applied by subjects according to typical painting practices.

“The subjects will be instructed to perform typical activities associated with and preceding paint spraying including, but not limited to, sprayer setup (positioning, hose and cord staging, spray gun setup, priming the spray line, stirring the paint, etc.), shaking and opening paint buckets, thinning the paint with water as needed, straining the paint to prevent clogging if needed, adjusting and testing the nozzle, portioning paint into other buckets as needed as well as spraying. The masking and placement of tarps will be done ahead of time by researchers.” (V2:33)

“Directions on how many containers of paint containing propiconazole should be used during the ME will be explained to the subjects. Which rooms and surfaces are to be painted will also be explained to the subject prior to starting the ME. Sprayed surfaces will include walls, shelves, doors, and ceilings. The opening of doors/windows and availability of floor fans or blowers to use and position as needed will be explained to test subjects. Beyond that, there will be no instructions.

The subjects will be allowed to handle the paint containers and airless sprayer as they normally do. How the subject opens, stirs, and attaches the containers of paint to the airless paint sprayer will be up to the individual test subject as will which nozzle is used, the spray pressure, and any peripheral equipment. The subjects will either use all of their allotted paint or will be asked to stop painting after 6 hours of monitoring.

After spraying is completed, additional associated clean-up activities include, but are not limited to, dealing with the remaining paint, immediate removal of masking tape and paper or plastic and/or folding of drop cloths as needed (if this is their normal practice), and cleaning and stowing the paint sprayer. These clean-up activities will be monitored, as they are typical work tasks for painters. However, sprayer cleaning will only be included up to the point where water is introduced to the cleanup activities. Since water would likely remove residue from the subject’s hands, the monitoring will terminate just prior to the point that the subject would normally rinse the spray line and nozzle with water.” (V2:33-34)

The duration of painting will be based on how long it takes each study participant to paint approximately 10, 15, or 30 gallons of paint. The painting time will be recorded. “In the 1995 Formella chlorothalonil study, it took, on average, about one hour to spray 5 gallons of paint. Based on this, it is anticipated that spraying in this study will take between 2 and 6 hours depending on the volume of paint being sprayed. In order to avoid saturation of the matrices and to ensure that there will be sufficient surface area to treat, the monitoring time will not be allowed to exceed 6 hours.” (V1:21) “Each subject monitored in the airless paint sprayer study will spray approximately 10, 15, or 30 gallons of paint. It is expected that the application of 10, 15, and 30 gallons of paint will take 2, 3 and 6 hours respectively. Based on painting 250 to 400 square feet per gallon of paint (industry standard), 30 gallons is expected to cover an area of 7,500 to 12,000 square feet.” (V1:21)

The EPA believes that the AEATF II airless sprayer paint study will represent the typical to high end commercial method of painting (Note: The painting with a brush/roller to represent the typical residential method of painting was previously conducted in a separate AEATF II study). The airless sprayer scenario will also be useful to estimate exposure to residential painters who also have access to airless sprayers. The selection of commercial subjects who handle more paint than consumers, test materials, amount of paint applied, airless sprayer and an assortment of spray nozzles to be selected by the subjects, indoor rooms with ceilings, closets, window and door trim, and associated activities (e.g., cleanup, excluding use of water) as described in the protocol is justified. The subjects will be allowed to paint as they normally would do.

- 3. Endpoints and Measures:** The AEATF II proposes to measure dermal and inhalation exposures resulting from painting with an airless sprayer. Dermal and inhalation exposure will be measured using whole-body dosimeters (WBD) (inner and outer), a painter's hat, a cloth dosimeter underneath the painter's hat, face/neck wipes, hand wipe/washes, and personal air monitors (V2:50-53). For the WBD, EPA is most interested in the inner dosimeters to assess potential exposure. The outer dosimeters will add to the existing data base on the development of protection factors for single layer of clothing. The potential for foot exposure is minimal and the feet will not be monitored. The hand and face/neck wipe/wash is an appropriate method to determine exposure to the hands and face/neck. The personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). Both OVS tubes to collect total inhaled residues and Parallel Particle Impactors (PPIs) containing PVC filters will be used to trap and measure respirable residues (50% cut point of 4 microns). Flow rates will be approximately 2 L/min for each of the samplers. (V2:50)

“Air temperature and relative humidity of the work area for the duration of exposure monitoring will be documented with automated instrumentation logging and recording at intervals appropriate for the duration of the work period per SOP AEATF II-10C. Environmental monitoring equipment will be calibrated or standardized according to field facility SOPs. The type and location of any fans or blowers will be documented in the raw data along with whether doors to the outside and/or windows are open during painting. The dimensions and layout of the rooms being painted will be documented in the raw data.” (V2:49)

- 4. QA/QC Plan:** The study will be conducted under the FIFRA GLP Standards (40CFR160) (V2:63). The AEATF II QA/QC plan for the airless sprayer paint study is described in sufficient detail and is adequate to ensure that the measurements are accurate and reliable. The QA/QC plan includes field recovery analyses, storage stability studies, and break-through analyses of the air samplers.

Primary components of the field recovery analyses include (V2:53-60 and SOP AEATF II-8E): samples to be fortified at a minimum of four times during the study; three fortification levels per matrix (table V2:54) with the low level 3x to 10x the LOQ and high level based on expected levels, triplicate samples per fortification level, fortified

samples exposed to ambient conditions for the maximum duration of exposure, and WBD not covered during exposure duration. Field recovery samples will be fortified in the “field” and stored in the same way as the actual study samples, and will be analyzed concurrently with the actual exposure samples. Correction for loss in field recoveries will correct for all phases of potential losses.

5. **Statistical Analysis Plan:** The results of monitoring data will be provided in the final report. The AEATF II will not statistically analyze the monitoring data. The EPA proposed statistical model for these data is a simple linear regression model for the logarithm of the exposure with an intercept term and with a slope coefficient multiplied by the logarithm of the amount of active ingredient. There are three groups of six MEs at different paint volumes. The MEs in each group will have very similar volumes (approximately 10, 15, or 30 gallons, limited to 6 hours of monitoring). Three of the MEs in each group will have concentration levels of 1,200 ppm and the other three will have concentrations of 12,000 ppm. All three groups have the same intercept and slope. The main statistical model will assume a slope of one, which is mathematically equivalent to assuming that the normalized exposure, defined as the exposure per pound of active ingredient, has the same log-normal distribution for all 18 MEs. The fitted model will be used to estimate the arithmetic means, geometric means, and 95th percentiles of the normalized exposure for each group, together with bootstrap confidence intervals. The bootstrap confidence intervals will be used to assess the fold relative accuracy against a goal of 3-fold relative accuracy. We will also investigate alternative models where the three volume groups can have different intercepts and/or different variances or where the six volume/concentration groups can have different intercepts and/or different variances. If the linear models do not fit the data sufficiently well, then we will also consider other models such as quadratic models, log-log-logistic models, logistic models and quantile regression models. It will also be important to test the proportionality assumption against independence by fitting models where the slope is not assumed to be one; confidence intervals for the slope will be used to determine if the slope is significantly different from 1 (proportionality) or from 0 (independence). The statistical analysis plan also includes the development of summary tables of the data, and various graphs of the data including exposure plotted against the amount of active ingredient showing the fitted regression models and the different concentration groups, and Q-Q plots of the normalized exposures (to assess the lognormality assumption) and of the studentized residuals (to assess the model performance of the final model).

The proposed approach uses the active ingredient propiconazole for the airless sprayer study but intends to use the results from the hand wash removal efficiency study for BIT to adjust the hand wash/wipe and face/neck wipe residues for possible incomplete removal. The hand wash removal efficiency study produced hand wash removal efficiency estimates of 73% at a BIT concentration of 0.44 µg/cm² and 60% at a BIT concentration of 1.5 µg/cm², giving an average of 66.8%. In addition to the main estimates for dermal exposure using the average 66.8% efficiency, EPA will also assess the effects of the uncertainty in the removal efficiency by recomputing the arithmetic means, geometric means, 95th percentiles, bootstrap confidence intervals, and slopes for dermal exposure using the alternative removal efficiency percentages of 60% and 73%.

This is a partial assessment since it does not account for possible differences between the removal efficiencies of BIT and propiconazole or for the variation in removal efficiencies between subjects.

D. Compliance with Applicable Scientific Standards

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

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

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

Recommendations:

The EPA provides the following recommendations and comments:

- The protocol does not explain how the sampling dates and rooms to be painted will be allocated to the test subjects. Once the building configuration and application dates have been determined, then these elements can be randomly assigned to the MEs. In particular, the differently sized and shaped rooms should be randomly allocated within each of the three groups (defined by gallons of paint) to avoid potential confounding between the gallons of paint used and the type of room painted.
- EPA notes additional consideration of the logistics during the cleanup routine is needed for the “stowing” of the airless paint sprayer if the test subject is not going to clean it with water (e.g., will the test subjects put away the dirty paint sprayer?).
- The AEATF-II is proposing to use the completed hand wash removal efficiency study conducted using BIT for the brush/roller study to allow EPA to correct for incomplete residue removal from the hand sampling from this study with propiconazole. The AEATF-II is currently completing the final report for the hand wash removal study conducted using BIT. Once the final report is submitted to the EPA, it will be reviewed concurrently with the brush/roller study and subsequently brought before the Human Studies Review Board (HSRB). The planned HSRB review date is early 2018. This airless sprayer protocol has provided a bridging rationale as to why the two chemicals (BIT and propiconazole) can be bridged for the hand wash removal efficiency study (V1:35-41).

- The study is designed to incorporate diversity and it captures many sources of variation in exposure from airless spraying (e.g., different nozzle types, different workers, different room sizes, different paint concentrations, different amounts of paint sprayed, etc.); however, not all plausible sources of exposure variation have been accounted for in the design (e.g., different types of paints, etc.). Therefore, the study captures a range of exposure conditions, but is not likely to cover the full range of variation that is expected to exist.
- The protocol should note that while paint is not expected to be diluted with water, if a subject feels it needs to be thinned in order to spray, he/she will do so and it will be documented by the observer.
- As indicated by the HSRB in the review of the AEATF II protocol for the brush/roller study, AEA07, (Parkin, 2014), the lack of justification and evidence for using only consumer (and in this case professionals) painters, does not detract from the data's scientific reliability but is a weakness when extrapolating exposure measurements to the other subpopulation (i.e., consumers or professionals).

E. Summary Assessment of Ethical Aspects of the Proposed Research

Here is a summary of EPA's observations about the ethical aspects of the proposed protocol, assuming that protocol is amended to address all of EPA's comments as outlined in Section F below. Supporting details are in Attachments 2-6.

- 1. Societal Value of Proposed Research:** The purpose of this study is to “*develop a baseline set of data to provide information for evaluating potential dermal and inhalation exposures of occupational workers who apply paints and coatings containing antimicrobials, with an airless sprayer.*” (V2:10) The data will be submitted to EPA to support registration and re-registration of antimicrobial pesticides. The existing data are not sufficient to answer the research questions. Some existing data reflect consumer, not occupational, exposure patterns, and some were collected using techniques that are no longer used. One existing data set lacks diversity in test subjects and amount of active ingredient handled. Additional dermal and inhalation exposure data are needed to accurately characterize the exposure potential of occupational use of airless sprayers. EPA will use this data in evaluating antimicrobial products applied using this method.
- 2. Subject Selection:** Twenty-two adult subjects will be recruited from the Orlando, Florida area (18 initially assigned for monitoring plus four alternates) through newspaper advertisements (paper and on-line), radio spots, and flyers posted in paint stores. The recruitment will be available in English and Spanish and posted concurrently for a week, or until a sufficient number of qualified candidates are scheduled for consent meetings. The recruitment efforts in two languages and using three different mediums furthers the goal of minimizing bias and achieving as much diversity as possible among respondents and subjects.

The recruitment materials will be targeted to the commercial and residential painting industry in and around Orlando. The study targets participants who are professional painters in commercial or residential settings with at least 3 months of experience using

an airless sprayer within the last 5 years. The rationale for restricting subjects to professional painters is that consumers/homeowners are not likely to use airless sprayers, and professional painters use a larger volume of paint and are more likely to have higher exposure. According to the protocol, the “*advertisements will contain a short description of the study and a toll-free number where interested respondents can leave a message either in English or Spanish. The messages will be automatically forwarded to the Study Director or designated recruiter, and/or bilingual recruiter.*” (V2:38) Callers responding to the newspaper advertisements will be screened in either in English or Spanish. If they meet the inclusion criteria, they will be scheduled for informed consent meetings and enrolled.

The inclusion/exclusion given in the study protocol are as follows:

Inclusion Criteria

- *Males or females between the ages of 18 and 65 years as verified by a government issued photo ID*
- *Self-identified as being in good health as defined as able to lift and move up to six 5-gallon buckets of latex paint; spray up to 30 gallons of paint using an airless sprayer while wearing a ~~NIOSH-approved~~ P95 filtering face piece respirator or half-face respirator and eye protection (goggles or safety glasses with side-shields)*
- *Willingness to sign the Informed Consent Form and the Subject Qualification Worksheet*
- *Speak and read English or Spanish*
- *Has a minimum of 3 months experience working as a professional painter using an airless sprayer to apply architectural paint (painting of residential, commercial, and/or industrial buildings) within the last 5 years*
- *Use a filtering face piece or half-face respirator while working as a professional painter and willing to bring and use the same type of respirator when participating in the study*

Exclusion Criteria

- *Skin conditions on the surface of the hands and face or neck (e.g., psoriasis, eczema, cuts or abrasions) as determined by a visual inspection*
- *Pregnant, as declared, or as shown by a urine pregnancy test*
- *Nursing/Lactating*
- *Allergies or sensitivities to chemical-based products particularly propiconazole, any triazole fungicide, isopropyl alcohol, and soaps*
- *Allergies or sensitivities to latex-based products particularly latex paint or latex gloves*
- *Unwilling or unable to participate in the study without gloves*
- *Is an employee or a spouse of an employee of any company represented by the AEATF, the contract research organizations conducting the study, Sherwin-Williams, or the American Chemistry Council (V2:19-20)*

With the EPA’s recommendations incorporated, the inclusion/exclusion criteria are complete and appropriate.

Pregnant or nursing women, as well as children, 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.

The protocol does not call for targeting recruitment to a vulnerable population, and contains adequate precautions to minimize any potential for coercion or undue influence. Recruitment materials and interactions with potential subjects will be conducted in English or Spanish, depending on subject preference. Subjects will be recruited through newspaper, radio, and flyers, rather than through employers, which will minimize the potential for coercion or undue influence. In addition, the compensation is not so high as to unduly influence participants, but represents fair remuneration in line with prevailing wages for professional painters for the subjects' time, travel, lost employment opportunity, and inconvenience.

3. **Risks to Subjects:** The proposed test material, propiconazole, is an EPA-registered antimicrobial pesticide active ingredient. It is registered as a fungicide in agriculture, for wood treatment, and as a materials preservative (biocide/antimicrobial pesticide). Paint containing propiconazole is sold commercially, and the maximum concentration permitted is 1.2%. In this study, the latex paint used would contain propiconazole at concentrations of either 1.2% w/w or 0.12% w/w, consistent with existing EPA approvals and its EPA-approved label.

Risks to subjects include the risks associated with exposure to the pesticide propiconazole, latex-based paints, and isopropyl alcohol; physical risks associated with painting activities; risk of heat illness; physical discomfort associated with wearing a personal air sampling pump; psychological risks associated with changing clothes in front of an unknown person and taking a pregnancy test; and the risk of unanticipated release of confidential information. All identified risks are characterized as of low probability.

The protocol proposes adequate precautions to mitigate the risks to subjects. The paint will contain propiconazole at concentrations at or below what is permitted under the EPA-approved label for the pesticide. Those who are allergic or sensitive to certain chemicals, latex or latex-based paints, isopropyl alcohol, as well as those who have skin conditions that could be exacerbated by exposure to any of these substances, are excluded from the study. Subjects will be wearing two layers of clothing, a hat, goggles/safety glasses, and a respirator to protect them from dermal, ocular, and inhalation exposure. EPA's recommendation to enroll only subjects accustomed to wearing respirators as part of their professional work should minimize the risks associated with respirator use.

Only subjects with experience using airless sprayers in a professional setting for a minimum of 3 months will be eligible to participate. In participating in the study, subjects will do many of the tasks they would normally do as part of their employment. It is not anticipated that participation in the study would expose them to more risks associated with painting than they would encounter on a daily basis at their job. Subjects will be

permitted to take rests as needed, and the study director will provide chairs and cold drinks.

Study staff will instruct subjects about the signs of heat stress and instruct them to stop painting if they begin to experience any symptoms. They will monitor conditions that could lead to heat stress and stop the monitoring event if the heat index reaches 95 degrees. The study is planned for winter in Florida, when temperatures should be reasonably low. Subjects will have access to fans and blowers, and will be permitted to open outside doors and windows as necessary.

The protocol proposes to minimize psychological risks by ensuring that the donning and doffing of the dosimeter and outer layer of clothing occur in a private area with a member of the study team who is the same gender as the subject. The pregnancy test instructions and verification will be conducted only by a female member of the study staff.

Information about subjects will be kept confidential by using numbers rather than names to identify subjects in study-related documents, keeping the key linking each subject's name and identifying number separate from other study records and in a locked cabinet, and removing any identifiable facial features from subjects in photographs used in study materials.

4. **Benefits:** This research offers no direct benefits to the subjects. The two benefits of this research are likely to be reliable data about the dermal and inhalation exposure of people applying latex paints containing antimicrobial products, and maintaining existing and adding new antimicrobial pesticides to protect products such as paints, stains, and adhesives from degradation.

According to the protocol, “*measuring exposure of workers in this research study will produce more reliable data about the potential dermal and inhalation exposure of painters applying paint containing an in-can preservative (antimicrobial pesticide) while using airless sprayers. The resulting data will improve the completeness and accuracy of the database used by industry and the EPA to assess exposure and risks to workers who are exposed to antimicrobial pesticides used in the preservation of paint and other in-can materials.*” (V2:24)

The study is likely to generate data that will support the new and ongoing registration of antimicrobial pesticides. The availability of these products will benefit society by “*improve[ing] the shelf life of products such as paints, stains, and adhesives by protecting products from degradation by microorganisms.*” (V2:24)

EPA recommends adding a discussion of the benefit to registrants, which is data that can be used to maintain existing antimicrobial pesticide registrations and to register new antimicrobial pesticides.

5. **Risk/Benefit Balance:** The study monitors activities that the subjects, professional painters, generally perform on a regular basis. It is unlikely that as a result of subjects’

participation in this research, they will experience additional risk beyond what they would ordinarily encounter when performing their jobs. With the recommendations of EPA incorporated, the risks to subjects have been thoughtfully and thoroughly minimized in the design of the research. The risks are reasonable in light of the likely benefits to society from new data supporting more accurate exposure assessments for antimicrobial products applied with airless sprayers.

6. **Independent Ethics Review:** The protocol, informed consent form, subject qualification form, and recruitment materials were reviewed and approved by the Schulman IRB in August 2017. This research may not be initiated until IRB approval is granted following EPA and HSRB review.
7. **Informed Consent:** Informed consent will be obtained from each prospective subject and appropriately documented in the language preferred by the subject. The ability to read and understand English or Spanish is a requirement for inclusion in the study.

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

At the consent meeting, potential subjects will be provided with two copies of the informed consent form and instructed to read it. After they have finished reading the form, a member of the study staff (plus a bilingual researcher if necessary) will review the consent materials. *“The experimental study and the inclusion and exclusion criteria will be described to each volunteer in detail, and potential subjects will be encouraged to ask questions or request clarification during the meeting and at any point during the study. The amount and form of compensation, the potential risks and discomforts, and treatment and compensation for injury will be fully explained.”* (V2:38-39) The potential subjects will be reminded that they are free to withdraw at any time without any penalty or loss of benefits to which they are entitled. Potential subjects will be permitted to take the form home to think about whether they want to participate. Once a qualified potential subject decides to participate, they must answer some questions about the study to ensure their comprehension of the consent materials, (V4:159), and then sign the consent form and the Subject Qualification Worksheet. Each subject will be assigned as a subject or alternate and given instructions about participation.

8. **Respect for Subjects:** The protocol includes measures to protect subjects' privacy, including identifying subjects by number rather than name; maintaining the record linking name and number separately from the other study-related records and in a locked cabinet; not including the subjects' faces in any photos used in study reports; and restricting access to records of the study to the study team, sponsor, EPA and the IRB. The protocol specifies that pregnancy testing will be conducted in a private location, the results will be verified by a female employee, and provision will be made for discrete disposal of the test. The process of dressing and undressing in the clothing required for

the study will be conducted in a private location with a member of the study team of the same gender as the subject.

The proposed compensation for subjects, \$20 for the consent meeting and \$200 for the study day, is adequate to compensate them for inconvenience, missed employment opportunity, and travel to and from the test location. It is in line with the average pay for a professional painter, and is not so high as to constitute undue inducement to participate or so low as to draw only economically disadvantaged participants.

Candidates and subjects will be informed that they are free to decline to participate or to withdraw at any time for any reason, without penalty, at multiple points in the recruitment, consent, and study processes.

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 2-6 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. This list of comments does not include all typographical and spelling edits, or minor suggestions about wording or language placement:

General comments

1. Clarify the time period that will elapse between monitoring events using the same rooms. At some points, monitoring events may be conducted every other day; at other points, the protocol calls for a 24 hour waiting period. It is unclear whether this period is measured from the start of each monitoring event, or from the end of one monitoring event to the initiation of a subsequent event. EPA suggests revising this discussion as follows (e.g., V2:13): “**No monitoring event will be initiated less than 48 hours after a previous monitoring event was initiated in the same rooms** ~~Rooms may be reused no more than every other day~~ to allow sufficient drying time between monitoring different subjects.” This would meet the intent of conducting monitoring events in the same room no more frequently than every other day.
2. Respirators:
 - a. A survey of professional painters showed that 6 out of 7 respondents wear respirators while using airless sprayers, but did not specify the type of respirator. (V1:32-33) Respirators must be fit tested to each user to ensure that is worn safely

- and fits properly. To protect subjects and to allow them to use the respirator they are familiar with, EPA suggests that the inclusion criteria be revised to enroll only those potential subjects who wear a filtering face piece respirator or half-face respirator as part of their routine work and who are willing to use the same respirator (or type of respirator) during the study, rather than having the research staff provide filtering face piece respirators to subjects.
- b. Remove “P95” and “N95” throughout; allow subjects to use the filtering face piece respirator or half-face respirator they would ordinarily wear when using an airless sprayer.
 - c. Replace “dust mask” with “filtering face piece respirator”.
 - d. Include a discussion of the risks of wearing a respirator, and how they will be mitigated.
3. Identify propiconazole as a pesticide (not surrogate chemical, chemical, etc.) throughout the protocol, consent form, and recruitment materials.
 4. Clarify whether the subjects will be using one color of paint (Sherwin Williams Extra White) or different colors to distinguish what has been painted during different monitoring events. The protocol discusses both.
 5. Clarify when and how alternates will receive compensation. The consent form seems to indicate that an alternate would only be compensated if he or she is called to the test site, but the protocol notes that alternates will be compensated even if they are not monitored (see V2:40). Include details about how alternates will be paid for their availability if they are not called in to the test site; subjects are being paid in cash at the test site at the end of the monitoring event.
 6. Provide booties to subjects to protect their shoes from splatter.
 7. EPA notes that the IRB approval includes the following: *“As a California site, you are required by California’s Health and Safety Code §24173 to provide the subject or subject’s conservator or guardian, or other representative, as specified in §24175, with a copy of the experimental subject’s bill of rights, prior to consenting to participate in any medical experiment. The copy must be signed and dated by the subject or the subject’s conservator or guardian, or other representative.”* (V2:158-159) The protocol calls for conducting the study in Orlando, Florida, not California. In addition, the proposed research is not a medical experiment. EPA recommends that the study sponsor clarify with Schulman IRB whether this provision applies to the proposed research.

Specific comments on the protocol

8. V2:15 – Revise the protocol to include more information on why subjects will not be wearing gloves, e.g., gloves absorb more active ingredient and give an overestimate of exposure compared to residue removal from bare hands?
9. V2:19 – Revise as follows: *“All protocol changes (amendments and deviations) must be reported to the IRB by email or through the Schulman web-site portal (eSubmission™). All amendments must be reviewed and approved by the IRB prior to implementation in the study, except for amendments deemed necessary to eliminate apparent immediate hazards to human subjects. Proposed changes (amendments) deemed necessary to eliminate apparent immediate hazards to the human subjects may be implemented without prior IRB approval; these must be reported to Schulman*

- IRB within 10 business days. All other amendments must be reviewed and approved by the IRB prior to implementation in the study. The protocol amendment procedure detailed in AEATF SOP 2C.3 will be followed. Approval of protocol amendments will be granted in accordance with the IRB policy and procedures, and may be granted by telephone provided it is also documented in writing (e.g., email). The final study report will contain a summary of all protocol changes and the associated documentation as specified in 40 CFR 26.1303. The IRB may provide expedited review of minor changes as defined by 40 CFR Part 26.1110 at its discretion.”*
10. V2:20 – Include a statement that a list of all of the chemical companies that make up the AEATF-II task force will be available during the consent process in the event any subject has a question related to employment.
 11. V2:20 – Revise as follows: “*The risk associated with exposure to the surrogate chemical pesticide propiconazole and latex-based paints*”
 12. V2:20 – Add to the risks to subjects section “*Risk of unanticipated release of confidential information*” and a corresponding description of how those risks will be mitigated.
 13. V2:22 – Revise as follows: “*As a study safety precaution all test subjects will be given eye protection (safety glasses with side-shields or goggles) and a NIOSH-approved P95 filtering face piece respirator to wear even though they are not a label requirement for the latex paint being used in the study. Subjects who wish to wear their own half face respirators instead of the provided dust mask will be allowed to do so will only be selected if they indicate that they already wear respiratory protection while using an airless sprayer as part of their job, and are willing to use the same respirator (or type of respirator) during their participation in the study.*”
 14. V2:24 – This study does not offer any benefits to subjects. Revise as follows: “*While there are no direct benefits to the subjects participating in this research study, beyond a nominal compensation for their time, there are indirect benefits to both the subjects and society.*”
 15. V2:24 – Add to the end of the “Benefits” section the following: “*Registrants of antimicrobials will benefit because the results of this research will provide EPA with data on exposure that may aid in maintaining existing antimicrobial pesticide registrations and in registering new antimicrobial pesticides.*”
 16. V2:24 – Under Section E, “Subject Privacy,” add to the protocol the steps that will be taken to maintain privacy.
 17. V2:38 – Revise as follows: “*Callers will be asked if they are between 18 and 64 years of age.*”
 18. V2:42 – Revise the protocol to require the Study Director to consult with the study’s on-site medical professional before making a determination of whether further medical management is appropriate.
 19. V2:43 – Clarify the purpose of the surface sampling, e.g., “*Duplicate wipe samples will be taken from one wall in each of three of the three rooms which that were painted in the preceding ME, and that are intended for exposure monitoring on that day to determine the potential for analytical interferences from the previous ME. Additional wipe samples may be taken at the request of Canada’s Pest Management Regulatory Agency. These samples would be collected using a weighted block and wet wipe, and used to evaluate potential exposure after a surface has been painted.*”

AEATF-II notified EPA that Canada's Pest Management Regulatory Agency has requested that the protocol include additional residue sampling of walls that have been painted to estimate exposure, but the details of the sampling have not been finalized. EPA's understanding is that the sampling will employ a weighted block dragged across a horizontal surface that has been painted, and wipes wetted with saline (no human subject exposure), and will follow an established protocol for collecting samples to measure residue transfer. EPA requests that the AEA10 protocol be amended to describe the agreed upon additional sampling and to reference any applicable protocols. EPA also requests to review the revised protocol before the study is initiated.

20. V2:44 – Revise as follows: “*Results of the pregnancy test will be kept in confidence; and they will be discussed only with the subject that provided the urine sample. A positive test result will not be recorded. The test results will not be disclosed to anyone other than the test subject, the verifying employee, and/or the Study Director. Opaque bags will be available where the pregnancy tests are taken to allow for discrete disposal.*”
21. V2:44 – Revise as follows: “*Care should will be taken to provide clothing of adequate fit by asking for subjects' clothing sizes on the Subject Qualification Worksheet.*”
22. V2:45 – Revise to reflect the subjects wearing their own respirators. “*Subjects will be given their choice of safety glasses with side-shields or goggles and a NIOSH-approved filtering face piece respirator (P95 rating) to wear. Subjects will be allowed to wear their own filtering face piece respirator or half-face respirator instead of the filtering face piece respirator if they prefer. Subjects that normally wear glasses will be given safety glasses designed to be worn over personal eyewear. At the subjects' request safety glasses will either be cleaned or changed and/or dust masks will be changed during the ME.*”
In addition, ensure that subjects are instructed to bring enough filtering face piece respirators or cartridges for half-face respirators based on the length of the sampling period, e.g., if the subject would ordinarily change out a filtering face piece respirator after about 2 hours and he or she is assigned to a 6 hour ME, he or she should bring 3 filtering face piece respirators.
23. V2:46 - Clarify this sentence: “*In the event a subject wants to take a break, he/she will remove his/her own PPE safety equipment and be given a drink with a straw to minimize transfer of hand residues to the drink container.*” Does this mean that the researcher will hold a drink with a straw for the subject to drink from, or the subject can hold his/her own drink but must use a straw?
24. V2:62 - Revise the protocol where appropriate to indicate that the final report will include the qualifications (e.g., credentials, experience) of the on-site medical professional.

Specific comments on the consent form

25. V2:110 – Replace “preservative” with “pesticide(s) used as preservatives” throughout the section “Purpose of this Study and Test Product”.
26. V2:110 – Revise as follows: “*Propiconazole is also registered as an antimicrobial pesticide commercial preservative to protect paints and stains from microbial*

- degradation.”*
27. V2:110 – Revise “Subject Selection” to include the criterion that a subject must wear his or her own respirator during the study. *“You must have experience using an airless paint sprayer for at least 3 months as part of your job, and you must have this experience using an airless sprayer within the last 5 years. You must wear a filtering face piece respirator or half-face respirator when using an airless sprayer as part of your job, and must be willing to use your own respirator during the study.”*
28. V2:111 – Revise as follows: *“The test will be supervised by a female researcher. You will take the test in a private bathroom. If the result is negative, you will need to show it to the female researcher so she can verify the result so you can participate. The results of your test will be kept confidential.”*
29. V2:112 – Revise the discussion of what will happen when the subject arrives at the test site as follows to provide more detail about the work clothing provided by the study team and the respirator requirement: *“After you arrive to the study site, the study staff will confirm that you have brought your own filtering face piece or half-face respirator to use during the study. You will change into new work clothing (long underwear, long sleeve shirt, pants, and painter’s hat) provided by the researchers. You will also get fitted with two small air-sampling pumps to sample the air you breathe and be given safety glasses or goggles. and a NIOSH approved P95 dust mask (or you can wear your own half face respirator).”*
30. V2:113 – Add an item explaining the subject’s responsibility to bring and wear his or her own respirator, e.g., *“The research team will verify that you have brought your own filtering face piece respirator or half-face respirator for use during the study. You are responsible for bringing the respirator you would wear in the course of your normal job duties when using an airless sprayer to apply latex paint. You cannot participate in the study if you are not wearing the respiratory protection you would ordinarily wear when using an airless sprayer to apply latex paint. If you have not brought your respirator, you will be asked to get your respirator and return to the study site, or to return for monitoring on another day.”*
31. V2:113 – Revise as follows: *“We will give you goggles or safety glasses with side-shields, and a painter’s hat, and a NIOSH approved particulate dust mask (N95 rating) such as the “3M Paint Odor Valved Respirator” to wear.”*
32. V2:114 – In item 11, clarify whether a subject will hold his/her own drink with a straw, or a researcher will hold the glass/bottle/can and let the subject drink from a straw.
33. V2:114 – Include information about how the subject’s contaminated respirator will be handled to minimize exposure to the subject.
34. V2:115 – In item #1, revise as follows: *“Risk of a reaction to the paint and/or pesticide being used as a chemical preservative being used in this study: At full strength the chemical preservative pesticide being used in this study can cause eye, skin, and respiratory irritation. However, the paint will contain diluted preservative pesticide which reduces the chance of you having a reaction to it.”*
35. V2:116 – Revise #6 as follows: *“Psychological stress related to pregnancy testing: In order to minimize the psychological stress, women will be given a private place to take the test, a female member of the study team will verify the test result, and the study director will ensure confidentiality of any test result. If you are female, You*

might be surprised to learn on the day of the research that you are pregnant. You do not have to share the results No one but you will know if the test shows that you're pregnant, and a positive result will not be recorded.”

36. V2:116 – Revise #7 as follows: “*Breach of Confidentiality: A potential risk of participation is unintentional release of confidential information. Researchers will take appropriate steps to protect any information they collect about you. However, there is a slight risk that information about you could be revealed inappropriately or accidentally.* There is potential for a breach of confidentiality because photographs and video will be taken while you are participating in the study. However, efforts will be taken to conceal your identity by not including your face or editing so that your facial features are not recognizable or deleted.”
37. V2:117 – Under “Benefits” delete the following sentence, because the study offers no benefits to subjects: “*This may indirectly benefit you and others who paint and use airless paint sprayers as part of their job.*”
38. V2:117 – Under “Costs and Payment” include specific information about how alternates will be selected and paid, whether or not they are called in to participate in a monitoring event.
39. V2:118 – Under “Right to Withdraw”, clarify this sentence: “*If you withdraw from the study after the exposure monitoring begins, you will still be paid for your time.*” It gives the impression that someone who is outfitted in work clothing and fit tested, and then decides to withdraw would not be compensated. The protocol notes that a female subject who shows up for pregnancy testing and then withdraws before monitoring begins will be compensated. Is the trigger for compensation being enrolled as a subject and showing up to the test site, or being an alternate whether or not the alternate participates in monitoring?

Specific Comments on the Subject Qualification Worksheet

40. V2:124 – Revise form to include questions about whether the potential subject wears a filtering face piece respirator or half-face respirator as part of his or her job when using an airless sprayer to paint, and whether they are willing to wear their own respirator while participating in the study.

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. EPA Scenario Review: AEATF II Airless Sprayer Painting Scenario Design dated July 21, 2017
2. EPA Protocol Review: “A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer” (AEA10) version dated July 21, 2017
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 Airless Sprayer Painting Scenario

Title: **AIRLESS SPRAYER SCENARIO: RATIONALE FOR STUDY DESIGN**

Date: July 21, 2017

Sponsor: American Chemistry Council
Antimicrobial Exposure Assessment Task Force II
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Washington, DC 20002

1. Scope of Scenario Design

(a) Is the scenario adequately defined?

"The primary purpose of the paint application with airless sprayer monitoring study is to develop more accurate information on potential worker exposures to antimicrobials in paints and coatings. These data will consist of dermal and inhalation exposure measurements derived from monitoring human test subjects under conditions constructed to broadly represent those expected under actual use conditions. For the paint application with airless sprayer scenario ... only a small number of expensive experimentally-obtained monitoring events are possible. Each ME represents the exposure possible for a single future handler-day. Although it is only a single work activity, paint application with an airless paint sprayer encompasses more handling conditions than any small number of MEs can practically include in a single study. For example, there are many possible active ingredients (ai), different types of paint or stain, different application equipment, multiple concentrations of active ingredient, different volumes of product, different workers and their associated behaviors, and multiple environmental and other handling conditions. All of these are expected to affect exposure to varying degrees. In view of this limitation, a practical goal for this study is that 18 MEs will be biased towards higher exposure elements and increased diversity of handling conditions. As a result, the diverse sample of MEs is expected to at least cover the middle and upper portions of the future exposure distribution, and capture the range of exposure variation that is expected to exist." (V1:13)

"For the purposes of the AEATF II Monitoring Program, the application with airless sprayer scenario is defined as the application by a professional painter of a formulated interior latex paint containing an antimicrobial chemical using a professional grade airless paint sprayer. This includes the task of painting for purposes of protection and beautification of architectural and other surfaces. The application of paint with an airless paint sprayer represents a common application method used by professional painters. Although airless sprayers can be used by non-professional painters (consumers) as an alternative to using a brush and roller, it is not as common nor would a consumer cover as much surface area or use as much paint in a day as a professional painter. For these

reasons, this study will be done with professional painters with a range of experience.” (V1:14)

“In this study, the preparatory work such as moving items, masking and placing plastic will be done ahead of time by someone who is not monitored. The subject will be allowed to do the standard tasks involved with getting the paint and sprayer ready for use. Subjects will be instructed to paint a mixture of horizontal surfaces (ceilings, shelves) and vertical surfaces (walls). Subjects will also be monitored during end of day cleanup, but only tasks that do not involve the use of water will be performed. The rationale is that the use of water could decrease exposure due to the washing of residues from the applicator’s hands.” (V1:15)

The AEATF II airless sprayer painting scenario design appropriately proposes to diversify the sampling characteristics by selecting different subjects for each monitoring event and allowing them to paint as they normally would do, selecting an indoor painting site (i.e., different size and shaped rooms and includes overhead painting on ceilings), conducting the study during multiple application dates, providing various nozzle types to be selected by the subjects, varying the amount of paint to be applied, as well as varying the active ingredient concentration in the paint. The test subjects will be drawn from the commercial painter population to represent painters who apply more paint than homeowners; and who will most likely be more experienced, especially in the use of airless sprayers.

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

“There are two studies that EPA is relying on in the EPA Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (November, 2016).

PHED Study 467. *This study contains 15 monitoring replicates, and each subject applied 5 gallons of stain to approximately 1,000 square feet using airless sprayer equipment. Eight different individuals were monitored at three sites to generate the 15 monitoring events. This study was conducted with the subjects wearing shorts, short-sleeved shirts, and no gloves to simulate a residential painting scenario. Dermal exposure was measured using gauze patches on the inside and outside of the clothing. Hand exposure was measured using cotton gloves that were worn over latex gloves. Inhalation exposure was measured using personal air-sampling pumps connected to cassettes containing polyurethane foam filters.*

MRID 43600102 (Formella, 1995). *Four professional painters were monitored while applying paint using airless spray equipment. Each subject was monitored three times for each of three different types of paint (exterior - latex; interior - latex; interior - alkyd) for a total of 36 monitoring events. Each monitoring event ranged from 22 to 88 minutes and each subject sprayed approximately 5 gallons of paint (approximately 0.5 lb chlorothalonil). Three commercial-grade Graco airless sprayers were used in this study; two Model GM 3500 were gasoline powered and were used to paint the exterior. A Graco Model EM 390 which was electric powered was used for the interior painting. Spray pressures were around 2000 to 2500 psi. The sprayers belonged to the*

commercial painting company who participated in the study. For the outdoor paint, subjects spray painted the exterior, including under the eaves, of a commercial building. In some cases, workers got up on ladders to spray the eaves. For indoor monitoring, workers spray painted offices and hallways of the same commercial building. Dermal exposure was measured using whole-body dosimeters worn under a long-sleeved shirt, long pants. Face/neck exposure was extrapolated from two gauze patches that were stapled to a baseball cap. Protected and unprotected hand exposure was measured using inner thin cotton gloves and outer canvas work gloves. Inhalation exposure was measured using personal air-sampling pumps connected to a cassette with a glass fiber filter followed by a sorbent tube containing Chromosorb 102. Workers wore 3M paint respirators and goggles (which were later removed due to paint getting on the lenses).

Evaluation of Existing Data. Both studies have limitations that reduce their value for an antimicrobial-oriented generic database. The first study (PHED 467) was done using clothing reflective of homeowners, not occupational workers. Additionally, the amount of stain (5 gallons) and surface areas (1,000 ft²) treated are not representative of typical occupational use. The other issue is with the dermal sampling dosimeters, which consisted of cotton gloves and patches; these are not used anymore due to the lack of accuracy associated with them. For these reasons, the dermal data from the PHED study are not considered to be acceptable to the AEATF although the air-sampling data could be reflective of occupational work and could be combined with newer data.

The Formella (1995) study does appear to reflect occupational work practices and was conducted using contemporary sampling methodology. However, there are some limitations to consider, mainly that a constant amount of paint was used (5 gallons) and only four different workers were monitored. Additional exposure data from other subjects applying paint with different equipment to other structures will improve the confidence in the data set.” (V1:15-16)

Compared to the proposed study, the PHED 467 study and the Formella (1995) study were performed by different researchers in different locations and time periods using similar but not identical study protocols and measurement methods. For these reasons a combined analysis of all three studies will likely lead to biased results because the underlying populations are different. Against this, the advantages of combining the studies include increased precision, due to higher sample sizes, and additional diversity in the monitoring events. EPA recommends the following approach once the new study is completed: First EPA will analyze the data from the proposed study as described in the statistical analysis plan under section C.5, including presentations of unit exposure arithmetic mean and 95th percentile estimates and confidence intervals. Those estimates will be tabulated together with summary values of the inhalation exposure from the PHED 467 study and of the dermal and inhalation exposure from the Formella (1995) study. If the goal of 3-fold relative accuracy is met, then a combined analysis is unnecessary. If that goal of 3-fold relative accuracy is not met, then instead of possibly carrying out a further study, a combined analysis of all three studies can be performed

to determine if the goal of 3-fold accuracy can be met using available data. The combined analysis would use the dermal and inhalation exposure data from the proposed study and the Formella (1995) study together with the inhalation exposure data from the PHED 467 study. To account for clustering effects due to within-study correlations, an appropriate statistical approach would be to add a random study effect term with three levels (one for each study) to each of the log-normal models so that the simple random sampling log-normal model is replaced by a mixed model.

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

2. Rationale for Scenario Sampling Design

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

The design choices in the airless sprayer paint scenario include: (1) using different commercial painters for each monitoring event; (2) selection of the type of spray nozzle by the subject from an assortment; (3) use of a painter's rag; (4) volume of paint; (5) active ingredient concentration; and (6) different indoor rooms. Additional descriptions of these key variables are provided:

Test Subjects. “*Subjects will be professional experienced painters who are available and consent to perform these tasks on the specified study dates. These are referred to as surrogate painters because they are not viewed as any sample from an existing population of painters. Rather they are viewed simply as another component of the synthetic ME that is being constructed to predict a single instance of a future day’s exposure to an arbitrary antimicrobial pesticide. Each surrogate painter provides his/her unique set of behaviors to the painting task. Use of the same painter for all monitoring events would over-represent a single type of behavior. As a result, diversification of painter behavior among MEs is accomplished by simply requiring that each ME be based on a different surrogate painter.*” (V1:22)

The one potential noteworthy source of underestimation is that the population being monitored will consist entirely of professional painters with at a minimum of 3 months of experience. The rationale for the selection of professional painters over consumers is two-fold: (1) it is not as common for consumers to use airless sprayers, and (2) consumers would paint less surface area. While these two rationales hold true, the data generated from this study will also be used to assess consumers who use airless sprayers; however, the antimicrobial regulatory approval process is based on the highest exposure scenario, which is commercial painters because of the higher amount of paint they handle in a day in comparison to consumers. As such, the subjects in this study will paint for a longer period of time and use higher volume spray equipment than what is typical for consumers which may tend to bias exposure to the higher end. The AEATF II does not foresee any other significant sources of

underestimation bias for exposure estimates derived from data resulting from the proposed scripted study. (V1:14)

Airless Sprayer & Nozzles. "Since all airless sprayers basically operate the same way by atomizing fluid into small droplets, the differences in exposure are a function of the worker technique, spray pressure, nozzle type/size, and structure or surfaces being painted as opposed to the sprayer itself. As such, all subjects painting in the simulated work-site will use the same airless sprayer. The airless paint sprayer will be a mid- to high-grade professional equipment that is commonly used by mid-size commercial paint companies. The "most commonly used" designation was determined by AEATF II from conversations with paint store personnel, and the equipment is defined by capability and grade. The Graco Ultra Max 695 PC Pro represents a typical professional grade airless paint sprayer, capable of delivering 0.95 gallons (water) per minute, and up to 3,300 psi (typical operating pressure is 2,000 psi). Subjects will also select the sprayer operating pressure that they would normally use. By allowing the test subjects to choose their spray tips and spray pressure, diversity in the spray application is achieved." (V1:19)

"A selection of five different nozzles based on recommendations from paint and paint equipment suppliers will be provided during the study: Graco Reverse-A-Clean (RAC) IV with SwitchTips 415, 417, 517, 619, and 521 that have fan swaths ranging from 8 to 12 inches and tip orifices from 0.015" to 0.021". This will allow the subjects to use the tip that they are most familiar with. New tips will be provided for each monitoring event and extras will be available should one clog. In addition to having a selection of nozzles to choose from, there will be three different tip extensions (10, 15, and 20 inches) available. The subjects will be allowed to select which they want to use, if any. The spray pressure will be adjusted by each subject and will be recorded along with their nozzle selection and whether they use a tip extension.

In order to ensure that subjects do not cross-contaminate their hands on the hose connected to the airless sprayer which will be reused each time, a new hose-cover will be placed on the hose prior to the start of each ME. An airless hose-cover or hose-guard is designed to protect the airless paint sprayer hose from paint and abrasion damage and using a hose guard can also reduce the clean-up time (Portland Compressor; GleemPaint.com). The main purpose of using a hose guard in this study is to minimize any potential cross-contamination between test subjects." (V2:32)

Painter's Rags. "As part of the painting task, painters will be allowed to use of dry "painter's rags." These rags are used to wipe excessive liquid paint drips and spills. AEATF II believes that the use of painter's rags represents standard practice for professional painters and is a practical necessity to deal with spills and large drips while painting." (V1:19-20)

Volume of Paint. “The actual amount of paint that a professional painter applies with an airless sprayer will vary from job to job, from day to day, and from person to person. Two key factors that influence the volume of paint sprayed in a day are the size of the company and the type of job. A survey of seven commercial painting companies was done to characterize painting companies and their work activities (Appendix B). Large companies have multiple people per crew, allowing one or more workers to be dedicated to using the airless sprayers while other workers do the preparatory work and move the paint buckets and sprayers. In cases of a large job where there is a large amount of surface area to be painted (i.e. commercial buildings or multiple family housing units), 40 to 50 gallons of paint could be sprayed by one worker in a work day if he is part of a large crew. Since 50 gallons of paint would require 12,500 to 20,000 ft² of paintable surface area (250-400 ft²/gallon), 50 gallons would rarely be sprayed by a single worker in one day. For comparison, the average house size in the US in 2014 was 2,690 square feet (US Census). [EPA notes that the total interior paintable area of walls and ceiling of this house is 8,900 ft². This is based on 8 foot ceilings which yields an interior volume of 21,520 ft³. Using the wall loading ratio of 0.29 ft²/ft³ from the Wall Paint Exposure Model (WPEM), the wall area of this house would be 6240 ft². Addition of the ceiling (2690 ft²) yields the total paintable area of 8930 ft².] According to the survey, 20 to 30 gallons per day is more typical when considering the range jobs done by small, medium, and large paint companies. Likewise the type of job, commercial or residential, the size of the job, interior or exterior, will determine whether someone will use an airless sprayer for the entire day or not.”

The amount of paint sprayed by an ME will be allocated to each test subject in terms of gallons to be applied. This will allow each person to spray the paint at his/her own speed, and the amount of time it takes to spray the prescribed volume of paint will be recorded.

Three discrete volumes of paint will be sprayed in the study: 10, 15, and 30 gallons, with 6 MEs assigned per volume. According to interviews with the seven commercial painting companies, on average a painter will spray 28 gallons per day, with a range from 12 to 50 gallons; the 90th percentile was 41 gallons per day (Appendix B).” (V1:20)

EPA notes that 50 gallons of paint sprayed per day is used in its assessment of commercial painters applying paint by an airless sprayer treated with an in-can paint preservative.

Active Ingredient Concentration. “All MEs in the study will use the same active ingredient, propiconazole, at one of two concentrations using pre-formulated latex paint. Propiconazole will be added to store-bought Sherwin-Williams paint (same brand of paint used in the brush and roller study) to achieve target propiconazole concentrations of approximately 1,200 ppm (0.12% w/w) and 12,000 ppm (1.2% w/w). The paint concentrations are expected to be sufficient to allow good method

sensitivity, but include an adequate safety margin to ensure propiconazole exposure does not exceed safe levels established by EPA.” (V1:20)

Indoor Site. “AEATF II believes that an indoor painting environment is likely to increase dermal exposure over an outdoor painting environment due to painting in restricted spaces which provides a significant source for overspray fallout, drips, and bounce-back. The AEATF II also believes that an indoor painting environment has a higher potential for inhalation exposure due to the limited space and restricted air movement compared to an outdoor painting environment.” (V1:14)

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

Random elements have been incorporated into the design as follows:

- “*The primary objective of this study is to use synthetic application-days called monitoring events (MEs) to monitor exposure to professional painters who apply paint containing antimicrobial pesticide products with airless spraying equipment.” (V2:17).*
- “*Subjects will be randomly assigned into three groups, each group applying a different volume of paint. Within those groups half of the subjects will apply paint containing approximately 1,200 ppm propiconazole; the other half will apply paint containing approximately 12,000 ppm propiconazole.” (V2:28).*
- “*A total of 22 test subjects will be recruited for this study; 18 will be monitored while four will serve as extras in case a scheduled subject withdraws from the study or is terminated. Surrogate painters will all be professional painters with at least 3 months of experience using airless sprayers for architectural painting (painting of residential, commercial, and/or industrial buildings) within the last 5 years. The type of training on the use of an airless sprayer such as from a trade school, journeyman program, or on-the-job will be recorded for each subject. Advertisements soliciting subjects will be posted in both English and Spanish local newspapers as well as on local radio stations. Additionally, postings will be placed in local retail and professional paint stores as allowed by store management.” (V1:22). “The recruitment ads will run for at least one week; if it appears that less than 22 potential test subjects will be signed up for consent meetings by the end of the week, the ads will be extended and will continue until at least 22 prequalified people will have signed up for consent meetings.” (V2:37). As discussed in V1:22 and V2:37, this procedure results in a random sample from those professional painters who see the advertisements and volunteer within the time period. This approximates a random sample from the population of future painting days for professional painters using airless sprayers.*
- “*A total of 22 subjects will be recruited for this study. Each subject will be assigned a unique identification number called a subject ID which will start at AEA10-W01 and ending with AEA10-W22. The subject numbers will be assigned to each test subject by having them randomly draw an ID code number out of a bowl. The first 18 numbers (AEA10-W1 through AEA10-W18)*

identify the subjects who will be scheduled for monitoring, while the four remaining subjects (AEA10-W19 to 22) will be held as alternates. The alternate subjects will be on-call for the duration of the study. Alternates will get compensated even if they do not get monitored in the study. Each subject will be randomly assigned to one of the three spray volume groups based on the ME number that they pull out of a second bowl. ME numbers (1 through 18) will be written on individual pieces of paper, folded, and placed into a bowl. Subjects W1 through W18 will draw one number from the bowl to obtain his/her ME number. The Subject ID number and the associated ME number for each subject will be recorded in the raw data” (V2:36).

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

The design says that diversity will be achieved by using multiple application dates, and different sets of rooms to be painted (as well as varying the concentrations of the active ingredient and the paint volumes): “*The ME construction approach used by the AEATF II achieves diversity by:*

- 1. Using multiple application dates*
- 2. Using a combination of different sized and shaped rooms (the same set of rooms will not be painted by every test subject)” (V1:16). The design does not explain how the dates and rooms will be allocated to the subjects. Once the building configuration and application dates have been determined, then these elements can be randomly assigned to the MEs. In particular, the differently sized and shaped rooms should be randomly allocated within each of the three groups (defined by gallons of paint) to avoid potential confounding between the gallons of paint used and the type of room painted.*

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

The test substance will be applied by subjects according to typical painting practices.

“Activities associated with and/or preceding spraying paint such as sprayer setup (positioning, hose and cord, spray gun setup, priming the spray line, stirring the paint, etc.) and paint preparation and staging (opening cans, portioning paint into buckets as needed) will be monitored in addition to spraying the paint. Masking and placement of drop cloths and tarps will not be monitored; these tasks will be done beforehand by study researchers. Spray painting will consist of painting walls, doors, door frames, built-in features such as shelves and closets, as well as ceilings. The test subjects will be experienced professional painters who will be told which rooms and surfaces to paint, but will not be instructed on how to paint. After spraying is completed, associated clean-up activities such as dealing with the remaining paint and cleaning and stowing the paint sprayer will be monitored, as these are typical work tasks for painters. However sprayer cleaning will only be included up to the point where water is introduced to the cleanup activities. Since water would likely remove residue from the subject’s hands, the monitoring will terminate just prior to the point that the subject would normally rinse the spray line and nozzle with water.” (V1:22)

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

The proposed study has purposely excluded using residential (consumer) test subjects. The AEATF II selected commercial painters over residential painters as test subjects because consumers use the airless sprayers less often than commercial painters and when they do they spray less area.

The AEATF II excluded the use of brush/roller in this study because they previously conducted a separate brush/roller study using consumer test subjects.

Painting indoors has been selected over painting outdoors. The rationale is that the indoor sites will provide overspray fallout, drips, and bounce-back from the airless sprayer and less air movement for a higher potential for inhalation exposure. The indoor sites would reasonably be expected to represent the high-end of exposure.

3. Is the proposed test material an appropriate surrogate?

The proposed test substance, latex paint treated with propiconazole, is an appropriate surrogate for the airless sprayer study. *“The paint that will be used in this study is commercially available Sherwin-Williams SuperPaint® Interior Acrylic Latex Paint in 5-gallon buckets. This is the same brand of paint used in the AEATF brush and roller study. The paint will be purchased from Sherwin-Williams and tested for propiconazole. Additional propiconazole (Wocosen® 500 SL, EPA Registration Number 43813-37) will be added to the paint to achieve target concentrations of 1,200 and 12,000 ppm. Samples from each bucket used will be assayed to confirm the propiconazole concentration in each container used in the study.”* (V1:17) *“The EPA does not require registration of paint containing propiconazole making no claims of antimicrobial activity; therefore no EPA registration number is available for the paint. Propiconazole was selected for use in this study based on its low mammalian toxicity, stability, presence as a preservative in paints at relatively high rates, and it not being a biocide used in clothing textiles or cleaning detergents.”* (V2:25) The vapor pressure for propiconazole is 4.2E-7 mmHg at 25° C (MRID 41720301) which is considered to be low (i.e., off-gassing expected to be minimal).

4. What is the rationale for the proposed sample size?

The benchmark objective in the AEATF II exposure studies is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure is accurate to within 3-fold 95% of the time (i.e., 3-fold relative accuracy goal or “k=3”). *“If the benchmark accuracy goal (i.e., k=3) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional monitoring events might be considered.”* (V2:60) See Attachment 2, sections 2.1(a) and 2.1(i), for a detailed statistical rationale applicable to this study.

EPA Protocol Review: AEATF II Airless Sprayer Painting Study Protocol (AEA10)

Title: A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer (Volume 2)

Date: Version 7/21/17

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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 use synthetic application-days called monitoring events (MEs) to monitor exposure to professional painters who apply paint containing antimicrobial pesticide products with airless spraying equipment." (V2:17)

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

EPA reevaluates existing uses of active ingredients, registers new uses for existing active ingredients, and registers new active ingredients, some of which involve the material preservation of paints. In the reevaluation of existing uses, EPA has recently called in many dermal and inhalation exposure studies involving application of treated paints. The dermal and inhalation exposure data generated from this study will be used by the EPA in assessing potential exposure and risks to users of antimicrobial products used to treat paint.

"The AEATF II monitoring program, as described in the Governing Document (2011), intends to develop a database of exposure monitoring data that can be used to support practical regulatory decisions about future exposures to antimicrobial active ingredients used in various products." (V2:11)

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

EPA will consider the dermal and inhalation exposure data from this study in assessing exposures of commercial and/or residential painters who apply latex paint containing an antimicrobial pesticide using an airless sprayer.

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

Due to the limitations of existing data, as discussed in Attachment 1 section 1(b) above, the research question cannot be answered with confidence relying solely on existing data.

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

"Human subjects are required in this study because they will normally conduct these activities when performing their routine job function. There are no acceptable methods or models that could be used to extrapolate exposure for this type of human activity." (V2:18).

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

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

2. Study Design

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

“The primary objective of this study is to use synthetic application-days called monitoring events (MEs) to monitor exposure to professional painters who apply paint containing antimicrobial pesticide products with airless spraying equipment.” (V2:17)

The benchmark objective in the AEATF II exposure studies is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time (i.e., 3-fold relative accuracy goal or “k=3”). *“If the benchmark accuracy goal (i.e., k=3) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional monitoring events might be considered.” (V2:60)*

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

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

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

2.1 Statistical Design

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

The benchmark objective in the AEATF II exposure studies is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time. A statistical rationale for the choice of sample size is presented in item 2.1(i) below. The proposed sample size and study design has six groups of 3 MEs each for different amounts of active ingredient. Based on the data from the Formella (1995) study, the proposed sample size and study design is estimated to meet the 3-fold relative accuracy goals.

“A total of 22 test subjects will be recruited for this study; 18 will be monitored while four will serve as extras in case a scheduled subject withdraws from the study or is terminated. Advertisements soliciting subjects will be posted in both English and Spanish local newspapers as well as on local radio stations. Additionally, postings will be placed in local retail and professional paint stores as allowed by store management. This process results in a simple random sample of qualifying subjects from the volunteer pool. Note, however, that this is not the same as a random sample from the existing population of professional painters. By definition, volunteers are self-selected and could have different characteristics than non-volunteers. Such distinctions have no relevance in this case, however. There is no particular need to obtain a random sample from the Orlando professional painter population. The MEs

are synthetic constructs that attempt to predict aspects of a future handler-day population. It is purposive by definition. Thus, a random sample of just one ME component (e.g. subject) from a subpopulation (e.g. Orange County, Florida) provides no statistical advantage. In fact, a random sample of subjects from the volunteer pool is not the only possibility. For example, a more diverse sample of surrogate painters from this pool could also be acceptable if a clear diversifying characteristic were available for all painters. Lacking this, the paint application with airless sprayer study uses the reasonable default option of a random sample from the volunteer pool.” (V1:22-23)

(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.

“A total of 22 subjects will be recruited for this study. Each subject will be assigned a unique identification number called a subject ID which will start at AEA10-W01 and ending with AEA10-W22. The subject numbers will be assigned to each test subject by having them randomly draw an ID code number out of a bowl. The first 18 numbers (AEA10-W1 through AEA10-W18) identify the subjects who will be scheduled for monitoring, while the four remaining subjects (AEA10-W19 to 22) will be held as alternates. The alternate subjects will be on-call for the duration of the study. Alternates will get compensated even if they do not get monitored in the study. Each subject will be randomly assigned to one of the three spray volume groups based on the ME number that they pull out of a second bowl. ME numbers (1 through 18) will be written on individual pieces of paper, folded, and placed into a bowl. Subjects W1 through W18 will draw one number from the bowl to obtain his/her ME number. The Subject ID number and the associated ME number for each subject will be recorded in the raw data.” (V2:36)

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

Yes, the proposed research includes developing unit exposures for the airless sprayer paint scenario and there is adequate justification for selecting test subjects from the commercial population only to provide the high-end of overall exposure. Note: Although there is the potential that a homeowner’s unit exposure may be higher

because of a lack of training and/or familiarity with an airless sprayer, the homeowner would not be expected to use the airless sprayer as often and would not spray as much paint as a commercial painter. There is a separate AEATF II residential brush/roller 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.

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

“The AEATF II will not statistically analyze the monitoring data in order to investigate the relationship between exposure and other factors (e.g., environmental conditions including temperature, humidity, air turnover rate, etc.) However, regulators and other users of the constructed database (BPHED) may choose to conduct such analyses...” (V2:60).

The EPA proposed statistical model for these data is a simple linear regression model for the logarithm of the exposure with an intercept term and with a slope coefficient multiplied by the logarithm of the amount of active ingredient. There are three groups of six MEs at different paint volumes. The MEs in each group will have very similar volumes (approximately 10, 15, or 30 gallons, limited to 6 hours of monitoring). Three of the MEs in each group will have concentration levels of 1,200 ppm and the other three will have concentrations of 12,000 ppm. All three groups have the same intercept and slope. The main statistical model will assume a slope of one, which is mathematically equivalent to assuming that the normalized exposure, defined as the exposure per pound of active ingredient, has the same log-normal distribution for all 18 MEs. The fitted model will be used to estimate the arithmetic means, geometric means, and 95th percentiles of the normalized exposure for each group, together with bootstrap confidence intervals. The bootstrap confidence intervals will be used to assess the fold relative accuracy against a goal of 3-fold relative accuracy. The EPA will also investigate alternative models where the three volume groups can have different intercepts and/or different variances or where the six volume/concentration groups can have different intercepts and/or different variances. If the linear models do not fit the data sufficiently well, then EPA will also consider other models such as quadratic models, log-log-logistic models, logistic models and quantile regression models. It will also be important to test the proportionality assumption against independence by fitting models where the slope is not assumed to be one; confidence intervals for the slope will be used to determine if the slope is significantly different from 1 (proportionality) or from 0 (independence). The statistical analysis plan also includes the development of summary tables of the data, and various graphs of the data including exposure plotted against the amount of active ingredient showing the fitted regression models and the different concentration groups, and Q-Q plots of the normalized exposures (to assess the lognormality assumption) and of the studentized residuals (to assess the model performance of the final model).

The proposed approach uses the active ingredient propiconazole for the airless sprayer study but intends to use the results from the hand wash removal efficiency study for BIT to adjust the hand wash/wipe and face/neck wipe residues for possible incomplete removal. The hand wash removal efficiency study produced hand wash removal efficiency estimates of 73% at a BIT concentration of $0.44 \mu\text{g}/\text{cm}^2$ and 60% at a BIT concentration of $1.5 \mu\text{g}/\text{cm}^2$, giving an average of 66.8%. In addition to the main estimates for dermal exposure using the average 66.8% efficiency, EPA will also assess the effects of the uncertainty in the removal efficiency by recomputing the arithmetic means, geometric means, 95th percentiles, bootstrap confidence intervals, and slopes for dermal exposure using the alternative removal efficiency percentages of 60% and 73%. This is a partial assessment since it does not account for possible differences between the removal efficiencies of BIT and propiconazole or for the variation in removal efficiencies between subjects.

"If the benchmark accuracy goal (i.e., k=3) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional monitoring events might be considered." (V2:60)

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

Yes.

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

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

The statistical power of the proposed study was estimated by treating the design as if it were a completely randomized design where the logarithm of the exposure equals the sum of an intercept, the slope multiplied by the logarithm of the amount of active ingredient, and a normally distributed error term. Under the proposed design, the amount of active ingredient is proportional to the product of the paint volume and a concentration of 1200, or 12000 ppm. The volume can be assumed to equal the nominal 10, 15, or 30 gallons for each group of MEs. The error variance is unknown but was estimated from the variance of the logarithms of the interior latex paint unit exposure data from the Formella (1995) study of dermal and inhalation exposures from the use of an airless sprayer. Since the Formella (1995) study measured four workers three times each, a random effects model with random effects terms for worker and random error was fitted to the natural logarithms of the unit exposures from the use of interior latex paint, and then the variance of the logarithms was estimated as the sum of the variance for workers and the variance of random errors. The estimated error variance for the proposed study was 0.0775 for total dermal exposure (mg/lb ai, without gloves) and

0.0581 for inhalation dose (mg/lb ai). In this calculation we are ignoring the variance attributable to the actual amount of active ingredient used and other design factors. The statistical power is the probability that complete independence (a log-log slope of zero) is rejected when there is complete proportionality (a log-log slope of one). EPA used a Monte Carlo simulation to demonstrate that if there are three MEs for each of the six amounts of active ingredient, then the statistical power for dermal or inhalation exposure was 100.0% using the Formella (1995) study variance, and remained at an estimated 100.0% even if the variance is five times larger than found in the Formella (1995) study.

EPA also used a similar Monte Carlo simulation to estimate the fold relative accuracy of the estimated arithmetic mean and 95th percentile unit exposure. Under the assumption of complete proportionality (a log-log slope of one) the fold relative accuracies for dermal exposure using the Formella (1995) study variance are 1.14 for the arithmetic mean and 1.22 for the 95th percentile. The fold relative accuracies are 1.38 and 1.58 if the variance is five times larger than found in the Formella study. The fold relative accuracies for inhalation exposure using the Formella (1995) study variance are 1.12 for the arithmetic mean and 1.19 for the 95th percentile. The fold relative accuracies are 1.32 and 1.49 if the variance is five times larger than found in the Formella study. This means that the arithmetic mean and 95th percentile can be estimated within a factor of 3 with 95% confidence.

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

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

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

2.2 How and to what will human subjects be exposed?

Each test subject will be exposed to latex paint treated with propiconazole while spraying indoors with an airless sprayer.

“The materials preservative Wocosen® 500 SL (EPA Registration Number 43813-37; nominal 50% propiconazole) which is sold by Janseen PMP for industrial and commercial use will be added to commercial Sherwin-Williams SuperPaint® latex interior paint by researchers to achieve target concentrations of approximately 1,200 ppm (0.12% w/w) and 12,000 ppm (1.2% w/w) propiconazole.” (V2:13)

“Subjects will be brought to the monitoring area containing airless paint sprayer, tools, PPE, and paint that they are expected to use. The subjects will be informed as to which rooms are to be painted, which room to start in, and what surfaces are to be painted. Subjects will be told that they can chose their nozzle and an extension wand if they want to use one, and once they are ready, they can start painting as they normally would do at a job site. The subject will be reminded of the label safety precautions, heat stress symptoms, and to let the observer know if he/she wants to take a break or use the restroom. They will also be told that there are floor fans and/or blowers available if they need to ventilate the room and to use them as they normally would. At this point the subjects will put on their safety equipment and hat, and the air sampling pumps will be turned on. The pump start time will be recorded and this will serve as the start time of monitoring.” (V2:45)

“In practice, workers involved in paint application typically also perform a multitude of tasks including preparatory work, masking, tarping, touch-up painting, and follow-up tasks such as final masking (applying protective barriers to non-target surfaces), staging of paint and spray painting equipment, end of day cleanup such as removing protective barriers from non-target surfaces, sprayer cleaning, etc. In this study, the preparatory work such as moving items, masking and placing plastic will be done ahead of time by someone who is not monitored. The subject will be allowed to do the standard tasks involved with getting the paint and sprayer ready for use; this will be monitored as well as painting with an airless sprayer and any clean-up tasks up to the point that water is introduced to the process, since water is likely to wash residues from the applicator’s hands. Since hand residues generally represent the major source of dermal exposure during a painting activity, AEATF II feels the more conservative approach is to not allow clean-up activities involving water.” (V2:12)

“The monitoring of the subjects painting with an airless sprayer will take place indoors in Orlando, Florida. The test site will be one or more buildings. The location will mimic the interior of a home and/or office space and will have, at a minimum, several rooms and hallways for painting. The paint application will be performed in a series of rooms inside the building, and subjects will be instructed to paint a mixture of horizontal surfaces (ceilings, shelves) and vertical surfaces (walls). Rooms may be reused no more than every other day to allow sufficient drying time between monitoring different subjects.” (V2:13)

“Each test room will measure at a minimum 10 feet by 10 feet with an 8 to 9 foot ceiling height; in addition a minimum of two hallways will be available. Each room will contain at a minimum finished drywall walls and ceiling, an entry door with paintable trim, a simulated window area with paintable trim, and baseboards. A minimum of two rooms will contain closets with at least one shelf that will be painted. In rooms that have ceiling exhaust fans, the fans will operate continuously during each ME. The test site will not have operating central heating or air conditioning during the monitoring. This will not negatively impact the study as it is standard during airless spraying of paint to turn off any air conditioning or heating units

to avoid drawing paint droplets into the HVAC system. As specified in the paint label, doors to the rooms will stay open while the subjects are painting, and, if needed, floor fans or blowers will be available to increase fresh air flow. The circumstances surrounding their use as well as air flow velocity, location of fans, and approximate distance between the test subject and the fans will be recorded. Doors and/or windows to the exterior of the building will be opened as needed to help improve ventilation. This will be recorded and photographs of the painting rooms will be maintained in the raw data. Rooms may be re-painted no more than every other day to allow sufficient drying time between MEs.” (V2:31)

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

The choice of the formulation type (i.e., latex paint) is to collect dermal and inhalation exposure data for painting using an airless sprayer while spraying a paint treated with an in-can preservative.

“The materials preservative Wocosen® 500 SL (EPA Registration Number 43813-37; nominal 50% propiconazole) which is sold by Janseen PMP for industrial and commercial use will be added to commercial Sherwin-Williams SuperPaint® latex interior paint by researchers to achieve target concentrations of approximately 1,200 ppm (0.12% w/w) and 12,000 ppm (1.2% w/w) propiconazole. These levels are expected to be sufficient to allow good method sensitivity and will provide a safety margin to ensure propiconazole exposure does not exceed EPA-established safe levels. The use of two different concentrations combined with a range in the amount of paint applied will ensure that a range of active ingredient is handled during the study.” (V2:13-14)

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

“The target volumes of paint to be sprayed by subjects in the study will be 10, 15, and 30 gallons which is estimated to take between 2 and 6 hours. This range was chosen as it represents the range of gallon of paint typically sprayed per day by a commercial painter (AEA10 Study Design Document, 2017).” (V2:14)

AEA10 Study Design Document, 2017, indicates the following:

“The actual amount of paint that a professional painter applies with an airless sprayer will vary from job to job, from day to day, and from person to person. Two key factors that influence the volume of paint sprayed in a day are the size of the company and the type of job. A survey of seven commercial painting companies was done to characterize painting companies and their work activities (Appendix B [EPA notes to see V1:30-34 for details on survey results]). Large companies have multiple people per crew, allowing one or more workers to be dedicated to using the airless sprayers while other workers do the preparatory work and move the paint buckets and sprayers. In cases of a large job where there is a large amount of surface area to be painted (i.e.,

commercial buildings or multiple family housing units), 40 to 50 gallons of paint could be sprayed by one worker in a work day if he is part of a large crew. Since 50 gallons of paint would require 12,500 to 20,000 ft² of paintable surface area (250-400 ft²/gallon), 50 gallons would rarely be sprayed by a single worker in one day. For comparison, the average house size in the US in 2014 was 2,690 square feet (US Census). According to the survey, 20 to 30 gallons per day is more typical when considering the range jobs done by small, medium, and large paint companies. Likewise the type of job, commercial or residential, the size of the job, interior or exterior, will determine whether someone will use an airless sprayer for the entire day or not.

Three discrete volumes of paint will be sprayed in the study: 10, 15, and 30 gallons, with 6 MEs assigned per volume. According to interviews with the seven commercial painting companies, on average a painter will spray 28 gallons per day, with a range from 12 to 50 gallons; the 90th percentile was 41 gallons per day (Appendix B). Companies with 4 employees or less typically spray 15 to 40 gallons of paint in a day. The larger the painting company, the more gallons that can be sprayed per day since the workers spraying the paint can focus on just spray painting while other employees are available to do the preparatory work and masking; additionally it is more likely that large companies will get larger jobs.

For this particular scenario the AEATF II is creating three monitoring groups to ensure diversity based on amount of active ingredient handled. With 6 MEs per group, this will result in a total of 18 MEs handling from 0.144 to 4.32 pounds of propiconazole (based on 12 pounds of SuperPaint® per gallon). The amount of active ingredient was calculated using the target propiconazole concentration in paint of 0.12% w/w and 1.2% w/w. The groups are defined in the following table.

	<i>Volume of Paint Sprayed</i>	<i>Propiconazole Concentration</i>	<i>Amount of Propiconazole Handled</i>	<i>Number of MEs</i>
<i>Group 1</i>	<i>10 gallons</i>	<i>1,200 ppm</i>	<i>0.144 lb</i>	<i>3</i>
		<i>12,000 ppm</i>	<i>1.44 lb</i>	<i>3</i>
<i>Group 2</i>	<i>15 gallons</i>	<i>1,200 ppm</i>	<i>0.216 lb</i>	<i>3</i>
		<i>12,000 ppm</i>	<i>2.16 lb</i>	<i>3</i>
<i>Group 3</i>	<i>30 gallons</i>	<i>1,200 ppm</i>	<i>0.432 lb</i>	<i>3</i>
		<i>12,000 ppm</i>	<i>4.32 lb</i>	<i>3</i>

Within these groups other characteristics will be varied to the extent feasible to provide for diversity in exposure. The purpose of creating these groups is to force diversity in the amount of active ingredient handled. The data from all three groups will be combined to generate a single unit exposure, one for dermal exposure and one for inhalation exposure.” (V1:20-21)

(c) What duration of exposure is proposed?

"Most respondents [from the AEATF II paint survey in Appendix B of Volume 1 of the AEA10 Study Design Document] indicated that they spend 4 to 6 hours a day spray painting; the largest company (13 employees) indicated that they will spend up to 10 hours a day spray painting. The average amount of time spent spray painting was 5.9 hours. When asked about clean up, most companies responded that they spend 20 to 40 minutes cleaning the spray equipment while the largest company indicated that unmasking the area can take 3 to 4 hours.

The exposure data generated from this study will be normalized by pounds of active ingredient handled, and can be extrapolated to the EPA daily default for airless spraying of 50 gallons per day for assessing occupational risks. In the 1995 Formella chlorothalonil study, it took, on average, about one hour to spray 5 gallons of paint. Based on this, it is anticipated that spraying in this study will take between 2 and 6 hours depending on the volume of paint being sprayed. In order to avoid saturation of the matrices and to ensure that there will be sufficient surface area to treat, the monitoring time will not be allowed to exceed 6 hours." (V1:21)

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 dermal and inhalation exposures resulting from painting with an airless sprayer. Dermal and inhalation exposure will be measured using whole-body dosimeters (WBD) (inner and outer), a painter's hat, a cloth dosimeter underneath the painter's hat, face/neck wipes, hand wipe/washes, and personal air monitors (V2:50-53). For the WBD, the Agencies are most interested in the inner dosimeters to assess potential exposure. The outer dosimeters will add to the existing database on the development of protection factors for a single layer of clothing. The potential for foot exposure is minimal and the feet will not be monitored. The hand and face/neck wipe/wash is an appropriate method to determine exposure to the hands and face/neck. The painter's hat and the cloth dosimeter underneath the painter's hat are appropriate methods to determine exposure to the head. The personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). Both OVS tubes to collect total inhaled residues and Parallel Particle Impactor (PPI) containing PVC filters will be used to trap and measure respirable residues. Flow rates will be approximately 2 L/min for each of the samplers. (V2:50)

"Air temperature and relative humidity of the work area for the duration of exposure monitoring will be documented with automated instrumentation logging and recording at intervals appropriate for the duration of the work period per SOP AEATF II-10C. Environmental monitoring equipment will be calibrated or standardized according to field facility SOPs. The type and location of any fans or blowers will be documented in the raw data along with whether doors to the outside and/or windows are open during

painting. The dimensions and layout of the rooms being painted will be documented in the raw data." (V2:49)

*"After the addition of the colorant and a minimum of 5 minutes on a mechanical shaker, triplicate samples of approximately 20 ml will be collected from each lot of paint before any propiconazole is added. These "pre-fortification" paint samples will be placed into labeled glass vials and shipped overnight at ambient temperature to the analytical laboratory for analysis. Aliquots of each sample will be analyzed separately and then averaged to provide the starting concentration of propiconazole in each lot of paint. The results will be reported to the Study Director as micrograms ~~propiconazole~~ **propiconazole** per gram of paint ($\mu\text{g ai/g paint}$), and this will be used to determine how much Wocosen® 500 SL will need to be added to each 5 gallon bucket." (V2:26)*

"Propiconazole will be added to each 5-gallon paint container by the field test site to achieve propiconazole concentrations in the paint of approximately 1,200 ppm (0.12% w/w) and 12,000 ppm (1.2% w/w) based on 5 gallons of paint and the density of the paint specified on the SDS (12 lb/gallon). Once the appropriate amount of Wocosen® 500 SL has been added to each 5-gallon bucket of paint, the buckets need to be placed onto a mechanical shaker for at least 5 minutes before triplicate aliquots of approximately 20 ml are collected from each bucket. After the aliquots have been collected, each bucket will be weighed on a GLP-maintained scale and the weights recorded. The paint samples (in glass vials) will be shipped overnight at ambient conditions to the analytical laboratory for GLP analysis. Samples are to be analyzed and reported separately and the results ($\mu\text{g ai/g paint}$) from each triplicate set of samples will be averaged. The average concentration of propiconazole in each 5-gallon bucket combined with the weight of paint sprayed will be used to calculate the pounds of active ingredient handled by each ME." (V2:27)

"Because it will be impossible to monitor the actual flow out of the spray nozzle and not all paint will be pumped out of the buckets, each bucket of paint will be weighed and recorded before and after use. The volume of paint that remains in the sprayer and hose once a worker is done spraying will be measured by researchers prior to the start of monitoring; this will be subtracted from the amount of paint used by each test subject. The paint weights combined with the measured concentration of propiconazole in each bucket will be used to determine the total amount of active ingredient handled by each ME." (V2:33)

Background/Pre-Sampling Air: *"Duplicate air samples using personal air sampling pumps and OVS tubes described for worker samples will be collected in the subject dressing area for approximately 60 minutes within a four hour period prior to the start of the dressing area's use on each day of the study. Similarly, a single air sample will be collected from each of three of the painting rooms which were used in the preceding ME, and that are intended for exposure monitoring on that day. These samples will also be collected over approximately 60 minutes within the four hours prior to the anticipated start time for the ME; the start and end times of*

sampling will be recorded. The OVS tubes will be suspended at approximately 5 feet off the floor during the sampling period.” (V2:43)

Surface Residues: “Duplicate wipe samples will be taken from one wall in each of the three rooms which were painted in the preceding ME, and that are intended for exposure monitoring on that day. Wipe samples will be collected within 4 hours of the scheduled monitoring event; the time of sampling will be recorded. A sample will consist of two dry cotton gauze pads held together and rubbed over an area of approximately 1 square foot (using a template) about mid-way up the wall for approximately 15 seconds. The two gauze pads will then be placed into a glass jar, sealed, and placed into frozen storage. This will be repeated with another two pads on a different part of the wall.” (V2:43)

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

“This study will be conducted according to FIFRA GLP Standards (40 CFR 160). This protocol will be reviewed by the lead quality assurance unit (QAU) prior to finalization. In-life field phase of this study will be monitored by the field facility QAU while the analytical phase will be audited by the analytical facility QAU to ensure compliance with the FIFRA GLP regulation and adherence to this protocol and relevant SOPs. The QAU(s) will submit copies of their inspection reports to the lead QAU, Study Director, Test Facility Management, AEATF Sponsor Representative, and Sponsor Monitor (40 CFR part 160.35 [4]). The final report will be audited by the lead QAU to ensure that the contents of the report accurately describe the conduct and findings of the study. QAU organization and responsibilities will follow current AEATF II SOPs as applicable. The final report will contain a signed Quality Assurance Statement from the lead QAU reflective of each contributing facility’s QA audits.” (V2:63-64)

(c) What QA methods are proposed?

“This study will be conducted according to FIFRA GLP Standards (40 CFR 160). This protocol will be reviewed by the lead quality assurance unit (QAU) prior to finalization. In-life field phase of this study will be monitored by the field facility QAU while the analytical phase will be audited by the analytical facility QAU to ensure compliance with the FIFRA GLP regulation and adherence to this protocol and relevant SOPs. The QAU(s) will submit copies of their inspection reports to the lead QAU, Study Director, Test Facility Management, AEATF Sponsor Representative, and Sponsor Monitor (40 CFR part 160.35 [4]). The final report will be audited by the lead QAU to ensure that the contents of the report accurately describe the conduct and findings of the study. QAU organization and responsibilities will follow current AEATF II SOPs as applicable. The final report will contain a signed Quality Assurance Statement from the lead QAU reflective of each contributing facility’s QA audits.” (V2:63-64)

“Sample matrix fortifications are designed to assess the stability of the active ingredient under field, storage, and transit conditions in or on the sampling matrices (inner dosimeters, hand wipe/wash solutions, hats, face/neck wipes, and air sampling matrices).” (V2:53) See the table below for the proposed sample matrix fortification levels.

Matrix	Target Field Fortification Level
Air Sampling 37 mm PVC Filters	100 ng, 1000 ng, 2,000 ng
Air Sampling OVS Tubes	100 ng, 2000 ng, 5,000 ng
Hand Wipe/Washes	400, 4000, and 12,000 ng/mL (220, 200 and 6600 µg/550 ml)
Face/Neck Wipes	1, 10, and 100 µg/sample
Inner Dosimeter Section	10, 1000, and 10,000 µg/sample
Painter’s Hats	10, 1000, and 10,000 µg/sample

(d) How will uncertainty be addressed?

“If the benchmark accuracy goal (i.e., k=3) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional monitoring events might be considered.” (V2:60)

3. Subject Selection

3.1 Representativeness of Sample

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

Airless paint sprayers can be used by commercial painters and homeowners. Commercial painters are the risk drivers in EPA’s assessments because they use airless sprayers more frequently and use more paint than homeowners (i.e., EPA assumes 50 gallons sprayed by commercial painters and 15 gallons sprayed by homeowners). Preserved paint is considered a treated article and as such there is no pesticide label to convey the need for risk mitigation (e.g., PPE), and therefore, no PPE is assumed in EPA’s assessments for commercial painters. Test subjects in this proposed study will be recruited from commercial painters rather than residential populations. “The one

potential noteworthy source of underestimation is that the population being monitored will consist entirely of professional painters with at a minimum of 3 months of experience. The rationale for the selection of professional painters over consumers is two-fold: (1) it is not as common for consumers to use airless sprayers, and (2) consumers would paint less surface area. While these two rationales hold true, the data generated from this study will also be used to assess consumers who use airless sprayers; however, the antimicrobial regulatory approval process is based on the highest exposure scenario, which is commercial painters because of the higher amount of paint they handle in a day in comparison to consumers. As such, the subjects in this study will paint for a longer period of time and use higher volume spray equipment than what is typical for consumers which may tend to bias exposure to the higher end.” (V1:14)

(b) From what populations will subjects be recruited?

“In order to obtain a subject pool that is familiar with the operation of airless paint sprayers in a professional setting, adult subjects who are currently or were previously employed in a position where they use/have used an airless paint sprayer will be recruited from the Orlando area (Orange County and surrounding counties). The commercial and residential painting industry will be targeted for the recruitment, and potential subjects must have at least 3 months of experience using an airless sprayer within the last 5 years. Individuals who work for a commercial or residential painting company, but do not have experience using airless paint sprayers will be excluded.” (V2:37)

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

The populations that have access to airless sprayers are both commercial painters and homeowners. *“The rationale for the selection of professional painters over consumers is two-fold: (1) it is not as common for consumers to use airless sprayers, and (2) consumers would paint less surface area. While these two rationales hold true, the data generated from this study will also be used to assess consumers who use airless sprayers; however, the antimicrobial regulatory approval process is based on the highest exposure scenario, which is commercial painters because of the higher amount of paint they handle in a day in comparison to consumers. As such, the subjects in this study will paint for a longer period of time and use higher volume spray equipment than what is typical for consumers which may tend to bias exposure to the higher end.”* (V1:14)

“Advertisements soliciting subjects will be posted in both English and Spanish local newspapers as well as on local radio stations. Additionally, postings will be placed in local retail and professional paint stores as allowed by store management.

This process results in a simple random sample of qualifying subjects from the volunteer pool. Note, however, that this is not the same as a random sample from the existing population of professional painters. By definition, volunteers are self-selected

and could have different characteristics than non-volunteers. Such distinctions have no relevance in this case, however. There is no particular need to obtain a random sample from the Orlando professional painter population. The MEs are synthetic constructs that attempt to predict aspects of a future handler-day population. It is purposive by definition. Thus, a random sample of just one ME component (e.g. subject) from a subpopulation (e.g. Orange County, Florida) provides no statistical advantage. In fact, a random sample of subjects from the volunteer pool is not the only possibility. For example, a more diverse sample of surrogate painters from this pool could also be acceptable if a clear diversifying characteristic were available for all painters. Lacking this, the paint application with airless sprayer study uses the reasonable default option of a random sample from the volunteer pool.” (V1:22-23)

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

“The AEATF II monitoring program, as described in the Governing Document (2011), intends to develop a database of exposure monitoring data that can be used to support practical regulatory decisions about future exposures to antimicrobial active ingredients used in various products.” (V2:11)

“The AEATF II program, as described in the Governing Document (2011), intends to develop a database of exposure monitoring data that can be used to support practical regulatory decisions about future exposures for different (including currently nonexistent) active ingredients and their associated products. The database addresses a variety of exposure scenarios for which no or limited data currently exist. The paint application with airless sprayer scenario is an important component of the AEATF II program. As noted in Section 4, the existing monitoring data for this scenario are considered incomplete. For this reason, the AEATF II is generating new exposure monitoring data that will supplement the limited existing data. The primary purpose of the paint application with airless sprayer monitoring study is to develop more accurate information on potential worker exposures to antimicrobials in paints and coatings. These data will consist of dermal and inhalation exposure measurements derived from monitoring human test subjects under conditions constructed to broadly represent those expected under actual use conditions. The general approach used by AEATF II to obtain such data is to conduct scripted simulated-condition exposure monitoring studies for scenarios of interest. In each study a set of monitoring events (ME) is constructed. Each ME simulates one set of possible conditions consistent with the scenario using a randomly selected volunteer who is monitored for dermal and inhalation exposure. The set of MEs is constructed so as to span a diverse set of conditions expected to impact exposure.” (V1:12-13)

3.2 Equitable Selection of Subjects

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

Inclusion/exclusion criteria are complete and appropriate, except that the reference to specific respirators should be deleted and an inclusion criterion should be added to reflect the need for subjects regularly wear a filtering face piece respirator or half-face respirator as when using an airless sprayer as part of their job. In addition, subjects must be willing to wear their own respirators in order to participate in the study.

The inclusion/exclusion criteria are listed in Volume 2, pages 19-20. The recommended revisions are shown below.

“Inclusion Criteria

- *Males or females between the ages of 18 and 65 years as verified by a government issued photo ID*
- *Self-identified as being in good health as defined as able to lift and move up to six 5-gallon buckets of latex paint; spray up to 30 gallons of paint using an airless sprayer while wearing a NIOSH approved P95 filtering face piece respirator or half-face respirator and eye protection (goggles or safety glasses with side-shields)*
- *Willingness to sign the Informed Consent Form and the Subject Qualification Worksheet*
- *Speak and read English or Spanish*
- *Has a minimum of 3 months experience working as a professional painter using an airless sprayer to apply architectural paint (painting of residential, commercial, and/or industrial buildings) within the last 5 years*
- *Use a filtering face piece or half-face respirator while working as a professional painter and willing to bring and use the same type of respirator when participating in the study*

“Exclusion Criteria

- *Skin conditions on the surface of the hands and face or neck (e.g., psoriasis, eczema, cuts or abrasions) as determined by a visual inspection*
- *Pregnant, as declared, or as shown by a urine pregnancy test*
- *Nursing/Lactating*
- *Allergies or sensitivities to chemical-based products particularly propiconazole, any triazole fungicide, isopropyl alcohol, and soaps*
- *Allergies or sensitivities to latex-based products particularly latex paint or latex gloves*
- *Unwilling or unable to participate in the study without gloves*
- *Is an employee or a spouse of an employee of any company represented by the AEATF, the contract research organizations conducting the study, Sherwin-Williams, or the American Chemistry Council” (V2:19-20)*

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

There is no relationship between the investigator and subjects. Employees and spouses of employees of the investigators are excluded from participation as subjects. (V2:20)

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

The protocol does not call for targeting recruitment to a vulnerable population, and contains adequate precautions to minimize any potential for coercion or undue influence. Recruitment materials and interactions with potential subjects will be conducted in English or Spanish, depending on subject preference. Subjects will be recruited through newspaper, radio, and flyers, rather than through employers, which will minimize the potential for coercion or undue influence. In addition, the compensation is not so high as to unduly influence participants, but represents fair remuneration in line with prevailing wages for professional painters for the subjects' time, travel, lost employment opportunity, and inconvenience.

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

The recruiting process is described in V2:37-39. Potential subjects will be recruited through newspaper advertisements (paper and online), radio commercials, and flyers posted in paint stores (as permitted by store management). All recruitment will be done in English and Spanish. A member of the study team (including a bilingual researcher, if necessary) will contact those who express an interest in participating by phone to provide more information about the study and to do a general eligibility screening. Respondents who are eligible and interested will be invited to meet with the Study Director (and a bilingual researcher if necessary) to review the consent form, review the study and what will occur during a monitoring event, and answer questions. Potential subjects will be permitted to take the consent form home to read, discuss with friends and family members, and consider whether to participate. Once a person decides he or she wants to participate, the consent process of signing the form and completing a Subject Qualification Worksheet will occur.

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

See the response to 3.2(c) above.

3.3 Remuneration of Subjects

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

"Potential subjects who attend the informed consent meeting whether they decide to participate or not will be paid \$20 in cash for their time and inconvenience. Subjects who qualify, sign the consent form, and report to the study site on their assigned day, will receive \$200 in cash for their time and inconvenience when they leave the study site, whether they are monitored or not. In the case of the four alternates, they will be compensated \$200 whether they are called in for monitoring or not." (V2:39-40)

(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, factoring in their experience as professional painters, and inconvenience. "*The value for remuneration is based roughly on a day's wage for a skilled painter of \$200 and represents potential lost time from secondary sources of employment, travel time, and incidental expenses incurred in study participation.*" (V2:40)

(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. (V2:40) EPA has requested that AEATF II clarify how alternate subjects who are enrolled but not needed for monitoring will be paid.

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 (propiconazole) 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?

The AEATF II identified six types of risks: (1) a reaction to the active ingredient propiconazole, (2) exposure to the isopropyl alcohol wash and wipes; (3) physical risks associated with painting activities; (4) heat related illness; (5) discomfort or inconvenience from wearing the air sampling device; and (6) psychological risks associated with changing clothes and the pregnancy test. (V2:20)

EPA has recommended that AEATF clarify the risks to subjects as follows. The first risk identified, "a reaction to the active ingredient propiconazole" should be modified to address the risks of reaction to latex-based paint as well. Under the same risk heading,

EPA has recommended addressing the risks of wearing a respirator. EPA has recommended adding another category: “risk of unanticipated release of confidential information.”

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

The AEATF II cited EPA’s assessment of propiconazole for the commercial spraying of propiconazole-treated paint using an airless sprayer. The following is a summary of that assessment as well as the recent background information on propiconazole.

- *“...in 2011 EPA conducted an updated airless spraying risk assessment using new dermal absorption data for propiconazole in paint which supported the use of a 1% dermal absorption factor instead of 41% which was used in the 2006 risk assessment (Leighton, 2011). Using the paint-specific dermal absorption factor of 1%, acceptable margins of exposure can be obtained for up to 1.2% (12,000 ppm) propiconazole in paint.”* (V2:21) The propiconazole toxicological endpoints used in Leighton (2011) are still the most recent endpoints and points of departure to represent propiconazole (D426494).

The most recent EPA assessment (D426494) indicates the following on the toxicity of propiconazole:

- *“The toxicology database for propiconazole is complete for evaluating and characterizing toxicity and selecting endpoints for purposes of this risk assessment. The primary target organ for propiconazole toxicity in animals is the liver. Liver effects observed in subchronic and chronic oral studies in rats and mice include lesions, hypertrophy and necrosis. There are mixed effects in the developmental and reproduction rat studies. In a rat developmental study, fetal effects were observed at doses lower than doses at which maternal effects were seen thereby demonstrating quantitative evidence of increased susceptibility of fetuses to in utero exposure to propiconazole. While in rabbits, developmental toxicity occurred at higher doses than maternally toxic doses. In the two generation reproduction study in rats, offspring toxicity occurred at a higher dose than the parental toxic dose suggesting lower susceptibility of the rat offspring to propiconazole. Propiconazole does not appear to be neurotoxic based on an acute and subchronic neurotoxicity studies. The concern for susceptibility is low since clear NOAELs were established in the rat and rabbit developmental studies and the points of departure selected for the risk assessment scenarios are protective of the susceptibility observed in the rat developmental study.”*
- *“Propiconazole has low to moderate acute toxicity in experimental animals by the oral (Category III), dermal (Category III) and inhalation routes (Category IV), is moderately irritating to the eyes (Category III), minimally irritating to the skin (Category IV) and is a dermal sensitizer.”*
- *“An acute POD of 30 mg/kg (NOAEL) for the general population was selected from an acute neurotoxicity study based on clinical signs of toxicity (piloerection, diarrhea, tip toe gait) at 100 mg/kg. An acute POD of 30 mg/kg (NOAEL) was*

selected for females age 13-49 years from a developmental study in rats based on increased incidence of rudimentary ribs, un-ossified sternebrae, as well as increased incidence of shortened and absent renal papillae and increased cleft palate at 90 mg/kg/day. The developmental effects of concern are presumed to occur after a single exposure and are relevant only to females aged 13-49 years old since they occur in utero. An uncertainty factor (UF) of 100x (10X to account for intraspecies extrapolation and 10X for intraspecies variation)...” is applied.

Other background information on propiconazole include the following:

- EPA conducted a Reregistration Eligibility Decision (RED) document in 2006: https://archive.epa.gov/pesticides/reregistration/web/pdf/propiconazole_red.pdf.
- EPA published the final work plan for registration review: <https://www.regulations.gov/document?D=EPA-HQ-OPP-2015-0459-0016>.
- The USEPA Propiconazole RED (2006) indicates the following: “*The Agency classified propiconazole as a Group C, possible human carcinogen, based on increased hepatocellular adenomas, combined adenomas/carcinomas, and hepatocellular carcinomas in male mice in a chronic oral feeding study. However, animals in the high dose group for this study showed excessive toxicity; furthermore, the high dose exceeded the Maximum Tolerated Dose determined in the 90-day range finding study. No treatment-related tumors were seen in female mice in this mouse chronic feeding study. No tumors were noted in a chronic rat study. Therefore, the Reference Dose (RfD) approach is considered to be protective of any carcinogenic effects and is recommended for use in cancer risk assessment for propiconazole. This approach is also consistent with results of voluntary nonguideline mechanism of action studies conducted by the propiconazole technical registrant.*” Thus the oral NOAEL of 10 mg/kg/day cited in the propiconazole RED (2006) from the 24-month oncogenicity study in mice is protective of any carcinogenic effects.
- “*In a dermal penetration study (MRID 47736303), [¹⁴C]-propiconazole (99.0% radiochemical purity; Lot No. RDR-I-84) in a commercial latex paint or alkyd stain solutions was applied to 10 cm² of clipped skin of 12 male Sprague Dawley (Crl:CD[SD]) rats/dose. Each application site was defined and protected by a protective device, glued to the skin surface and fitted with non-occlusive cover. Nominal doses were 0.1, 0.35, or 1.0 mg [¹⁴C]-propiconazole/rat; equivalent to 0.45, 1.6, or 4.5 mg [¹⁴C]-propiconazole/kg bw, respectively. The exposure durations were 10, 24, and 72 h, at which time 4 rats/time point/dose were sacrificed, and samples were collected and analyzed for radioactivity. For commercial paints, the majority of the applied dose (81-96%) remained on the skin surface and was readily removed by mild skin washing. The absorbed [¹⁴C]-propiconazole following 10-hour exposure for the low-, mid- and high-dose group was 0.85%, 0.89%, and 0.99%, respectively. Absorption values for 24- and 72-hour exposures were similar.*” (D365243)

A summary of Leighton (2011) cited by the AEATF II for the commercial assessment of airless sprayers applying propiconazole-treated paint is provided below:

Attachment 2

- Anticipated exposure levels for commercial painters using airless sprayers are based on the airless sprayer data in EPA's Pesticide Handler's Exposure Database (PHED). Based on the PHED data, the unit exposure for inhalation is 0.83 mg/lb ai. The dermal unit exposure for single layer and no gloves is 38 mg/lb ai for long pants, long sleeved shirts; and no gloves. The assessment is based on the high end of amount paint sprayed by commercial painters which is assumed to be 50 gallons per day (assuming paint density of 10 lbs per gallon x 50 gallons = 500 lbs of paint). The two points of departure are based on the oral NOAELs of 30 mg/kg/day for short-term durations and 10 mg/kg/day for assessing long-term effects (including cancer). The dermal and inhalation target MOEs are 100 based on 10x for the interspecies extrapolation and 10x for intra species variation.
- Table 3 provides a comparison of the anticipated dermal and inhalation airless sprayer exposures to the point of departures (PODs) as cited in the AEATF II protocol by citing Leighton (2011) (i.e., 50 gallons of paint @ 0.35% ai using PHED data) and as adjusted in this review by EPA to represent the highest exposed test subject in this proposed study (i.e., 30 gallons of paint @ 1.2% ai) using EPA's most current unit exposures for airless sprayers (PHED data plus Formella (1995). Based on the comparisons of the anticipated exposures and subchronic (and chronic to be inclusive of cancer) endpoints selected, there are minimal inhalation and dermal risks for the test subjects spraying the maximum amount of paint and propiconazole proposed in this study.

Table 3. Short- and Long-Term Occupational Handlers Exposures and MOEs

Exposure Scenario --Application Method	Application Rate ^a	Quantity Handled/ Treated per day ^b	Unit Exposure (mg/lb a.i.)		Absorbed Daily Dose (mg/kg/day) ^e		MOE ^f		
			Dermal ^c	Inhalation ^d	Dermal	Inhalation	Dermal (Target = 100)	Inhalation (Target = 100)	TOTAL MOE ^g (Target = 100)
Short-term Exposure Duration									
Airless Sprayer (Leighton 2011)	0.35% a.i. by weight	500 lbs	38	0.83	0.0095	0.021	3200	1400	990
Airless Sprayer (Anticipated subject's risks)	1.2% a.i. by weight	360 lbs	43	0.56	0.023	0.030	1300	990	560
Long-Term Exposure Duration (Including Cancer)									
Airless Sprayer (Leighton 2011)	0.35% a.i. by weight	500 lbs	38	0.83	0.0095	0.021	1100	480	330
Airless Sprayer (Anticipated subject's risks)	1.2% a.i. by weight	360 lbs	43	0.56	0.023	0.030	430	330	190

- a Application rates are 0.35% ai by weight in Leighton (2011) and 1.2% propiconazole by weight in this proposed AEATF II airless sprayer study.
- b Amount handled per day values are estimates based on AD's standard assumptions (50 gallons paint x 10 lb/gal paint density) used in Leighton (2011) and 30 gallons of paint x 12 lbs/gallon paint density proposed in this AEATF II airless sprayer study.
- c All dermal unit exposures (UEs) represent workers wearing long-sleeve shirt, long pants, and no gloves. Leighton (2011) UE based solely on PHED while current EPA UEs are based on PHED plus Formella (1995) as presented in <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-exposures-and-risk-assessments>

[pesticide-handler-exposure-data](#) and <https://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf>.

- d No respiratory protection is assumed for material preservatives in paint (Note: test subjects in proposed AEATF II airless sprayer study will be wearing their own respiratory protection, providing a protection factor which has not been factored into this equation/MOE estimates). Leighton (2011) UE based solely on PHED while current EPA UEs are based on PHED plus Formella (1995) as presented in <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data> and <https://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf>.
- e Absorbed Daily dose (mg/kg/day) = [unit exposure (mg/lb a.i.) * application rate (% a.i. weight/100) * quantity treated (lb/day) * absorption factor (0.01 for paint for dermal; and 1.0 for inhalation)]/ Body weight (70 kg in 2011 & currently 80 kg).
- f MOE = NOAEL / Absorbed Daily Dose. [Where short- and long-term oral NOAELs = 30 and 10 mg/kg/day, respectively, for both dermal and inhalation]. Target MOE is 100.
- g Total MOE = 1/((1/Dermal MOE) + (1/Inhalation MOE)). The target MOE is 100. Results rounded by spreadsheet.

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

The potential dermal and inhalation risks have been evaluated by EPA through a comparison between the POD and the anticipated dermal and inhalation exposure. The comparison indicates minimal dermal and inhalation risks. Please see part 4.1(c) (above) for details. The AEATF II references the EPA for the MOEs (V2:21).

(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 or sensitivities to any triazole fungicide, propiconazole, to latex paint or latex gloves, soaps, or isopropyl alcohol, or with cuts/abrasions. (V2:20)

4.2 Risk Minimization

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

“Safety glasses with side-shields or goggles and NIOSH-approved P95 filtering face piece respirators such as the “3M Paint Odor Valved Respirator” for nuisance level latex paint, stain and solvent odors will be provided to each test subject.

The NIOSH-approved P95 particulate filtering face-piece respirator filters at least 95% of airborne particles and is strongly resistant to oil. However, subjects will be allowed to substitute their own half-face respirator for the filtering face piece respirator if they chose to. Full-face respirators and face-shields will not be allowed as they cover the face preventing an accurate measurement of face and neck residue. Although not required by the paint label, the use of these PPE will be provided as a safety precaution for the study. It is common practice in the painting industry to wear such PPE when operating an airless sprayer. However,

if the use of these protective equipment become obstructed with paint or otherwise hinder the subject's ability to do his/her job, researchers will either clean or switch out the safety equipment with new/clean safety equipment. If a subject does not wear the required PPE, or does not follow research personnel instructions within reason, or does so in a manner that presents safety issues in the judgment of the research personnel, the Study Director may terminate the subject's participation as per SOP AEATF II-11H. As per SOP 11H if the monitoring event is terminated for noncompliance, the samples will not be collected.

Soft foam ear plugs will be available for subjects concerned about hearing protection.

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

A physician, nurse, emergency medical technician (EMT), or physician's assistant unaffiliated with the study researchers will be hired for the study and will be on site for each monitoring event and will provide medical support if needed. This individual will be responsible for examining the test subject's hands, face and neck for open cuts or abrasions or skin conditions that would disqualify the subject from participating. The medical professional will also be responsible for examining the subjects' hands and face/neck for possible signs of dermal irritation following sample collection." (V2:35)

"Stop Criteria and Medical Management

"It is not expected that test subjects will experience any adverse effects due to propiconazole from participation in this study due to the low concentration of the antimicrobial being used (1.2% and 0.12% propiconazole). In addition, the biocide being tested is currently on the market as a common additive to commercially available paint. However, based on the paint label and SDS, there are potential adverse effects associated with the use of the paint. Exposure to the paint and the biocide preservative will be mitigated by the personal protective equipment that will be worn (two layers of clothing, an N95 filtering face piece respirator or half-face respirator, and safety glasses/goggles).

In the unlikely event that adverse effects are experienced, based on the paint SDS, they will most likely be eye irritation, skin irritation, or respiratory irritation. According to the SDS, overexposure can lead to eye irritation and upper respiratory irritation while prolonged contact with the skin can result in irritation. In addition the paint SDS warns that in confined areas exposure to high concentration of paint vapors can cause headache, nausea, or dizziness. The paint label warns about exposure to crystalline silica and recommends increasing fresh

air or wearing a respirator if the user experiences headaches, dizziness or eyewatering. The Wocosen® 500 SL label (50% propiconazole) indicates that the preservative can cause moderate eye irritation and is harmful if swallowed or absorbed through the skin. An eye wash station and soap and water will be available in case a subject experiences eye or skin irritation during the study.

The extra layer of clothing (inner dosimeter) worn by subjects may increase the risk of heat-related illness. However, the possibility of heat stress will be minimal for subjects in this study due to the study being conducted indoors and the monitoring taking place in the winter or spring. If the temperature at the indoor study site exceeds 80 degrees Fahrenheit research personnel shall monitor the heat index, and stop subjects' work if the heat index exceeds 95. SOP AEATF II-11B describes the procedure for identification and control of heat stress. The poster "Controlling Heat Stress Made Simple" will be posted in the subject dressing area so that it is visible to subjects and research personnel at the field site.

The Study Director or designee will discuss the propiconazole and paint label safety warnings and heat stress with the subjects at the consent meeting and again just prior to participation in the study. Subjects will be instructed to inform the Study Director or research staff immediately if they feel ill, suffer eye or skin irritation or breathing difficulties or experience any other unanticipated adverse effects they feel may be related to the study during or following conduct of the study. The on-site medical professional will be available to assist should someone experience any adverse effects.

The medical professional will examine the hands and face/neck of each test subject immediately prior to the monitoring period to ensure there are no existing abrasions, cuts or skin conditions that increase the risk of skin irritation during the painting activities or the hand and face/neck sampling. A member of the research team who is bilingual in English and Spanish will be present during monitoring events involving subjects whose preferred language is Spanish.

If a subject reports eye/skin/respiratory irritation (or other adverse effect) during the work period, they will be asked to immediately stop working. Research staff will then move the subject to a clean area and notify the on-site medical professional and Study Director. If necessary the medical professional will assist the subject by gently washing affected area with water and soap or help administer the eye wash. The medical professional will determine whether additional medical treatment is necessary.

During the study, researchers will observe subjects for possible signs of early heat illness such as fatigue, dizziness, irritability, or decreased concentration especially if the subject has been working for several hours. If these symptoms are observed, the subjects will be asked whether they would like to rest for a moment. If they answer affirmatively, they will stop working, be given their choice of water or a sports drink and a chair, and the Study Director and on-site medical professional will be immediately contacted for further medical management

instructions. If the subject answers negatively, he/she will be permitted to continue working, and frequently thereafter asked whether he/she would like to rest for a moment. Any affirmative answer will be handled as described above.

If subjects develop visible signs or report symptoms of distress such as pronounced fatigue, headache, cramps, feeling faint, increased pulse, muscle spasms, heavy sweating (or dry skin if previously sweating), extreme thirst, or rapid breathing, the subjects will be required to stop working immediately, and given their choice of water or a sports drink and a chair. The on-site medical professional will immediately be contacted for further medical management instructions and the Study Director and Study Monitor will be contacted. If the subject's condition appears to be serious, the medical professional will either call 911 or, accompanied by the Study Director or Principle Field Investigator, take the subject to the identified medical facility and allow the medical personnel to respond and treat the subject. The AEATF will pay for reasonable and appropriate medical treatment for a study-related injury or illness that is not paid for by the subject's own insurance or the insurance of a third party under which the subject is covered.

Study personnel will be instructed to inform the Study Director and medical professional immediately of any eye or skin irritation, respiratory irritation, heat stress, or unanticipated adverse effect observed or reported during conduct of the study. The medical management procedures set forth in SOP AEATF II-11C will be implemented for any instance where the subject's work is halted for medical reasons (other than solely because of a heat stress index above 95), and for any post-study reports of illness, eye, skin, or respiratory reactions or unanticipated adverse effects. If two or more subjects withdraw or are withdrawn from the study for the same medical reason, the study will be suspended until the cause of the withdrawal is fully investigated and determined. If two or more subjects develop an adverse skin reaction after they leave the study site, all subjects will be contacted by the Study Director to determine whether further medical management is appropriate.

The Study Director will maintain a record of adverse health observations and reports, and follow the Study Sponsor, IRB, and EPA policies for medical event reporting as described in SOPs 11C and 11F. Sufficient personnel will be present at the study site to maintain an appropriate level of technical support, scientific supervision, and observations relevant to the safety of test subjects.” (V2:40-42)

Other protections include:

- Candidates with skin conditions on the surface of the hands and face or neck (e.g., psoriasis, eczema, cuts or abrasions) are excluded (V2:20)
- Candidates will wear a respirator during the monitoring event (V2:19)
 - Note: EPA recommends that the criteria be revised to enroll subjects who already wear a filtering face piece respirator or half-face respirator while painting with an airless sprayer as part of their

profession, and who are willing to wear the same respirator or type of respirator during their participation in the research.

- Candidates known to be allergic to propiconazole, triazole fungicides, latex paint or gloves, soaps, or isopropyl alcohol are excluded (V2:28)
- Candidates who are pregnant, nursing, or in poor health are excluded (V2:28)
- The consent form alerts subjects to signs and symptoms of eye and skin reactions and advises them to stop the painting if they experience a reaction to the paint, or if they feel faint or too hot (V2:115)
- The ambient temperature will be monitored, and subjects will be observed for signs of heat stress. There are appropriate stopping rules if the heat index becomes unsafe (SOP 11B.1, Heat Stress). (V4:131-142)
- A medical professional will be hired for this study and will be on site during the monitoring events. (V2:40-42)
- 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). (V4:128-130)

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

Heat stress index above 95 (V2:40)

Subject reported “*eye/skin/respiratory irritation (or other adverse effect)*” (V2:41)

“*...visible signs or reported symptoms of distress such as pronounced fatigue, headache, cramps, feeling faint, increased pulse, muscle spasms, heavy sweating (or dry skin if previously sweating), extreme thirst, or rapid breathing...*” (V2:41)

“*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.*” (V2:42)

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

The protocol calls for a trained medical professional to be on site for all monitoring events. (V2:40-42). The protocol also references to SOPs: SOP 11.B.1 for Management of Heat Stress (V4:131-142) and SOP 11.C.2 for Emergency Procedures (V4:143-147).

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

“*It is not expected that test subjects will experience any adverse effects due to propiconazole from participation in this study due to the low concentration of the antimicrobial being used (1.2% and 0.12% propiconazole). In addition, the biocide being tested is currently on the market as a common additive to commercially available paint. However, based on the paint label and SDS, there are potential adverse effects*

associated with the use of the paint. Exposure to the paint and the biocide preservative will be mitigated by the personal protective equipment that will be worn (two layers of clothing, an N95 filtering face piece respirator or half-face respirator, and safety glasses/goggles).

“In the unlikely event that adverse effects are experienced, based on the paint SDS, they will most likely be eye irritation, skin irritation, or respiratory irritation. According to the SDS, overexposure can lead to eye irritation and upper respiratory irritation while prolonged contact with the skin can result in irritation. In addition, the paint SDS warns that in confined areas exposure to high concentration of paint vapors can cause headache, nausea, or dizziness. The paint label warns about exposure to crystalline silica and recommends increasing fresh air or wearing a respirator if the user experiences headaches, dizziness or eye-watering. The Wocosen® 500 SL label (50% propiconazole) indicates that the preservative can cause moderate eye irritation and is harmful if swallowed or absorbed through the skin. An eye wash station and soap and water will be available in case a subject experiences eye or skin irritation during the study.

“The extra layer of clothing (inner dosimeter) worn by subjects may increase the risk of heat-related illness. However, the possibility of heat stress will be minimized for subjects in this study due to the study being conducted indoors and the monitoring taking place in the winter or spring. If the temperature at the indoor study site exceeds 80 degrees Fahrenheit research personnel shall monitor the heat index, and stop subjects’ work if the heat index exceeds 95. SOP AEATF II-11B describes the procedure for identification and control of heat stress. The poster “Controlling Heat Stress Made Simple” will be posted in the subject dressing area so that it is visible to subjects and research personnel at the field site.

“The Study Director or designee will discuss the propiconazole and paint label safety warnings and heat stress with the subjects at the consent meeting and again just prior to participation in the study. Subjects will be instructed to inform the Study Director or research staff immediately if they feel ill, suffer eye or skin irritation or breathing difficulties or experience any other unanticipated adverse effects they feel may be related to the study during or following conduct of the study. The on-site medical professional will be available to assist should someone experience any adverse effects.

“The medical professional will examine the hands and face/neck of each test subject immediately prior to the monitoring period to ensure there are no existing abrasions, cuts or skin conditions that increase the risk of skin irritation during the painting activities or the hand and face/neck sampling. A member of the research team who is bilingual in English and Spanish will be present during monitoring events involving subjects whose preferred language is Spanish.

“If a subject reports eye/skin/respiratory irritation (or other adverse effect) during the work period, they will be asked to immediately stop working. Research staff will then move the subject to a clean area and notify the on-site medical professional and Study

Director. If necessary the medical professional will assist the subject by gently washing affected area with water and soap or help administer the eye wash. The medical professional will determine whether additional medical treatment is necessary.

“During the study, researchers will observe subjects for possible signs of early heat illness such as fatigue, dizziness, irritability, or decreased concentration especially if the subject has been working for several hours. If these symptoms are observed, the subjects will be asked whether they would like to rest for a moment. If they answer affirmatively, they will stop working, be given their choice of water or a sports drink and a chair, and the Study Director and on-site medical professional will be immediately contacted for further medical management instructions. If the subject answers negatively, he/she will be permitted to continue working, and frequently thereafter asked whether he/she would like to rest for a moment. Any affirmative answer will be handled as described above.

“If subjects develop visible signs or report symptoms of distress such as pronounced fatigue, headache, cramps, feeling faint, increased pulse, muscle spasms, heavy sweating (or dry skin if previously sweating), extreme thirst, or rapid breathing, the subjects will be required to stop working immediately, and given their choice of water or a sports drink and a chair. The on-site medical professional will immediately be brought to the subject to give further medical management instructions and the Study Director and Study Monitor will be contacted. If the subject’s condition appears to be serious, the medical professional will either call 911 or, accompanied by the Study Director or Principle Field Investigator, take the subject to the identified medical facility and allow the medical personnel to respond and treat the subject. The AEATF will pay for reasonable and appropriate medical treatment for a study-related injury or illness that is not paid for by the subject’s own insurance or the insurance of a third party under which the subject is covered.

“Study personnel will be instructed to inform the Study Director and medical professional immediately of any eye or skin irritation, respiratory irritation, heat stress, or unanticipated adverse effect observed or reported during conduct of the study. The medical management procedures set forth in SOP AEATF II-11C will be implemented for any instance where the subject’s work is halted for medical reasons (other than solely because of a heat stress index above 95), and for any post-study reports of illness, eye, skin, or respiratory reactions or unanticipated adverse effects. If two or more subjects withdraw or are withdrawn from the study for the same medical reason, the study will be suspended until the cause of the withdrawal is fully investigated and determined. If two or more subjects develop an adverse skin reaction after they leave the study site, all subjects will be contacted by the Study Director to determine whether further medical management is appropriate.

“The Study Director will maintain a record of adverse health observations and reports, and follow the Study Sponsor, IRB, and EPA policies for medical event reporting as described in SOPs 11C and 11F. Sufficient personnel will be present at the study site

to maintain an appropriate level of technical support, scientific supervision, and observations relevant to the safety of test subjects.” (V2:40-42)

(e) 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, respiratory irritation, eye reaction, or other physical injury that you believe is due to your participation in the study you should seek medical treatment and call the Study Director, Brian Lange, immediately at 1-877-298-7008.*” (V2:116)

“The medical management procedures set forth in SOP AEATF II-11C.1 will be implemented for any instance where the subject’s work is halted for medical reasons (other than solely because of a heat stress index above 95), and for any post-study reports of illness, eye, skin, or respiratory reactions or unanticipated adverse effects. If two or more subjects withdraw or are withdrawn from the study for the same medical reason, the study will be suspended until the cause of the withdrawal is fully investigated and determined. If two or more subjects develop an adverse skin reaction after they leave the study site, all subjects will be contacted by the Study Director to determine whether further medical management is appropriate. (V2:42) (SOP 11C.2 is located in Volume 4, pages 100-103)

EPA recommends that the Study Director consult with the medical professional before making a determination about whether further medical management is appropriate.

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

The AEATF II will pay for injuries to subjects due to their participation in the study. As the informed consent form states: “*If you get 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 II will pay for reasonable and appropriate medical treatment for a study-related injury or illness that is not paid for by your own insurance or insurance provided by your employer. The Study Director in consultation with the medical professional who will be present during the study and other key study and Task Force personnel will decide if you have an illness or injury that is due to your participation in the study. If within 24 hours of participation in the study you experience a skin reaction, respiratory irritation, eye reaction, or other physical injury that you believe is related to your participation in the study you should seek medical treatment and call the Study Director, Brian Lange, immediately at 1-877-298-7008.*” (V2:116)

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?

As a result of the data from this study, which will be used to inform risk assessments, society will benefit from the continued availability of antimicrobial pesticides used to preserve products.

EPA notes that the antimicrobial pesticide being monitored in this study is intended to represent biocides that are used as in-can preservatives to prevent microbes from spoiling the paint before it is applied. Registration of these in-can preservatives based on the data generated by this study can provide a societal benefit by allowing the use of water-based, low-VOC paints, which are more prone to spoilage than solvent containing paints.

*"The other benefit is that measuring exposure of workers in this research study will produce more reliable data about the potential dermal and inhalation exposure of painters applying paint containing an in-can preservative (**antimicrobial pesticide**) while using airless sprayers. The resulting data will improve the completeness and accuracy of the database used by industry and the EPA to assess exposure and risks to workers who are exposed to antimicrobial ~~chemicals~~ **pesticides** used in the preservation of paint and other in-can materials."* (V2:24)

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

Society, EPA, and registrants would benefit from this research. Society will benefit from the continued availability of antimicrobial pesticides used as materials preservatives. EPA will benefit from the submission of data that reduces uncertainty around the exposure experienced by those using airless sprayers to apply paint containing antimicrobials, allowing for more precise risk assessments. Registrants of antimicrobials will benefit because they will provide EPA with data on exposure that may aid in maintaining existing antimicrobial pesticide registrations and in registering new antimicrobials.

(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 apply paint using an airless sprayer, with resulting societal benefits in the form of more accurate and confident assessments of exposure and risk.

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

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

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Schulman 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 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. (V2:20)

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

“A Spanish-speaking member researcher 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.” (V2:38)

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

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

All written recruitment, consent, and risk communication materials will be available in both English and Spanish (including consent form, recruiting materials, flyers, and poster titled “Controlling Heat Stress Made Simple”). (V2:18)

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). (V4:159)

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

“3.0 Ensuring Comprehension

- “3.1 During the consent process, time will be allocated for questions and answers. The IRB-approved Consent Form (and all supporting documents, except product labels and MSDS forms) will be presented in English or an alternative language (e.g. Spanish if they cannot read English) to the subject. Alternative language specifications will be protocol specific and dependent on the demographics of where the study is conducted; further information is provided in the Governing document of the AEATF II. All sections of the Consent Form must be explained in detail to the subject.*
- “3.2 When the person obtaining consent is finished, he/she must ascertain whether the potential subjects really understand the procedures, requirements, and risks associated with participation in the study. This assessment of comprehension will be done by asking specific questions of the potential subjects to indicate their understanding of key issues. The form in Attachment 11-J-1 will be used to establish general understanding of the informed consent form and what is being asked of the volunteer. This must be filled out for each study participant and retained with their signed consent form.*
- “3.3 If after this process the subject demonstrates comprehension of the material, meets the requirements, and wants to participate, he/she will be asked to sign and date the Consent Form. Once the form is signed, the person obtaining consent will provide a copy of the signed form to the subject. If the subject needs more time to decide on his participation, he can take the unsigned consent form home and set up a follow-up appointment.*
- “3.4 The Study Director (or designee) obtaining the consent will not sign the Consent Form unless he/she believes that the process has been free of coercion or undue influence and that the candidate fully understands the information presented.” (V4:157)*

(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.*” (V4:157)

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.*” (V2:117)

9. Respect for Subjects

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

“*Subjects’ names will not be revealed in the final report or in the field trial notebook; instead information relating to each subject will be done using the subject identification code only. Records correlating subject names to their identification codes and personal information such as the signed consent forms and Subject Qualification Worksheets will be kept separately from the field trial notebook in another study file clearly marked “CONFIDENTIAL”. This file will be kept in a secure location (i.e., locked file cabinet) at the field test site with limited access as described in SOP 11J.1 until transferred to Quality Associates Inc. in Maryland for archiving.*” (V2:36)

“*The study subjects will not be photographed at any time while changing into or out of the dosimetry clothing. Photos in the final report will not show faces or identifying marks such as tattoos to preserve anonymity of participants.*” (V2:49)

EPA recommends adding the following to the protocol in Section X.B., Risks to the Subjects: “*In order to minimize the psychological stress, women will be given a private place to take the test, a female member of the study team will verify the test result, and the Study Director will ensure confidentiality of any test result. The results of the test will not be discussed with or released to anyone beyond the verifying study team member, Study Director, and subject. The confidentiality of the pregnancy testing will be discussed during the consent process.*”

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

The protocol notes that subjects will be informed at multiple points about their freedom to withdraw from the study at any point without penalty.

Potential subjects will be informed through reading the consent form and the discussion with the study personnel during the consent meeting: “*You are free to withdraw from this study at any time, for any reason. Simply tell any member of the research team that you no longer want to participate. If you decide not to participate in this study or to withdraw from it at any time, you will not be penalized or reprimanded in any way.*” (V2:118)

During the preparations on the day of the monitoring event, subjects will also be reminded: “*The research team will review with you what will happen during the study and you'll have another chance to ask questions. We will remind you that you may change your mind about being in the study at any time before or after the study begins. All you need to do is tell us you've changed your mind. There will be no penalty of any kind to you if you decide to withdraw from the study.*” (V2:113)

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

“*Potential subjects who attend the informed consent meeting whether they decide to participate or not will be paid \$20 in cash for their time and inconvenience. Subjects who qualify, sign the informed consent form, and report to the study site on their assigned day, will receive \$200 in cash for their time and inconvenience when they leave the study site, whether they are monitored or not. In the case of the 4 alternates, they will be compensated \$200 whether they are called in for monitoring or not.*” (V2:39-40)

References

D365243. (2009) Propiconazole – Toxicological Review and Dermal Absorption Factor Determination for the Proposed Increase in Application Rate for Use in Paints and Stains. Memorandum from Jenny J. Tao to Stacey Grigsby. USEPA. DB Barcode D365243. Dated November 23, 2009. Attachment Data Evaluation Record (DER) for MRID 47736303.

D426494. (2015) Propiconazole Human Health Risk Assessment for the New Uses of Propiconazole on dill, leafy brassicas crop subgroup 5B, ti palm, watercress, and quinoa, along with expansion to fruit, stone, group 12-12; except plum, and nut, tree, group 14-12. Memorandum from Thurston G. Morton to Sidney Jackson/Barbara Madden. USEPA. DP Barcode D426494. Dated December 2, 2015.

Attachment 2

Formella, T. (1995) Potential Exposure of Workers to Chlorothalonil when Handling and Applying Paint Containing Chlorothalonil: Lab Project Number: 94-0204: ISKB-1894-002-02: 5227-94-0204-CR-001. Unpublished study prepared by Ricerca, Inc. 272 p. MRID 43600102.

Leighton 2011. Propiconazole: Update of the Paint & Stain Risk Assessment based on New Dermal Absorption Data. Memorandum from Timothy Leighton to Rebecca von dem Hagen, USEPA. DP Barcode 393026. Dated August 23, 2011.

MRID 46250701: Hassler, S. (2000) The in vitro Percutaneous Absorption of (Phenyl-U-(Carbon 14)) CGA 64250 Formulated as Tilt 250 EC (A-6097 K) Through Rat and Human Epidermis: Propiconazole: Final Report. Project Number: 044AM02. Unpublished study prepared by Novartis Crop Protection, AG.

MRID 47736503: McClanahan, R. (2008) Propiconazole in Paints and Stains - In Vivo Dermal Penetration in Rats: Final Report. Project Number: 021081/1, 021801, T002914/06. Unpublished study prepared by Ricerca Biosciences, LLC.

Parkin, R. T. "April 8-9, 2014 EPA Human Studies Review Board Meeting Report." Dated June 25, 2014. <https://www.epa.gov/sites/production/files/2014-11/documents/hsrb-final-report-april-2014-meeting.pdf>

**§ 26.1111 Criteria for IRB approval of research
AEATF II Airless Sprayer Study Scenario/Protocol AEA10: August 21, 2017**

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 Airless Sprayer Study Scenario/Protocol AEA10: August 21, 2017**

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 described.
	(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 Airless Sprayer Study Scenario/Protocol AEA10: August 21, 2017**

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	

**§26.1125 Prior submission of proposed human research for EPA review
AEATF II Airless Sprayer Study Scenario/Protocol AEA10: August 21, 2017**

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 <ul style="list-style-type: none"> • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects. 	Y n/a Y n/a	V2:3-1071 V2:108-119	
(2) Minutes of IRB meetings . . . in sufficient detail to show <ul style="list-style-type: none"> • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution. 	Y	V3:223-227	
(3) Records of continuing review activities.	n/a		
(4) Copies of all correspondence between the IRB and the investigators.	Y	V3:142-206	
(5) <ul style="list-style-type: none"> • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant. 	Y	On file with EPA	
(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 IRB under confidentiality claim	
(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).	n/a		
The following information, to the extent not already included:			
§1125(a) a discussion of:	(1) The potential risks to human subjects (2) The measures proposed to minimize risks to the human subjects; (3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and (5) The balance of risks and benefits of the proposed research.	Y Y Y Y Y	V2:20-23 V2:20-23, 34-35, 40-42 V2:24 V2:16-18 V2:24
§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Original – V3:128-141 IRB edits – V3:161-171 Approved – V2:108-129	
§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	V2:37-39, 120-129	
§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	V2:19-20, 37-39, 128-129	
§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	V3:142-206	
§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.	Y	V2:159-159 V3:179-194, 207-222	