UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

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MEMORANDUM

SUBJECT: Science and Ethics Review of AEATF II Pressurized Hand-Wand and Electrostatic Spraying Scenarios 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 Pressurized Hand-Wand Spraying of Antimicrobial Products"* along with "Study Addendum: Addition of Electrostatic Sprayers" (AEA14) submitted by the Antimicrobial Exposure Assessment Task Force II (AEATF II) from both scientific and ethics perspectives. The study's protocol was submitted to EPA in early March 2020. The AEATF-II submitted to EPA the Electrostatic Sprayer (ESS) Addendum, dated June 2, 2020, to specifically address the interest in the use of these types of sprayers for SARS-CoV-2, the virus that causes COVID-19. This protocol and ESS Addendum propose to evaluate potential dermal

and inhalation exposure to both consumers and occupational workers during the spraying of surfaces using an antimicrobial product in the following three main scenarios:

(1) outdoor spraying (e.g., siding on buildings/sidewalks),

(2) indoor "dry" environments (e.g., indoor living areas/sanitizers/disinfectants), and

(3) indoor "wet" environments (e.g., food & beverage/livestock/animal housing).

Scientific aspects of the proposed research are assessed in terms of the recommendations of the EPA Guidelines Series 875 and of the Human Studies Review Board (HSRB). 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 HSRB.

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 provided by Advarra Institutional Review Board (IRB).

B. Summary Assessment of the Scenario Design

Supporting details are in Attachment 1.

1. **Scenario Design:** The EPA assesses potential exposures from various antimicrobial products that are applied by a multitude of application techniques, including treatment by various types of pressurized hand-wands. Pressurized hand-wands in this proposed study include spray nozzles connected to hoses connected to spray tanks that are either manually or mechanically pressurized, excluding trigger pump sprayers and aerosol cans. Hand-wand sprayers are typically an occupational application but may also be used by consumers in a more limited fashion. Therefore, this study proposes to use both occupational workers and consumers as test subjects and separate the exposure scenarios specific to each user population.

   "Information collected from AEATF II members in a 2013-14 survey regarding products labeled for pressurized hand-wand spray applications revealed that the majority are intended for professional use only with just a few that would be used by both professionals and consumers, and none labeled solely for consumers use. The main categories of workers who apply antimicrobial products using pressurized hand-wand spray equipment are institutional/industrial/janitorial workers including sanitation crews, contractors/construction workers, agricultural workers, and pest control operators. The majority (approximately 60%) of use sites labeled for treatment by pressurized hand-wand spraying are indoor use sites (e.g., food handling and food processing facilities, livestock production, and mushroom houses) while approximately 20% are outdoors (such as outdoor wood surfaces, cooling towers, and exterior hard surfaces). Approximately 20% of the use sites could be either indoors or outdoors such as livestock housing, wood

preservation, and mold control." (V1:13-14)[1]

Note: The AEATF II's protocol was developed pre-COVID-19 and at the time, the following was the industry practice for applying disinfectants: "*Schools, hospitals, nursing homes, medical facilities, day care facilities, restaurants, hotels, offices, and similar public institutions are not designed or constructed for wet cleaning so the application of antimicrobials with spray wands is not normally used, although under certain circumstances a pressurized wand-spray treatment could take place when vacant (for example mold remediation). These establishments rely on mopping, trigger sprayers, aerosol cans, and RTU-wipes for cleaning and sanitizing/disinfection."* (V1:24) However, post-COVID-19 there is greater interest in using electrostatic sprayers in hospitals, nursing homes, etc. *"Electrostatic spraying has played a minor role in conventional pesticide and antimicrobial applications for decades, in part due to the high cost of this type of technology; however, the use of electrostatic sprayers has been brought to the forefront in the last few months as a result of the COVID-19 pandemic. There is now an urgent need to quickly, efficiently, and economically sanitize and/or disinfect large areas with hard and soft surfaces in commercial and institutional settings in a safe manner that will allow for rapid reentry. The use of electrostatic sprayers to dispense antimicrobial solutions is gaining popularity because these sprayers use less solution, can be applied faster, and have improved droplet spatial deposition than standard sanitizing methods such as trigger sprayers, RTU wipes, and conventional pressurized hand-wand sprayers."* (ESS Addendum:7)

In this study, the AEATF II is sub-dividing the hand-wand application techniques/circumstances into 3 main exposure scenarios which are referred to herein as outdoor, indoor "dry", and indoor "wet". The outdoor scenario is further subdivided into two separate scenarios: occupational and consumer. The subdivision of these scenarios are further described below and numbered throughout the document as Scenarios 1a, 1b, 2a, 2b, 3a, and 3b. Subjects recruited for this study will be from populations with occupational experience with these application techniques (including experience with electrostatic sprayers) as well as consumers with experience using hand-wand sprayers. The second scenario, indoor "dry" is subdivided by hand-wand vs electrostatic sprayers. The third scenario, indoor "wet" is also subdivided for hand-wand sprayers to distinctly capture differences in dermal exposures from baseline clothing attire versus those attributed to wearing personal protective equipment (PPE). Once the study is completed, each scenario will be represented by its own set of inhalation and dermal unit exposures. The AEATF II defines each of the three main scenarios as the following: *"…the pressurized hand-held wand spraying study will be divided into three key exposure/use groupings: (1) outdoor spraying of exterior hard surfaces; (2) indoor surface spraying of hard porous surfaces (e.g., wood and drywall) in use sites that are typically dry; and (3) indoor environmental sanitizing/disinfecting spraying of hard non-porous surfaces (e.g., stainless steel and painted concrete) in use sites where the surfaces and environment are*

[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. AEATF II's studies include Volumes 1 through 4; plus "ESS Addendum" referencing the electrostatic sprayer design.

typically wet when sanitizers are sprayed. This grouping captures the majority of use sites/use patterns for antimicrobials that are applied by pressurized hand-held spraying." (V1:30). The ESS Addendum proposes to further subdivide Scenario 2 to capture the electrostatic sprayers as a separate set of unit exposures. A summary of the design of the three scenarios are as follows:

- **Scenario 1: Outdoor spraying** – Two separate sets of unit exposures will be developed for the outdoor spraying, one for consumers and one for occupational workers. The design of this scenario is characterized as "*…outdoor applications to hard exterior surfaces such as siding and sidewalks, would be done by generating two sets of exposure data, one using consumers* [Scenario 1a] *applying with manually-powered hand-held tank and hose-end sprayers and another set with professionals* [Scenario 1b] *using mechanically-powered wand-type portable spray units (on wheels or truck-mounted)."* (V1:30).

- **Scenario 2: Indoor spraying (dry environments)** - The design of this scenario is characterized as [Scenario 2a] "*…indoor applications to dry areas will include a mixture of manually powered hand-held tank and backpack sprayers. These applications will simulate indoor surface applications to hard porous surfaces in locations that are typically dry such as attics, crawlspaces, interior living spaces, and commercial indoor areas. Antimicrobial products used in this manner are primarily fungi/mold prevention and remediation products and sanitizers/disinfectants used by the pest management industry or janitors."* (V1:30).

  For the electrostatic sprayers [Scenario 2b], *"Subjects will be told to spray the surfaces as they normally do; there will be no instruction on how to use the sprayer or how long to spray in a given room. The dimensions of each treated room will be recorded along with the start and end time of spraying within each room. The total volume of spray solution applied during the ME will be measured and recorded in the field notebook, and the duration of each monitoring event will be recorded.*" (ESS Addendum:12). The reader is referred to the electrostatic sprayer ESS Addendum to get a better understanding on how these sprayers work and the types of sprayers available in the marketplace [see "*Electrostatic Spraying Theory and Spray Equipment*" (ESS Addendum:6-11)]. In summary, this study will provide test subjects with six different electrostatic sprayers and allow the subjects to choose among them. To gain diversity, "*…a minimum of 3 MEs will be conducted with each brand … with at least three MEs done using a backpack sprayer and three MEs using a cart sprayer. Subjects using sprayers with 3-in-1 nozzles will be allowed to choose between the small and medium spray setting, but not the largest. This will be done to bias the study towards the smaller droplet sizes."* (ESS Addendum:11)

- **Scenario 3: Indoor spraying (wet environments)** - Two separate sets of unit exposures will be developed for the indoor spraying (wet), one for baseline clothing attire (Scenario 3a), which is defined as no additional protective clothing/no gloves worn over the whole-body dosimeters but wearing a hard hat, protective eyewear, and respiratory protection (covering a portion of the face for the dermal exposure

monitoring). The second set of unit exposures (Scenario 3b) is based on PPE with the subjects wearing rain pants and rain jacket over the whole-body dosimeters, rubber boots, hard hat, chemical resistant gloves, protective eyewear, plus respiratory protection (covering a portion of the face for the dermal exposure monitoring). The design of this group is characterized as *"…a mixture of mechanically-powered wand-type portable spray units (on wheels or carts) and in-line Venturi-injection utilizing wall-mounted hook-ups. This scenario represents environmental sanitizing/disinfecting spraying and spray practices commonly done in wet environments as part of an overall cleaning procedure… in such locations as food and beverage processing and packaging facilities, animal housing, and livestock production… To simulate actual use conditions, the surfaces will be sprayed with water prior to the test subjects being monitored to create a wet and humid environment."* (V1:30-31).

The study location (Scenarios 1 & 2 will be conducted in FL and Scenario 3 in WI) and test sites are described in the protocol as follows: "*Each scenario will take place in one geographic location. The use of a single geographic area and location is based on the premise that pressurized hand-wand spraying being performed at a site in one geographical area will not differ substantially spraying being performed at sites in another geographical area. The variation in exposure associated with pressurized hand-wand spraying inside or outside of a building in one location would not be expected to differ substantially from any other location across the country. This premise is supported by the Popendorf et al. (1992) antimicrobial exposure monitoring study that concluded that variability in dermal and inhalation exposures across workers was primarily influenced by the application method and, by implication, each individual worker's implementation of that application method (i.e., their work practices and behavior), rather than the location or setting in which the application method is performed. This implies that monitoring multiple subjects and capturing diversity in pressurized hand-wand spraying techniques that might influence exposure is more important than geographic or site diversity."* (V1:39).

EPA intends to use these data developed by the AEATF II for the hand-wand and electrostatic sprayers to characterize typical consumers' and occupational handlers' daily exposure to antimicrobial formulated products used as sanitizers, disinfectants, algaecides, etc. in both outdoor and indoor settings when applied to hard surfaces.

EPA believes that the AEATF II hand-wand and electrostatic sprayer scenarios are well defined, though some recommended revisions that are provided below, and expects that the resulting data will meet the needs of regulatory agencies. The diversity of daily exposures as defined in this proposal will adequately describe typical to high-end consumer and occupational daily exposures to the antimicrobial applications. The use of both consumer and occupational workers as test subjects is representative of the use patterns based on the equipment types. The hand-wand and electrostatic sprayer exposure data, normalized by AaiH, will be used by EPA to extrapolate to the likely exposure expected from future events of applying antimicrobial products to hard surfaces.

2. **Sampling Design:** The AEATF II has described in detail their sampling design for the three hand-wand sprayer scenarios (and subsets of consumer vs. occupational, hand-wands

vs. electrostatic sprayers, and with and without PPE) 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 application of antimicrobial products to hard surfaces in various indoor and outdoor settings.

The proposed sample size is a total of 108 monitoring events (MEs) distributed among the three "main" scenarios which are further subdivided by consumers vs. occupational, electrostatic sprayers, and baseline PPE vs PPE (i.e., 18 MEs per sub-scenario; see Table 2 below for specifics). The plan is to use 18 individual test subjects for each sub-scenario (use of the same subject for multiple scenarios is allowed only for scenario 3 (V2:47)) recruited from a population of consumers and occupational workers who had relevant experience within the last 1 year (consumer) and 2 years (occupational) (V1:41-42). Subjects recruited for electrostatic sprayers will be experienced applicators, but the level of experience is not specified. 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 planned sample size is discussed in more detail below.

The study is being designed to be scripted in such a manner as to encompass the diverse set of conditions that will impact exposure, an approach that has been defined within the AEATF II Governing Document as purposive diversity sampling. The diversity is being achieved using a range of application equipment for each scenario. Within the basic selection of equipment, the subjects will be allowed to choose which ones they are more apt to use. The test substance in the formulated product will be diluted from concentrate, measured, and poured into the application equipment by the researcher for each scenario, rather than by the test subjects. This phase of the application is not being monitored in this study because the formulation type for future use of these data could be liquid, powder, or granules and the addition into the sprayers could be open pouring or automated systems (V1:26). Exposure data for the open pouring of these formulation types are available from prior AEATF II exposure studies. The following is a description of the planned diversity in the design of each scenario:

- **Outdoor spraying** – Two separate unit exposures will be developed under the outdoor spraying scenario: one for consumers and one for "occupational" (i.e., professional/commercial). The test subjects in the consumer group will use *"…manually-powered hand-held tank and hose-end sprayers and another set with professionals using mechanically-powered wand-type portable spray units (on wheels or truck-mounted). The manually-powered sprayers* [consumers] *dispense product a short distance from the user and are designed to apply product in a targeted manner to small areas. The mechanically-powered units* [occupational] *have a bigger throw distance and are used to treat larger areas and high surfaces such as siding on the sides of commercial buildings or awnings or agriculture premises (such as barn, coops, and animal runs). The direction of spray for this scenario* [consumers and occupational] *would be downward to sidewalks, to vertical surfaces such as fences and*

siding, and upward to reach tall vertical surfaces such as siding on a warehouse." (V1:30) The subjects will be told to spray/treat the surfaces "*as they normally would"* (V2:20)

- **Indoor spraying (dry environments)** – Two sets of unit exposures will be developed for the indoor spraying scenario using occupational test subjects. The first set of unit exposures will be based on "…*indoor spray applications to dry areas and will be done in an indoor environment designed to mimic indoor residential or commercial spaces and/or crawl spaces. Rooms with shelves and/or cabinets to simulate bathrooms and kitchens will be included, and the interior of cabinets will be sprayed. Items such as lockers will also be sprayed. Subjects will be allowed to choose from a mixture of manually powered hand-held tank and backpack sprayers and battery-powered backpack sprayers. These applications will simulate indoor surface applications to hard porous surfaces in locations such as attics, crawlspaces, interior residential and commercial spaces. Antimicrobial products used in this manner are primarily fungi/mold prevention and remediation products as well as sanitizers/disinfectants."* (V2:20). The test subjects will select from "…*a mixture of manually-pressurized hand-held tank sprayers as well as manual piston-operated and battery-operated backpack sprayers"* (V2:17).

  The sampling design of the electrostatic unit exposures has target spray volumes between 0.5 and 3 gallons. "*As an upper-end use scenario, it is assumed that a worker will sanitize 70 hotel rooms, 300 sq ft per room, per day. This is equivalent to 21,000 sq ft. Using the output of 130 ml/min and 18,000 sq ft treated per hour from the Clorox Total 360 Cart Sprayer website, this is equivalent to spraying approximately 0.014 fl oz/sq ft and would require around 294 fl oz (~2.25 gallons). Using this, the target maximum spray volume for cart and backpack sprayers is 2.25 gallons. For the hand-held sprayers that hold 32 fl oz (0.25 gallons) the target maximum volume sprayed will be 2 gallons (8 refills). The smallest hand-held spray, the EMist EPIX360 only holds 8 fl oz and will be used only in the smallest stratum (target of 0.5 gallons) which would require it to be refilled 8 times."* (ESS Addendum:12). In a revised submission, AEATF II revised the target maximum spray volume from 2.25 gallons to 3 gallons for the cart-mounted unit (AEATF 2020).

  "Although there are several different types and brands of electrostatic sprayers on the market, they all operate in a fundamentally similar manner, have similar tank capacities based on whether they are hand-held or backpack/cart-mounted, and have a similar range of mean particle size and spray output (with the exception of the largest nozzle in the 3-in-1 nozzles). Because of this, the actual brand of sprayer used and whether it is a hand-held, backpack, or cart-mounted unit is expected to be less of a determinant of exposure potential than the individual worker's spray practices and behavior. For this reason, all electrostatic sprayers will be grouped together in one scenario.

  There will be a selection of six electrostatic sprayers … available for the test subjects to choose from. This will allow subjects to use the sprayer that they are most familiar

with. In case a subject is not familiar with the specific brands and models of sprayers available for use in the study, the equipment user guides will be available.

The following is a list of the electrostatic sprayers targeted to be used in this monitoring scenario. Because of the high demand for these sprayers during the COVID-19 pandemic, it may not be possible to obtain all the desired sprayers. However, a minimum of four different sprayers (a minimum of two hand-held, one backpack, and one cart) will be purchased for the study.

Hand-Held, EMist EPIX360, Victory VP200ES

Backpack, EMist EM360, Victory VP300ES

Cart-Mounted, EMist EM360, ByoPlanet/Clorox Total 360 Electrostatic Sprayer

To make sure that there is a variety in the spray equipment used in this scenario, people who respond to the recruitment ads will be asked what type and brand of electrostatic sprayer they normally use and this will be used to ensure that potential participants do not all spray the same piece of equipment. To ensure that this scenario represents the range of available electrostatic sprayers, a minimum of 3 MEs will be conducted with each brand (ByoPlanet/Clorox, EMist, and Victory), with at least three MEs done using a backpack sprayer and three MEs using a cart sprayer.

Subjects using sprayers with 3-in-1 nozzles will be allowed to choose between the small and medium spray setting, but not the largest. This will be done to bias the study towards the smaller droplet sizes." (ESS Addendum:10-11). However, there is no mention on whether the electrostatic sprayers will be switched to the "on" position (EPA recommends that the researchers check at the beginning of the ME to make sure the sprayers are switched on to enable the electrostatic spraying function).

- **Indoor spraying (wet environments)** – Two separate unit exposures will be developed under the indoor spraying (wet environments) scenario: one for occupational subjects wearing "baseline" clothing attire and one for occupational subjects wearing "PPE". The sprayer equipment in this scenario for both sets of clothing attire include: *"…a mixture of mechanically-powered wand-type portable spray units (on wheels or carts) and in-line Venturi-injection utilizing wall-mounted hook-ups. This scenario represents environmental sanitizing/disinfecting spraying and spray practices commonly done in wet environments as part of an overall cleaning procedure. The wet and humid environment, hard non-porous surfaces combined with the ability to apply higher spray volumes than in dry environments reflects treatment in such locations as food and beverage processing and packaging facilities, animal housing, and livestock production, and is expected to result in a different exposure potential than grouping 2* [i.e., indoor spraying (dry environments)]. *To simulate actual use conditions, the surfaces will be sprayed with water prior to the test subjects being monitored to create a wet and humid environment."* (V2:21)

The AEATF II proposes to monitor six MEs per three differing amounts of spray volumes (gallons) and three concentrations of the test substance in each of the scenarios as

outlined in Table 2 below (except for Scenario 3a where two instead of three concentrations of the test substance will be used). EPA has determined that based on the proposed ranges of volumes and concentrations (and hence the amount of active ingredient handled (AaiH), there is sufficient power (at least 80%) to detect proportionality of AaiH and exposure given the sample size for most scenarios except for Scenarios 1a and 2a where the power is estimated to be 75% (see Table 2).

3. Choice of Surrogate Material: The active ingredient to be used in this study is the quaternary ammonium compound, commonly known as "Quats". Specifically, alkyl dimethyl benzyl ammonium chloride (ADBAC) C-14 carbon length side chain will be analyzed on the sampling matrices as the surrogate compound (CAS number 139-08-2). ADBAC has a low vapor pressure (3.5E-12 mmHg @ 25 °C). Two EPA-registered products containing Quats will be used this study, Maquat® 5.5-M (EPA Registration Number 10324-81) and Maquat® 7.5-M (EPA Registration Number 10324-81). From these two master labels, the researchers will use distributor labels/sub-registrant labels as outlined in Table 1. The master labels are referred to throughout this review. The composition of the ADBAC Quat in the formulated products is 50% C_{14}, 40% C_{12}, and 10% C_{16}. (V2:37). The C_{14} chain of ADBAC was also used as the surrogate compound in previous AEATF II exposure studies (liquid pour, aerosol can, and immersion/dip/soak).

Table 1. Test Substance and Registered Products for the Hand-Wand and Electrostatic Sprayer Study

Monitoring Scenario	Test Substance Master Label	Sub-registrant Label
1a & 1b (outdoor spraying)	Maquat 5.5-M EPA Reg. No. 10324-80 5.5% quaternary ammonia	Nisus DSV EPA Reg. No. 10324-80-64405 5.5% quaternary ammonia
2a (indoor spraying, dry environment)	Maquat 5.5-M EPA Reg. No. 10324-80 5.5% quaternary ammonia	Nisus DSV EPA Reg. No. 10324-80-64405 5.5% quaternary ammonia
2b (indoor spraying, dry environment, ESS)	Maquat 5.5-M EPA Reg. No. 10324-80 5.5% quaternary ammonia	Nisus DSV EPA Reg. No. 10324-80-64405 5.5% quaternary ammonia
3a & 3b (indoor spraying, wet environment)	Maquat 7.5-M EPA Reg. No. 10324-81 7.5% quaternary ammonia	4Quat EPA Reg. No. 10324-81-82882 7.5% quaternary ammonia

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 the three groupings for the hand-wand and electrostatic sprayer use patterns (resulting in six sets of unit exposures). 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 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 will be considered."* (V2:76).

Table 2 shows the AEATF II proposed target spray volumes and concentrations of the test substance. Table 3 shows the estimated fold relative accuracy values for each scenario and exposure route. Note that under any of the proposed options given in Table 2 below, using the assumed geometric standard deviations tabulated in Table 3, the fold relative accuracy goals are estimated to be met for inhalation exposure and to almost be met (maximum fold relative accuracy 3.08) for dermal exposure. The accuracy of these estimates depends upon the representativeness of the results of the manually-pressurized backpack sprayer greenhouse exposure study that were used for the geometric standard deviations. The details of these fold relative accuracy calculations are given below in Attachment 2, section 2.1(a) and section 2.1(i).

Table 3 also shows the estimated statistical power for detecting proportionality for each scenario and exposure route. The goal of 80% power is estimated to be almost met for every scenario. Exceptions are a minimum estimated power of 75% for dermal exposure in Scenario 1a and an estimated power of 75% for dermal exposure in Scenario 2a. The details of these power calculations are given below in Attachment 2, section 2.1(i). Values are rounded to 2 decimal places.

Table 2: Stratification of Key Parameters within each Monitoring Scenario

Scenario	Target Spray Volume (gallons)	Anticipated Spraying Duration[5]	Target Total Quat Concentration (ppm)	Number of MEs
1a. Outdoor spraying, consumers[1]	2 (20)[4]	10 min	215	6
	4 (40) [4]	20 min	430	6
	6 (60) [4]	30 min	860	6
1b. Outdoor spraying, occupational[2]	40	10 min	215	6
	80	20 min	430	6
	160	40 min	860	6
2a. Indoor spraying, dry environments[3]	2	10 min	215	6
	4	20 min	430	6
	6	30 min	860	6
2b. Indoor spraying, electrostatic sprayers	0.5	15 - 30 min	215	6
	1	30 - 60 min	430	6
	2 (hand-held) 3 (backpack or cart)	60 - 120 min	860	6
3a. Indoor spraying, wet environments, baseline PPE[2]	20	5 min	100	6
	40	10 min	400	6
	80	20 min	400	6
3b. Indoor spraying, wet environments, full PPE[2]	20	5 min	290	6
	40	10 min	580	6
	80	20 min	1160	6

[1] Based on manually-pressurized nozzle output of 0.25 gal/min and hose-end sprayer of 2 gal/min

[2] Based on mechanically-pressurized nozzle output of 4 gal/min

[3] Based on manually-pressurized nozzle output of 0.25 gal/min

[4] First number is the target volume of spray solution applied by manually-pressurized nozzle; number in parentheses is the target volume of spray solution applied by hose-end sprayer

[5] Spray durations are approximate, ME durations will be based on how long it takes to spray the target spray volumes

Table 3: Fold Relative Accuracy and Statistical Power for each Monitoring Scenario

Scenario	Dermal Exposure			Inhalation Exposure		
	Geometric Standard Deviation[1]	Fold Relative Accuracy for Mean, P95	Statistical Power[2,3]	Geometric Standard Deviation[1]	Fold Relative Accuracy for Mean, P95	Statistical Power[2,3]
1a. Outdoor spraying, consumers	4.64	3.08, 3.03	0.75 to 0.96	2.63	1.75, 2.01	0.99 to 1.00
1b. Outdoor spraying, occupational	4.64	3.08, 3.03	0.83	2.63	1.75, 2.01	1.00
2a. Indoor spraying, dry environments	4.64	3.08, 3.03	0.75	2.63	1.75, 2.01	0.99
2b. Indoor spraying, electrostatic sprayers	4.64	3.08, 3.03	0.83 to 0.92	2.63	1.75, 2.01	1.00 to 1.00
3a, Indoor spraying, wet environments, baseline PPE	4.64	3.08, 3.03	0.86	2.63	1.75, 2.01	1.00
3b, Indoor spraying, wet environments, full PPE	4.57	3.02, 3.00	0.84	2.63	1.75, 2.01	1.00

[1]Geometric standard deviations from Mixer/Loader/Applicator, Manually-pressurized Backpack Sprayer greenhouse exposure study (MRID 43623202, Study Design Document, page 35)

[2]For scenario 1a, the statistical power values depend upon the assumed probability p that a consumer prefers to use the hose-end sprayer instead of the manually pressurized sprayer. The range of estimated power values for different values of p is shown.

[3]For scenario 2b, the statistical power values depend upon the assumed probability p that a worker prefers to use the hand-held sprayer instead of the backpack or cart-mounted sprayer. The range of estimated power values for different values of p is shown.

2. **Proposed pattern of human exposure:** The test substance in the formulated product will be added to the treatment solution and into the sprayers by the researchers (not the test subjects) because formulation types can vary (i.e., liquid, powder, granule) and open pouring data are available from previous AEATF II exposure studies (plus some of the sprayers are loaded automatically in closed systems). The prepared treatment solution will be used by subjects according to typical use practices for the particular scenario. The pattern of exposure will be based on the subject's experience conducting the tasks as designed in the scenarios (described above) and the influences each subject brings as they work "*as they normally would do*". The researchers indicate the following:

Outdoor spraying: *"Subjects will be told to spray the various outdoor surfaces, which will include vertical and horizontal surfaces, as they normally would. Subjects will not be allowed to rinse the treated surfaces with water as this could potentially remove residues from the subjects. At the end of the monitoring period, subjects will not clean out their spray equipment as this has the potential to remove residues from their hands."* (V2:20)

Indoor spraying (dry environments): *"Subjects will be told to spray the various indoor surfaces (floor, walls, ceilings, cabinets) as they normally would. Subjects will not be allowed to rinse the treated surfaces with water. At the end of the monitoring period, subjects will not clean out their spray equipment as this has the potential to remove residues from their hands."* (V2:21)

For the electrostatic sprayer scenario, *"Subjects will be told to spray the surfaces as they normally do; there will be no instruction on how to use the sprayer or how long to spray in a given room."* (ESS Addendum:12)

Indoor spraying (wet environments): *"Subjects will be told to spray the various indoor surfaces (floors, walls, and equipment) as they normally would. At the end of the monitoring period, subjects spraying from point-of-use Venturi-injection units will simply turn off the wall-mounted valve. Subjects spraying from portable spray units will not clean out their spray tanks as this has the potential to remove residues from their hands."* (V2:20)

Subjects in scenarios 1 and 2 (outdoor and indoor spraying (dry environments)) will wear baseline clothing attire, which is defined as long-sleeved shirt, long pants, shoes & socks, protective eyewear, and no gloves. The scenario 3 subjects are split into two separate sets of clothing attire to represent baseline and PPE. The subjects in the baseline attire will be wearing long-sleeved shirt, long pants, shoes & socks, protective eyewear, hard hat, no gloves, and a respirator. The subjects in the PPE attire will be wearing long-sleeve shirt, long pants, rain pants and rain jacket, rubber boots, hard hat, chemical resistant gloves, protective eyewear, and a respirator. (V1:38)

The duration of each of the MEs will be based on how long it takes to complete spraying of the assigned volume of spray.

The EPA believes that the design of the AEATF II hand wand and electrostatic sprayer scenarios will represent the middle and upper portions of the daily exposure distribution expected for consumer and occupational workers applying antimicrobial products (e.g., sanitizers/disinfectants/algaecides/mold remediation/etc.) to hard surfaces, food processing equipment, etc.

3. **Endpoints and Measures:** The AEATF II proposes to measure dermal and inhalation exposures resulting from spraying with a hand wand. Dermal and inhalation exposure will be measured using whole-body dosimeters (WBD) (inner and outer), head patches, face/neck wipes, hand wipe/washes, and personal air monitors. (V2:63-65) 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 exposures to the feet are low (but not as low as some of the other previously monitored scenarios) but will not be monitored. The hand and face/neck wipe/wash are an appropriate method to determine exposure to the hands and face/neck. Two personal air samplers will be used to collect residues from the breathing zone with the sampling cartridges facing downwards (mimicking nostrils). An OSHA Versatile Sampler (OVS) "*…(SKC Catalog Number 226-30-16 containing a glass fiber filter and 270/140 mg sorbent beds, 13 mm diameter x 75 mm length)…"* will be used to collect inhalable particles. Additionally, "*Parallel Particle Impactor (PPI) (SKC Catalog # 225-3851) containing a 37 mm PVC filter and 37 mm support pad will be used to collect respirable residues."* (V2:63) Flow rates will be approximately 2 L/min for each of the samplers. (V2:63)

"Air temperature and relative humidity of the work area for the duration of exposure monitoring will be recorded with automated instrumentation at a minimum of 15-minute intervals for the duration of the work period. During the outdoor monitoring wind speed and direction will be collected. Environmental monitoring equipment will be calibrated or standardized according to field facility SOPs. The type and location of any HVAC system and whether it is operating will be documented in the raw data. A facilities maintenance engineer with HVAC training or an industrial hygienist will measure the airflow in the test room(s) and record the direction of airflow. The dimensions and layout of the room(s)/building(s)/surfaces(s) and the relative position of the test subjects with respect to them and the airflow direction will be documented in the raw data for each test site." (V2:61)

"The total time spent conducting the work activities will be documented for each ME." (V2:60)

"The volume of sanitizing solution used by each ME will be measured and documented. For the manually-pressurized hand-held and backpack sprayers, battery-powered backpack sprayers, and the mechanically-pressurized portable sprayers this will be done by measuring how much solution is poured into the tank at the beginning of the ME and how much is left at the end of the ME. For the hose-end sprayer, a flow meter will be placed at the faucet so that the total gallons sprayed can be documented. In addition, the starting and ending volumes of test substance in the reservoir attached to the sprayer end of the hose will be documented. To measure how much spray solution is applied using the in-line Venturi-injection system, a flow meter will be attached to the hose to measure total gallons sprayed. Additionally, the starting and ending amount of test substance in the concentrate container will be measured and recorded. Details of the spray equipment such as model/brand, spray pressure, tank capacity, hose or wand length, hose diameter, and nozzle/tip/gun type and model will be recorded." (V2:60-61)

"*The dimensions of each treated room will be recorded along with the start and end time of spraying within each room. The total volume of spray solution applied during the ME will be measured and recorded in the field notebook, and the duration of each monitoring event will be recorded."* (ESS Addendum:12)

4. **QA/QC Plan:** The study will be conducted under the FIFRA GLP Standards (40 CFR 160) (V2:79). The AEATF II QA/QC plan for the hand wand sprayer 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 are described in SOP AEATF II-8E. In summary, field samples are to be processed at a minimum of three times for each scenario. Triplicate samples will be prepared at each of the fortification levels outlined below. Fortified samples will be exposed to ambient conditions for the duration of exposure. Field recovery samples will be 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. Control (blank) samples for each matrix will also be processed with the field recovery samples.

Table 4: Field Recovery Targets

Matrix	Target Field Fortification Level (C_{14}-ADBAC)	LOQ (C_{14}-ADBAC)
OVS Tubes	3, 30, and 100 µg/tube	1 µg/tube
37 mm PVC filter	0.5, 5, and 50 µg/filter	0.1 µg/filter
Hand Wash*	100, 1,000, and 10,000 µg/sample 10 and 100 µg/sample**	1 µg/sample
Face/Neck Wipe	100 and 1000 µg/sample	10 µg/sample
Inner Dosimeter	30, 3000, and 30,000 µg/sample	10 µg/sample
Ball Cap	1,000 and 10,000 µg/sample	100 µg/sample
Inner Hat Dosimeter	50 and 500 µg/sample	1 µg/sample

*Sample volume is 500 mL
**Scenario 3b (Indoor spraying, wet environmental, PPE)

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. Each combination of scenario and exposure route will be separately analyzed by EPA. Since each scenario is stratified into three groups based on the combination of volume and concentration (six groups for scenario 1a), we will compare the group geometric means using analysis of variance. Most of the following analyses will use all 18 MEs in a scenario, and the results of those analyses will not be stratified by group, due to small sample sizes (6 MEs), unless useful patterns are found. For scenario 1a, we will use analysis of variance to compare the geometric means between the hose-end and manually pressurized back-pack sprayer, but otherwise we will not stratify the analyses of scenario 1a by the sprayer type unless useful patterns are found. For scenario 2b, we will use analysis of variance to compare the geometric means between the hand-held, backpack,

and cart-mounted sprayers, but otherwise we will not stratify the analyses of scenario 2b by the sprayer type unless useful patterns are found.

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 (pounds) of active ingredient handled (AaiH). 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 AaiH, has the same log-normal distribution for all 18 MEs. The fitted model will be used to estimate the arithmetic means, geometric means, and 95^{th} percentiles of the normalized exposure overall, and 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. 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. As previously recommended by the HRSB we will also evaluate models using the gamma distribution, with a much more flexible set of distributional shapes, instead of the log-normal distribution. These alternative models will be compared graphically using scatter plots of the predictions and will also be compared statistically using the Akaike Information Criterion.

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). If the width of the confidence interval is more than 1.4, then this implies that the post-hoc power to detect proportionality is less than the benchmark power of at least 80% calculated in Table 3 (except for dermal exposure in two scenarios where the estimated power was 75%), suggesting that the study was underpowered because the geometric standard deviation (GSD) was underestimated.

The main statistical modeling will substitute values below the limit of quantitation (LOQ) by half the LOQ, but the results will be compared with alternative approaches for censored data such as the maximum likelihood method. 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 AaiH showing the fitted regression models, 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). We will evaluate the potential impacts of adding some other measured explanatory variables to the statistical models by examining plots of the residuals against those explanatory variables if those variables can be controlled for on the label; these analyses will be most useful in cases where those extra variables can be practically regulated on a pesticide label.

Finally we will evaluate the potential for bias and uncertainty in scenarios 3a and 3b if some subjects are in both scenarios. Bias might occur if those subjects “learn” from their previous ME and there will potentially be additional uncertainty caused by within-subject correlations. Using all the data from scenarios 3a and 3b, we will fit regression models

for the logarithm of exposure against the logarithm of AaiH where the intercepts and slopes depend upon the scenario and there is a random subject effect as well as the random error term. We will also examine scatter plots of log exposure versus log AaiH where each point is labeled by the scenario and the subject ID.

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 researcher needs to make sure that the electrostatic sprayers are "turned on" (for the sprayers that have such an option) so that they are operating during the monitoring event (some sprayers will still spray when the electrostatic option is turned off, some sprayers do not have an option to be sprayed without the electrostatic function).
- Researchers need to specify how much experience is needed for the subjects using the electrostatic sprayers (the design document notes that subjects need to be experienced in using this type of equipment but no criteria for how much experience is provided (months?, years?)).
- The protocol notes that the subjects will not be provided instructions on how to use the electrostatic spray equipment. Instead, "*In case a subject is not familiar with the specific brands and models of sprayers available for use in the study, the equipment user guides will be available.*" (ESS Addendum:10-11). Nonetheless, if subjects specifically ask the researchers about the operation of the equipment, what type of instructions, other than the user guides will be provided (e.g., user guides might be insufficient to safely operate the ESS if it is a model unfamiliar to the subject)?
- The researcher should clarify the instructions to be given to the subjects to ensure that the target volumes are (approximately) met in each scenario, e.g., spray until the tank is empty, or spray a certain number of loads.

- The increase in the total Quat concentration above 400 ppm (as noted in AEATF 2020) in any of the scenarios that involve food contact surfaces (e.g., Scenario 3b) now need to be subsequently rinsed with a potable water rinse (PWR) per label directions.
- The statistical power to detect proportionality between AaiH and exposure is estimated to be 75% for scenarios 1a and 2a. EPA recommends that we work with the AEATF II to increase the power to at least 80% by increasing the spread of the concentration to be applied (note: increasing the maximum concentration will need to be within the label's maximum rate as well as within the acceptable margin of exposure (MOEs)).
- The AEATF II has demonstrated in many previous studies using ADBAC as the surrogate test compound that for the inhalation samplers, aerosols and not vapors are collected in the OVS samplers (as one would expect with such a low VP chemical). EPA would accept if the AEATF II wants to combine the glass filters with the two adsorbent sections when analyzing the OVS tubes.
- The study is designed to incorporate diversity and it captures many sources of variation in exposure from hand-wand spraying activities (e.g., different types of sprayers, different spray pressures, different spray volumes, different environments, different PPE, different workers, etc.); however, not all plausible sources of exposure variation have been accounted for in the design (e.g., mushroom houses, etc.). Therefore, the study captures a sufficient range of exposure conditions, but is not likely to cover the full range of variation that is expected to exist.

E. Summary Assessment of Ethical Aspects of the Proposed Research

This section summarizes EPA's evaluation of the ethical aspects of the proposed study based on the 4-volume submission from the AEATF II dated March 20, 2020, as well as the following additional documents:

- ESS Study Scenario Addition to Study AEA14 06_02_2020
- AEA14 Updated Test Substances and Rate 6_17_2020
- Email exchange between Advarra IRB and EPA
- Rosenheck Protocol Approval with Modifications Notice Feb2520 - Revised Jun1620

This summary assumes that all relevant documents are amended to address all of EPA's comments as outlined in Section F below. Details supporting EPA's assessment are in Attachments 2-6.

1. **Societal Value of Proposed Research:** The purpose of this study is to "*develop new data for evaluating potential dermal and inhalation exposures of consumers and/or professional workers who conduct manual pressurized hand-wand spraying of antimicrobials such as sanitizers, disinfectants, and fungicides/mildewcides using manually or mechanically-pressurized hand-wand spray equipment."* (V2:10) In addition, recognizing the increased use of electrostatic sprayers to disinfect indoor spaces in light of the outbreak of SARS-CoV-2, the virus that causes COVID-19, the AEATF II proposes to include an additional scenario that "*will measure exposure to workers spraying antimicrobial products indoors using electrostatic sprayers*." (ESS Addendum:2). 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. Additional dermal and inhalation exposure

data are needed to accurately characterize the exposure potential for consumers and occupational users applying antimicrobial pesticides using these methods. EPA will use this data in evaluating antimicrobial products applied using these methods.

2. **Subject Selection:** A total of up to 108 subjects will be required to conduct the study – 18 subjects per scenario. An additional 4 individuals per scenario will be recruited as alternate subjects, and enrolled if a subject becomes ineligible or withdraws from the study. Monitoring for scenarios 1a, 1b, 2a, and 2b will occur in Florida. Subjects are eligible to participate in only one of these scenarios. Monitoring for scenarios 3a and 3b will occur in Wisconsin. Subjects participating in these scenarios may participate in one or both if interested "*because of the anticipated difficulty in locating and recruiting people who have the specialized experience with the spray equipment used in food processing facilities*," (V2:47) so it is possible that fewer than 36 individuals will be needed to complete all monitoring events for scenarios 3a and 3b. All monitoring events will be held in a major metropolitan area to draw from a large, diverse, and experienced pool of candidates.

   Recruitment is discussed in section XV of the protocol (V2:48-50). Candidates will be recruited through newspaper advertisements and radio spots, run in English and Spanish. If necessary, additional recruitment will be conducted through online job posting websites and social media. The recruitment materials/advertisements will be run for a 7-day period. At the end of that period, if an insufficient number of candidates have been prequalified, the advertisements will be renewed and will run until a sufficient number of prequalified candidates has been achieved. meetings. The recruitment efforts in two languages and using 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 candidates with experience conducting the tasks to be monitored. The rationale for restricting subjects to those with experience is to ensure that the subjects are familiar with the tasks to be conducted. According to the protocol, the "a*dvertisements will contain a short description of the study and the scenario of interest, 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, or bilingual recruiter*." (V2:48) The protocol calls for making three attempts to contact each candidate who expresses interest in learning more about the study. Callers responding will be screened in either in English or Spanish. The phone screening will include a brief description of the study, and determine whether the candidate has sufficient experience doing the task(s) to be monitored and the candidate's age. Candidates for scenarios 3a and 3b will be asked whether they want to participate in one or both of the scenarios. Pre-qualified candidates will be invited to the study center for a consent meeting.

   The inclusion/exclusion criteria in the study protocol are as follows, with EPA's recommended additions in red:

   Inclusion Criteria

All scenarios

- Males or females at least 18 years old as verified by a government issued photo ID
- Willingness to sign the Informed Consent Form and the Subject Qualification Worksheet
- Speak and read English or Spanish
- Non-smoker or willing to refrain from smoking for the duration of the testing period

For the consumer outdoor scenario (1a):

- Self-identified as being in good health as defined as able to do the following tasks: lift and carry a hand pump spray tank containing up to 2 gallons of solution (~16 pounds) or a hose-end sprayer, walk the exterior of a large building while spraying various surfaces, including surface above shoulder height; spray up to 6 gallons (or 60 gallons with a hose-end sprayer).
- Have experience using a manually-pressurized hand-held tank sprayer (also called a manual pump-up sprayer) or a garden hose-end sprayer to sanitize/disinfect or remove mildew, mold, algae, or bacteria from exterior hard surfaces such as brick, siding, sidewalks, roof shingles, fences, or awnings at least one time within the last 12 months
- Willing to conduct the work without wearing gloves

For the occupational outdoor spraying scenario (1b):

- Self-identified as being in good health as defined as able to do the following tasks: maneuver/carry a hose, walk the exterior of a large building, and spray various outdoor surfaces, including surfaces above shoulder height; spray up to 160 gallons
- Have employment experience within the last 2 years in a position that requires the use of a use a mechanically-pressurized hand-wand sprayer (on wheels or in the bed of a truck) to sanitize/disinfect or remove mildew/mold/bacteria from exterior hard surfaces (e.g., professional power washing, siding contractors, exterior home cleaning, mold removal, handyman, pest management professional)
- Willing to conduct the work without wearing gloves
- Willingness to wear a NIOSH-approved respirator (filtering facepiece or half-face respirator) while spraying in the study
- Certification of respirator fit testing within the past year as verified by a copy of the respirator fit test certificate or willingness to be fit tested for a respirator and complete an OSHA medical evaluation questionnaire as part of the respirator fit testing procedure
- ~~Willing to conduct the work without wearing gloves~~

For the occupational indoor surface spraying using manually-pressurized hand-held tank sprayers, piston-operated backpack sprayers, and battery-powered backpack sprayers scenario (2a):

- Self-identified as being in good health as defined as able to do the following tasks: lift, operate, and carry a 1-3 gallon capacity hand-held tank sprayer (~8 to 24 pounds) or a 4 gallon (~32 pounds) capacity piston-pump or battery-powered backpack sprayer and spray various indoor surfaces, including surfaces above shoulder height; spray up to 6 gallons
- Have occupational experience using a manually-pressurized hand-held tank sprayer (also called a manual pump-up sprayer) or a piston-pump or battery operated backpack sprayer for indoor mold remediation (or prevention) or to sanitize/disinfect indoor surfaces (including attics and crawlspaces).
- Either currently employed in such a position or was employed within the last 2 years in such a position
- Willing to conduct the work without wearing gloves

For the occupational indoor surface spraying using hand-held, backpack, and cart-mounted electrostatic sprayers scenario (2b):

- Self-identified as being in good health as defined as able to do the following tasks: operate and carry or move an electrostatic sprayer; spray various indoor surfaces, including surfaces above shoulder height; spray up to 3 gallons of diluted solution
- Have [insert amount] occupational experience using an electrostatic sprayer to sanitize/disinfect and/or decontaminate indoor surfaces
- Currently employed in a position where you use an electrostatic sprayer at least once a month
- Willing to spray without wearing gloves
- Willing to wear a NIOSH-approved respirator (N95 disposable filtering facepiece or half-face respirator) while spraying in the study
- Certification of respirator fit testing within the past year as verified by a copy of the respirator fit test certificate or willing to be fit tested for a respirator and complete an OSHA medical evaluation questionnaire as part of the respirator fit testing procedure
- Able and willing to fill out the OSHA medical evaluation questionnaire on a provided computer

For the occupational indoor environmental spraying scenario (3a and 3b):

- Self-identified as being in good health as defined as able to do the following tasks: operate either a mechanically-pressurized sprayer, central distribution spray system, or point-of-use Venturi-injection spray system; walk around equipment and move hoses; and spray various indoor hard surfaces, including surfaces above shoulder height; spray up to 80 gallons.
- Have occupational experience using a mechanically-pressurized portable tank sprayer or a wall-mounted Venturi-injection system to sanitize/disinfect indoor hard surfaces in industrial sites such as food processing facilities (including meat/poultry processing, slaughter houses, creameries, dairies, breweries, and cheese-making), food/beverage handling facilities, livestock/poultry production, animal transportation, and food storage locations

- Either currently employed in such a position or was employed within the last 2 years in such a position
- Willingness to wear a NIOSH-approved respirator (filtering facepiece or half-face respirator) while spraying in the study
- Certification of respirator fit testing within the past year as verified by a copy of the respirator fit test certificate or willingness to be fit tested for a respirator and complete an OSHA medical evaluation questionnaire as part of the respirator fit testing procedure
- Able to fill out the OSHA medical evaluation questionnaire on a provided computer

For the occupational indoor environmental spraying scenario (3a):

- Willing to conduct the work without wearing gloves or water-proof pants and jackets

For the occupational indoor environmental spraying scenario (3b):

- Willing to conduct the work wearing a rain suit (pants and jacket) over a long-sleeved shirt and long pants, rubber boots, hard hat, and chemical-resistant gloves

Exclusion Criteria

For all scenarios:

- Skin conditions on the surface of the hands, forearms, face, or neck (e.g., psoriasis, eczema, cuts or abrasions) as declared by volunteer, or as determined by a visual inspection by the medical professional
- Pregnant, as declared by volunteer, or as shown by a urine pregnancy test
- Nursing/Lactating (as declared by volunteer)
- Allergies or sensitivities to chemical-based cleaning or disinfecting products, isopropyl alcohol (rubbing alcohol), and soaps (as declared by volunteer)
- Allergies or sensitivities to latex gloves
- Unwilling to be photographed or videotaped
- Is an employee or a spouse of an employee of any company represented by the AEATF II, the contract research organizations conducting the study, or the American Chemistry Council (as declared by volunteer)

For scenarios 1a, 2a:

- Unable to provide documentation of medical clearance/fit test if subject usually wears an elastomeric half-face respirator (type that is reusable with replaceable chemical cartridges or canisters) and wants to wear it during the study

For scenarios 1b, 2b, 3a, 3b:

- Unable to wear a respirator or there is insufficient information to make a determination or there are restrictions for using a respirator based on the OSHA medical evaluation questionnaire or other source

- Unable to pass a respirator fit test

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. Females will be screened for pregnancy according to SOP AEATF II-11A.1. Females will be asked to confirm that they are not nursing during the screening. 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 and radio, and potentially through online postings, 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 for the subjects' time, travel, lost employment opportunity, and inconvenience.

3. **Risks to Subjects:** The proposed test products for all scenarios contain quaternary ammonia. The protocol calls for using Maquat® 5.5-M (Nisus DSV) for the outdoor and indoor non-food contact scenarios. Maquat® 7.5-M (4Quat) will be used for indoor food-contact spraying. These products are registered with the US EPA (see Table 2) and contain a mixture of four quaternary ammonia components. These product are representative of active ingredients that are commonly used in consumer and professional grade sanitizing and disinfecting products. EPA has characterized the risks associated with exposure to these substances in Attachment 2, Section 4.1 and has found that all proposed application amounts are within the range of acceptable MOEs.

   Risks to subjects include the risks associated with exposure to the test substance and to isopropyl alcohol, physical risks associated with the activities monitored under each scenario, risks associated with wearing a respirator, risk of heat-related illness, physical discomfort associated with wearing a personal air monitoring pump, psychological risks, and 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, including following AEATF II SOPs related to protection of human subjects (11A.1, 11B.1, 11C.4, 11F.1, 11G.0, 11H.0, 11I.1, 11J.1, 10C.1, and 10E.1). (V2:15-16)

   An active ingredient (ADBAC) in the test substance, in its concentrated form, is classified as Category II (danger) for acute oral, dermal, and inhalation toxicity, and Category I for eye and dermal irritation. To minimize the risks associated with exposure to the test substance, the substances provided for use in each of the scenarios will contain the test substance diluted in water to concentrations at or below what is permitted under

the EPA-approved label. Dilution will be done by researchers following the label. Test subjects will be exposed to the diluted test substances outlined in Table 2 above, ranging from 100 to 1160 ppm total Quats. At the concentrations from 100 to 860 ppm proposed in the study, users are not required to wear any PPE by the product labeling based on the product toxicity as evidence in Maquat 86-M, a ready-to-use product with the same active ingredients (EPA Reg. No. 10324-85) (V2:31). However, for Scenario 3b, up to 1160 ppm is proposed and the subjects will be wearing the proper labeled PPE. For general safety, all subjects in all scenarios will wear protective eyewear. EPA's updated risk assessment for ADBAC showed that a NIOSH-approved filtering face piece or half face respirator is required when spraying indoors using mechanically-pressurized sprayers.

To minimize the risks of exposure to the test substance, those who are allergic or sensitive to chemical-based cleaning or disinfecting products, isopropyl alcohol, and soaps, as well as those who have skin conditions that could be exacerbated by exposure to any of these substances, are excluded from the study. A medical professional will check subjects' skin prior to and after participation to ensure they are qualified to participate and to treat any skin-related issues that arise during or after the study. Subjects will wear appropriate PPE as necessary. Study staff will be observing workers, and per SOP 11H.0 will advise the subject if they are not wearing the necessary PPE or if they are doing something in conflict with the label; the Study Director has discretion to stop a subject's participation if the behavior continues. (V4:163-165)

To mitigate the risks associated with exposure to the test substance and the physical tasks of performing each of the scenarios, different PPE is required as summarized in the table below (which contains both the protocol requirements and AEATF/EPA agreed upon recommendations). All subjects will be wearing two layers of clothing and goggles/safety glasses to protect them from dermal and ocular exposure. For scenarios 1b, 2b, 3a, and 3b, subjects will be required to use a NIOSH-approved respirator (N95 disposable filtering facepiece or half-face respirator). For scenario 1b, this is required by labeling when the application is 60 psi or greater. Because the application pressure will not be known until the application is being made, all subjects will be required to use respiratory protection. For scenario 2b, subjects will be required to wear a NIOSH-approved respirator (N95 disposable filtering facepiece or half-face respirator) as a safety precaution, though not required by the product labeling or risk assessment. For scenarios 3a and 3b, "*[a]lthough not required by the label, subjects participating in the indoor spraying scenario with mechanically-pressurized sprayers (Scenarios 3a and 3b) will be required to wear NIOSH-approved respiratory protection (N95 filtering face piece or a half-face respirator) based on an inhalation risk assessment done using EPA's most current toxicological data for ADBAC.*" (V2:18) To minimize the risks associated with wearing a respirator, all subjects required to wear a NIOSH-approved respirator as part of their participation in the study will undergo a medical evaluation and fit test, sponsored by the AEATF. Alternatively, subjects may demonstrate their qualification to wear a respirator by providing a valid fit-test certification (no more than 12 months old) to the AEATF study staff prior to participation.

Per the protocol, "*subjects in scenarios 3a and 3b will be required to wear hard hats which is a requirement in OSHA compliant facilities when working in areas where there is a potential for head injury from falling objects*." (V2:21) Subjects in scenario 3b will wear specific PPE (though not required by the product label) to represent typical practices, which include following Good Manufacturing Practice and staying dry during the pre-sanitizing spraying and washing (note: for scenarios 3a and 3b surfaces will be sprayed by study staff approximately 30 minutes prior to the monitoring event).

In addition to the required PPE, subjects in scenarios 1a and 2a will be offered the option to wear a dust mask or other respiratory protection during their participation for their own comfort. To ensure subjects' safety while performing these physically demanding tasks, any subject in these scenarios who wants to use their own respiratory protection beyond a dust mask will need to provide evidence of medical clearance and a valid fit test certification.

AEATF will provide all PPE that subjects are required to wear as part of their participation in the study, as well as the optional dust masks. AEATF will also coordinate the required medical evaluation and fit test at a time convenient for the subject and at no additional cost to the subject.

Table 5: Summary of PPE Requirements

Scenario	PPE
1a. Consumer Outdoor Spraying	Long-sleeve shirt, long pants, shoes, socks, protective eyewear, ball cap
1b. Occupational Outdoor Spraying	Long-sleeve shirt, long pants, shoes, socks, protective eyewear, ball cap, NIOSH-approved respirator (N95 disposable filtering facepiece or half-face respirator)
2a. Occupational Indoor Surface Spraying in Dry Environments (manual and battery powered backpack sprayers, manual hand-held tank sprayers)	Long-sleeve shirt, long pants, shoes, socks, protective eyewear, ball cap
2b. Occupational Indoor Surface Spraying in Dry Environments (electrostatic sprayers)	Long-sleeve shirt, long pants, shoes, socks, protective eyewear, ball cap, NIOSH-approved respirator (N95 disposable filtering facepiece or half-face respirator)
3a. Occupational Indoor Environmental Spraying	Long-sleeve shirt, long pants, shoes, socks, protective eyewear, NIOSH-approved respirator (N95 disposable filtering facepiece or half-face respirator), hard hat
3b. Occupational Indoor Environmental Spraying (full PPE)	Rain pants, rain jacket, nitrile gloves, rubber boots, NIOSH-approved respirator (N95 disposable filtering facepiece or half-face respirator), hard hat

To further minimize the risks associated with performing the tasks being monitored, only subjects with experience performing the tasks being monitored will be eligible to participate. In participating in the study, subjects will do tasks they would normally do as part of their employment or that they have done around their own homes. It is not anticipated that participation in the study would expose them to more risks associated with these activities than they would encounter when performing these tasks on their own or as part of their job. Subjects will be permitted to take rests as needed, and the study director will provide chairs and cold drinks. Additionally, an independent medical professional will be on-site monitoring subjects' health and safety during each monitoring event.

AEATF's SOP on managing heat stress (SOP AEATF II-11B.1) will be followed (V4:138-149). Study staff will instruct subjects about the signs of heat stress and instruct them to stop the activity being monitored if they begin to experience any symptoms. staff will monitor conditions that could lead to heat stress and stop the monitoring event if necessary. Spraying during monitoring events is not expected to take longer than an hour, and subjects will be permitted to rest as necessary. Additionally, SOP AEATF II-11C.4

on handling subject illness and/or injury will be followed. (V4:150-158) This includes procedures for handling an adverse event or accidental exposure during the study, providing coverage for reasonable and appropriate medical treatment not covered by insurance, and checking subjects' arms, hands, face, and neck for signs of irritation or open cuts.

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, according to the AEATF SOP on pregnancy testing (SOP AEATF II-11A.1; V4:135-137).

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 or other features from subjects in photographs used in study materials.

4. **Benefits:** This research offers no direct benefits to the subjects.

   According to the protocol, "*measuring exposure of workers and consumers will produce more reliable data about the potential dermal and inhalation exposure to antimicrobials used during these sanitizing and disinfecting activities. The resulting exposure data will improve the completeness and accuracy of the database used by industry and the EPA to assess exposure and risks to workers and consumers who are exposed to antimicrobial chemicals during pressurized hand-wand spraying."* (V2:35)

   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 "*maintaining and adding new antimicrobial products to control bacteria and fungi on food contact and non-food contact surfaces."* (V2:34-35) Effective antimicrobial products used for sanitizing and disinfecting food and non-food contact surfaces benefit society by preventing adverse health effects from exposure to bacterial contamination.

5. **Risk/Benefit Balance:** The study monitors activities that the subjects generally perform on a regular basis as part of their employment or home maintenance. 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 these tasks. 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 in a variety of locations using different types of sprayers.

6. **Independent Ethics Review:** The protocol, informed consent form, subject qualification form, and recruitment materials were reviewed and approved by the Advarra IRB on February 20, 2020. (V3:47-48) The IRB approved the study protocol subject under an

expedited review, and subject to modifications with a note that "There is no expiration date for this study and it is not subject to requirements for continuing review under the revised Common Rule (2018 Requirements)." (AEA14 Approval w Modifications 2-25-2020, p. 2) This proposed research does not meet any of the conditions that would allow the IRB to waive continuing review. EPA contacted the IRB to clarify the rationale for this approval. EPA also noted to the IRB that the research is not eligible for expedited review, as presents more than minimal risk. Subsequent reviews of the protocol will follow all of the applicable regulations at 40 CFR 26, Subparts K-L. On June 16, 2020, the IRB revised the approval subject to modifications to indicate that the research is subject to continuing review requirements (AEA14 Approval w Modifications rev 6-16-2020).

This research may not be initiated until IRB approval is granted following EPA and HSRB review.

Advarra IRB is registered with FDA and OHRP, and has a Federal-wide Assurance approved by OHRP (00023875). Advarra is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

7. **Informed Consent:** The SOP AEATF II-11J.1 will be followed for obtaining informed consent (V4:169-173). 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.

   Consent meetings will be held one-on-one between the volunteer and research staff member, unless the volunteer chooses to bring a friend, family member, or advisor. Prior to the consent process, the volunteer's government-issued identification will be checked to verify the volunteer's age. Any volunteer without valid identification will not be enrolled in the study, but no other action will be taken.

   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. This review will cover all aspects of the consent form, including the study design, eligibility criteria, freedom to withdraw, compensation, coverage in the event of a research-related injury, and potential risks and discomforts. 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, (V4:173), 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 study report outlines measures to demonstrate respect for the subjects. (V2:35-36) The protocol describes 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 is adequate considering the inconvenience, missed employment opportunity, and travel to and from the test location. All individuals who attend a consent session will receive $50 for the consent meeting regardless of whether they enroll in the study. Subjects who are required to wear a respirator (1b, 2b, 3a, 3b) will receive an additional $20 for completing the online medical questionnaire to determine whether they are eligible to wear a respirator. Those who are eligible and attend a fit test session will receive an additional $100, regardless of whether complete the fit test successfully. For scenarios 1a, 1b, 2a, and 2b, enrolled individuals (subjects and alternates who are not monitored) will be compensated $150 for their participation. Subjects and alternates in scenarios 3a and 3b will be compensated $200 for their participation in each scenario; the higher amount is appropriate because these tasks require more specialized skill.

   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. 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:

1. Revise the protocol to include the electrostatic sprayer ESS Addendum; draft and submit for review recruitment materials and informed consent documentation for this scenario.
2. Revise the protocol and all related documents to reflect the updated test substance and rate information submitted to EPA on June 14.
3. Revise the protocol to acknowledge risks associated with COVID-19 that are not directly related to the activities monitored during the study, the precautions that will be followed, and that the study's conduct will comply with all federal, state, and local requirements and guidance related to this virus outbreak in effect at the time of the study. Examples of include wearing a mask/face covering when social distancing is not possible, delaying monitoring if the subject is not feeling well, and having a process in place to notify study staff and/or subjects if anyone they had contact with during the study becomes ill.
4. Revise the inclusion criteria for all scenarios to indicate the minimum amount of experience (months, years, number of months over the past number of years) subjects need, rather than "occupational experience".
5. The screening for scenario 2b asks what type of equipment subjects have experience using. If operation of equipment differs significantly between brands/types, consider only enrolling (or prioritizing enrollment of) subjects who are familiar with using the types of equipment that will be available for the study to minimize the risks of using unfamiliar equipment without instruction or advice.
6. Revise consent forms for scenarios 1a and 2a to note that respiratory protection is not required by the label or as a condition of participating in the study. Also indicate that subjects have the option to wear a dust mask or the respiratory protection they normally use this type of equipment during application. AEATF will provide dust masks for subjects to use. If a subject normally wears an elastomeric half-face respirator and wants to wear it during the study, they must provide evidence of a medical clearance and valid fit test certification in order to participate.
7. Revise consent forms and protocol for scenario 1b to indicate that respiratory protection is necessary for all subjects to ensure their safety, regardless of whether they spray at a pressure of 60 psi or more. Subjects have the option to provide fit testing documentation for their respirator or to go through the medical clearance/fit test process sponsored by AEATF at no cost to the subject and with compensation for time.
8. Revise telephone screening scripts to reflect respirator requirements for each scenario and to ask subjects about their occupational practices and what equipment they normally use.
9. Clarify how Spanish-speaking subjects will complete the online medical questionnaire for respirator use. Will it be available in English and Spanish? If not, will the bilingual staff member be onsite and available to assist if necessary? Will the bilingual staff member proactively offer assistance when the Spanish-speaking subject is directed to the computer where the online questionnaire can be completed?

EPA Ethics Conclusions

An IRB-approved protocol addressing all of the necessary elements in 40 CFR 26, Subpart K (see Attachments 2-6) has been submitted to EPA for review, along with an additional scenario that will be incorporated into the protocol and reviewed by the IRB prior to implementation. EPA has reviewed the protocol and all associated documents, and is presenting the documents and EPA's review to the HSRB. All subjects enrolled in this study will give voluntary, informed consent and be notified about the pesticide to which they will be exposed.

In addition, 40 CFR 26 Subpart L, at §26.1703, as amended effective September 23, 2019, 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's reliance 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 is likely to 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 Hand-Wand Scenario
2. EPA Protocol Review: AEATF II Hand-Wand Study Protocol
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 Pressurized Hand-Wand Spraying Scenario

Title: **PRESSURIZED HAND-WAND SPRAYING SCENARIO: RATIONALE FOR STUDY DESIGN (Volume 1 & ESS Addendum)**

Date: March 19, 2020

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

1. Scope of Scenario Design

(a) Is the scenario adequately defined?

"This will be a scripted study conducted at several simulated work sites containing a variety of spray equipment and surfaces. The three groups…will cover the wide range of different use sites and conditions and are expected to result in different exposure potentials. Group 1, spraying of exterior hard surfaces, is divided into two scenarios to capture the differences between the two main categories of users: consumers and professional workers. These two user groups tend to use different types of sprayers which is reflected in the study design. Group 2 will involve monitoring subjects who have occupational experience spraying antimicrobial products indoors in dry environments. Group 3, indoor environmental sanitizing, is divided into two scenarios to generate exposure data with the minimum amount of PPE allowed by a label and with full PPE, representative of what is typically worn by sanitation workers in food processing facilities. This design results in a total of five [six, including the new scenario 2b] *distinct monitoring scenarios which are summarized as follows:*

1. Outdoors, spraying downward, vertical, and upwards/overhead. Baseline PPE (long-sleeve shirt, long pants, and no gloves).

a. Manually-pressurized hand-held tanks and hose-end sprayers (consumers)

b. Mechanically-pressurized portable sprayers (occupational workers)

2[a]. Indoors, spraying downward, vertical, and upwards/overhead to porous surfaces in a dry environment. Baseline PPE (long-sleeve shirt, long pants, and no gloves). Manually-pressurized hand-held tank sprayers, piston-operated backpack sprayers, and battery-powered backpack sprayers (occupational workers)

[2b.] "This new scenario will measure exposure to workers spraying antimicrobial products indoors using electrostatic sprayers. The addition of this scenario is based on a mutual agreement between the US EPA and the Study Sponsor. The use of electrostatic sprayers to sanitize and/or disinfect large areas is of key area of interest, both to industry and regulators, right now given the current situation with COVID-19. The EPA has received many inquiries about electrostatic spray applications and the efficacy and safety of this equipment type was brought up at the April 30, 2020 COVID-19 Review Panel EPA Science Advisory Board meeting. Since the AEATF II pressurized hand-wand spraying

protocol was developed pre-COVID-19, at which time there was minimal use of electrostatic sprayers, the AEATF II has agreed to include electrostatic sprayers in the study… the AEATF II agreed to add a separate monitoring scenario for electrostatic spraying to Scenario 2, indoor spraying, dry environments. The indoor, dry environment spraying with manually powered conventional hand-held tank and backpack sprayers and battery-powered backpack sprayer will remain as planned since this still represents how many (non-COVID19) indoor surface applications are made. Adding a separate scenario will allow the task force to generate dermal and inhalation unit exposures for electrostatic sprayers separate from conventional hand-wand sprayers." (ESS Addendum:2)

"Hand-held, backpack, and cart-mounted electrostatic sprayers. Baseline PPE (long-sleeve shirt, long pants, no gloves, and respiratory protection). Includes spraying [indoor] *horizontal and vertical surfaces, including surfaces above shoulder height as needed."* (ESS Addendum:3)

3. Indoors, spraying downward, vertical, and upwards/overhead to non-porous surfaces in a wet environment (mechanically-pressurized portable sprayers and hydraulically-pressurized in-line Venturi-injection)

a. Baseline PPE (long-sleeve shirt, long pants, and no gloves) (occupational workers)

b. Full PPE (rain pants and rain jacket over long-sleeve shirt and long pants, chemical-resistant gloves, and rubber boots) (occupational workers)

There will be a total of 18 MEs per scenario, for a total of 90 [108, including the new scenario 2b] *monitoring events. Eighteen different individuals monitored under reasonably diverse conditions will characterize the exposure potential for each application scenario."* (V2:12-13)

The AEATF II further defines each of the three scenarios as the following:

(1) **Indoor spraying:** "*The first scenario, outdoor applications to hard exterior surfaces such as siding and sidewalks, would be done by generating two sets of exposure data, one using consumers applying with manually-powered hand-held tank and hose-end sprayers and another set with professionals using mechanically-powered wand-type portable spray units (on wheels or truck-mounted). The manually-powered sprayers dispense product a short distance from the user and are designed to apply product in a targeted manner to small areas. The mechanically-powered units have a bigger throw distance and are used to treat larger areas and high surfaces such as siding on the sides of commercial buildings or awnings or agriculture premises (such as barn, coops, and animal runs). The direction of spray for this scenario would be downward to sidewalks, to vertical surfaces such as fences and siding, and upward to reach tall vertical surfaces such as siding on a warehouse."* (V1:30)

(2) **Outdoor spraying (dry environments):** *"The second scenario involving indoor applications to dry areas will include a mixture of manually powered hand-held tank and backpack sprayers. These applications will simulate indoor surface applications to hard porous surfaces in locations that are typically dry such as attics, crawlspaces,*

interior living spaces, and commercial indoor areas. Antimicrobial products used in this manner are primarily fungi/mold prevention and remediation products and sanitizers/disinfectants used by the pest management industry or janitors." (V1:30)

The electrostatic sprayer scenario "Includes spraying [indoor] *horizontal and vertical surfaces, including surfaces above shoulder height as needed."* (ESS Addendum:3)

"There will be a selection of six electrostatic sprayers … available for the test subjects to choose from. This will allow subjects to use the sprayer that they are most familiar with. In case a subject is not familiar with the specific brands and models of sprayers available for use in the study, the equipment user guides will be available.

The following is a list of the electrostatic sprayers targeted to be used in this monitoring scenario. Because of the high demand for these sprayers during the COVID-19 pandemic, it may not be possible to obtain all the desired sprayers. However, a minimum of four different sprayers (a minimum of two hand-held, one backpack, and one cart) will be purchased for the study.

Hand-Held, EMist EPIX360, Victory VP200ES

Backpack, EMist EM360, Victory VP300ES

Cart-Mounted, EMist EM360, ByoPlanet/Clorox Total 360 Electrostatic Sprayer

To make sure that there is a variety in the spray equipment used in this scenario, people who respond to the recruitment ads will be asked what type and brand of electrostatic sprayer they normally use and this will be used to ensure that potential participants do not all spray the same piece of equipment. To ensure that this scenario represents the range of available electrostatic sprayers, a minimum of 3 MEs will be conducted with each brand (ByoPlanet/Clorox, EMist, and Victory), with at least three MEs done using a backpack sprayer and three MEs using a cart sprayer.

Subjects using sprayers with 3-in-1 nozzles will be allowed to choose between the small and medium spray setting, but not the largest. This will be done to bias the study towards the smaller droplet sizes." (ESS Addendum:10-11)

(3) **Outdoor spraying (wet environments):** *"The third scenario focuses on a mixture of mechanically-powered wand-type portable spray units (on wheels or carts) and in-line Venturi-injection utilizing wall-mounted hook-ups. This scenario represents environmental sanitizing/disinfecting spraying and spray practices commonly done in wet environments as part of an overall cleaning procedure. The wet and humid environment, hard non-porous surfaces combined with the ability to apply higher spray volumes than in dry environments reflects treatment in such locations as food and beverage processing and packaging facilities, animal housing, and livestock production, and is expected to result in a different exposure potential than grouping*

2. To simulate actual use conditions, the surfaces will be sprayed with water prior to the test subjects being monitored to create a wet and humid environment." (V1:30-31)

The scenario is limited to the spraying of the diluted treatment solution, not the preparation of the solution (i.e., subjects will not pour the active ingredient to make-up the treatment solution). The product containing ADBAC will be poured by the researcher for each scenario. The pouring of the product is not being monitored in this study because the formulation type for future use of these data could be liquid, powder, or granules (some systems even use closed loading/filling). Exposure data for pouring these formulation types are available from prior AEATF II exposure studies.

The AEATF II hand-wand and electrostatic spraying scenario designs appropriately propose to diversify the sampling characteristics by selecting different subjects for each monitoring event and allowing them to spray surfaces as they normally would do, conducting the study during multiple application dates, providing various sprayer equipment types, varying the size of the rooms to be used, varying the surfaces and equipment in the rooms to be sanitized, as well as varying the active ingredient concentration in the treatment solution. The test subjects will be drawn from both the consumer and occupational populations to represent residential and janitors/professionals who apply antimicrobial products using these hand-wand and electrostatic sprayers (albeit less so by consumers as reflected in the design of the study).

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

There are some exposure data available involving hand-wand sprayers and no data available specifically for electrostatic sprayers. The data that are representative of antimicrobial uses, however, are older studies judged to be of lesser quality than today's standards (e.g., dermal exposure measured using intermittent patch dosimetry instead of whole-body dosimeters, cotton gloves instead of hand wash/rinse, etc.) or newer studies conducted under today's standards but not representative of antimicrobial uses (e.g., Agricultural Handlers Exposure Task Force's rights-of-way sprayer). EPA agrees with the AEATF's review of the existing data (V1:43-48) and conclusion that antimicrobial-specific hand-wand sprayer data are needed to be more reflective of these uses compared to the existing data generated for agricultural chemicals. Additionally, with the industry moving towards the use of electrostatic sprayers as an application technique for disinfectant applications for COVID-19, the electrostatic sprayer-specific exposure data generated by the AEATF II will be useful in ongoing and future risk assessments.

2. Rationale for Scenario Sampling Design

(a) Are the variables in the hand-wand and electrostatic sprayer scenario design likely to capture diverse exposures at the high-end?

The design choices in the hand-wand and electrostatic sprayer scenarios to capture diversity in exposure include: (1) monitoring the subjects over multiple days; (2) varying

the room layouts and surfaces to be treated; (3) varying the study locations for each of the three different scenarios; (4) varying the spray equipment within each scenario; (5) varying the spray duration [by varying the volume sprayed] for the monitoring events (MEs) within each scenario; (6) varying the active ingredient concentration; and (7) diversity among test subjects (i.e., not using the same subject twice in the same scenario). Additional descriptions of these key variables are provided below. (V1:36-37)

The study is being designed to be scripted in such a manner as to encompass the diverse set of conditions that will impact exposure, an approach that has been defined within the AEATF II Governing Document as purposive diversity sampling. The diversity is being achieved using a range of application equipment for each scenario. Within the basic selection of equipment, the subjects will be allowed to choose which ones they are more apt to use. For example, in the outdoor spraying scenario for the consumers, the subjects will be provided two different hand-pump tank sprayers and two hose-end sprayers so that they can choose the one they want to use. The following is a description of the planned diversity in the design of each scenario:

Indoor spraying: "*At least two different hand-pump tank sprayers and two hose-end sprayers will be available for Scenario 1a* [consumers]. *Subjects will be allowed to choose the sprayer they are most familiar with to use. Scenario 1b* [occupational] *will have a minimum of three different mechanically-pressurized sprayers (either on wheels, skid, or in the bed of a pick-up truck) and subjects will be allowed to choose the sprayer they are most familiar with. In addition, each subject will be responsible for pressurizing his or her sprayer, and if the nozzle is adjustable, the subject will make his/her own adjustment. For sprayers that allow different nozzles to be used, there will be a selection of nozzles for the subjects to choose from. Information on the sprayer including spray wand length, tank capacity, and a description of the nozzle will be documents. If the sprayer has a pressure gauge, the spray pressure will be recorded."* (V1:40)

Outdoor spraying (dry environments): *"The equipment in Scenario 2*[a] *will consist of at least two different manually-pressurized tanks sprayers, two different manual piston-operated backpack sprayers, and two different battery-powered backpack sprayers. For wands that allow different nozzles to be used, there will be a selection of nozzles for the subjects to choose from. Information on the sprayer including spray wand length, tank capacity, and a description of the nozzle will be documents. If the sprayer has a pressure gauge, the spray pressure will be recorded."* (V1:40)

The electrostatic sprayer ESS Addendum provides a section for "*Electrostatic Spraying Theory and Spray Equipment*" that details how these sprayers operate, the array of equipment available to users, etc. (ESS Addendum:6-11) From the list of potential electrostatic spray equipment, the AEATF II is providing the test subjects with *"…a selection of six electrostatic sprayers … to choose from. This will allow subjects to use the sprayer that they are most familiar with. In case a subject is not familiar with the specific brands and models of sprayers available for use in the study, the equipment user guides will be available.*" (ESS Addendum:10-11)

"To make sure that there is a variety in the spray equipment used in this scenario, people who respond to the recruitment ads will be asked what type and brand of electrostatic sprayer they normally use and this will be used to ensure that potential participants do not all spray the same piece of equipment. To ensure that this scenario represents the range of available electrostatic sprayers, a minimum of 3 MEs will be conducted with each brand (ByoPlanet/Clorox, EMist, and Victory), with at least three MEs done using a backpack sprayer and three MEs using a cart sprayer. Subjects using sprayers with 3-in-1 nozzles will be allowed to choose between the small and medium spray setting, but not the largest. This will be done to bias the study towards the smaller droplet sizes." (ESS Addendum:11)

Outdoor spraying (wet environments): "*Scenario 3 will be done using point-of-use Venturi-injection systems with wall-mounted hook-ups that are part of the food or meat processing facility and with at least three different mechanically-pressurized portable sprayers on wheels or carts. Subjects will be allowed to select and use the system that they are most familiar with. Subjects using the mechanically-pressurized sprayers will be responsible for pressurizing his or her sprayer, and if the nozzle is adjustable, the subject will make his/her own adjustment. For sprayers that allow different nozzles to be used, there will be a selection of nozzles for the subjects to choose from. Information on the sprayer including spray wand length, tank capacity, and a description of the nozzle will be documents. For the in-line Venturi-injection system, information on the hose length and spray gun/nozzle will be documented. If the sprayer has a pressure gauge, the spray pressure will be recorded; spray output from the hydraulically pressurized hose will be collected to determine gallons per minute."* (V1:40)

Although the researchers have selected the types of equipment (e.g., hand pump tank versus hose-end sprayer) for the study, the exact make/models/brands have not been determined/purchased yet. The study design indicates the following: "…*sprayers to be used in the study will be selected based information collected from retail stores, websites, and from conversations with industry personnel and end-users."* (V1:41)

Test Subjects. *"Another important meta-characteristic that will be formally diversified is the test subject, i.e., the person volunteering to perform the various spraying tasks. People with experience using pressurized hand-wand sprayers will be recruited from the local area in which the test site is located."* (V1:41)

Indoor spraying: *"Since both consumers and professionals may apply antimicrobials to exterior hard surfaces using hand-wand sprayers, subjects with home-use experience will be recruited for Scenario 1a while those with occupational experience will be recruited for Scenario 1b. Given that most homeowners do not purchase large commercial mechanically-pressurized sprayers designed to spray large volumes of solution, only people with occupational experience will be recruited for Scenario 1b (mechanically-pressurized sprayers). The experience criteria for potential test subjects in Scenario 1a will be that they have used a manually-pressurized (pump-up) hand-held tank sprayer or hose-end sprayer at least once within the last year to sanitize/disinfect or remove mildew/mold/bacteria from exterior hard surfaces such as brick, siding, sidewalks, shingles, fences, or awnings. The experience criteria for potential test subjects in*

Scenario 1b will be that they are currently employed or were employed within the last 2 years in a position where they use a mechanically pressurized hand-wand sprayer (on wheels or in the bed of a truck) to sanitize/disinfect or remove mildew/mold/bacteria from exterior hard surfaces (e.g., professional power washing, siding contractors, exterior home cleaning, mold removal, handyman, pest management professionals).” (V1:41).

Outdoor spraying (dry environments): “*People with occupational experience using pressurized hand-wand spray equipment to sanitize or treat for fungi/mold on indoor hard surfaces will be recruited. This will include people working for pest control companies, mold remediation companies, construction companies, handymen, and janitors. Potential subjects must either be currently employed in a position or have worked in such a position within the last 2 years where they use a manually-pressurized hand-held tank sprayer or back-pack sprayer to apply mold prevention/mold remediation products or sanitizers to interior surfaces in such areas as crawlspaces, attics, homes, and commercial buildings.”* (V1:41)

For the electrostatic sprayer scenario, “*Only subjects who have experience using electrostatic sprayers will be recruited for this study. Given the rapid increased use of electrostatic sprayers as a tool to disinfect and sanitize surfaces as a response to COVID-19 in the food service, transportation, medical, hospitality, and personal care industries, no problems are anticipated to recruit 22 people (18 to be monitored and 4 alternates) with this experience.*” (ESS Addendum:3). However, the number of months or years of years of experience using the electrostatic sprayer is not mentioned.

Outdoor spraying (wet environments): *“People with occupational experience using mechanically-pressurized hand-wand sprayers, central distribution spray systems and/or wall-mounted Venturi-injection systems to sanitize indoor hard non-porous surfaces will be recruited. The populations of interest are sanitation workers who work at food processing facilities (including meat/poultry processing, slaughter houses, creameries, dairies, breweries, and cheese-making), food/beverage handling facilities, livestock/poultry housing, animal transportation, and food storage locations. Potential subjects must either be currently employed in a position where they use a mechanically-pressurized hand-wand sprayer, central distribution spray system, and/or wall-mounted Venturi-injection system to apply a sanitizer or disinfectant as part of their sanitation tasks or have worked in such a position within the last 2 years.”* (V1:42)

Active Ingredient Concentration. The proposed approach is for the first two scenarios, indoor and outdoor (dry environments) spraying, to test 6 MEs with each of three total Quat concentrations, as shown in Table 2. The proposed concentrations for these two scenarios are 215, 430, and 860 ppm total Quat. For scenario 3a, indoor spraying (wet environments) with baseline PPE, the proposed concentrations are 100 ppm total Quat at 20 gallons sprayed, and 400 ppm total Quat at 40 and 80 gallons sprayed. For scenario 3b, indoor spraying (wet environments) with full PPE, the proposed concentrations are 290, 580, and 1160 ppm total Quat. EPA recommends no changes in most of these concentrations as these concentrations meet the goal of 80% statistical power for detecting proportionality between (expected) exposure and concentration as discussed in

Table 3 above (i.e., log-log-linearity with a slope of one for each scenario and exposure route). However, EPA recommends working with the AEATF II to increase the range of the concentrations in Scenarios 1a and 2a to increase the statistical power from75% to at least 80%.

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

Random elements have been incorporated into the design as follows: *"Once a test subject has signed the consent form, his/her Subject ID will be assigned. This will be accomplished by having the subject randomly draw a Subject ID number out of a container. The first 18 numbers (W01 through W18) identify the subjects who will be scheduled for monitoring, while the four remaining subjects (W19 to W22) will be held as alternates. In addition to drawing the Subject ID number, each subject, unless they have been assigned to be an alternate, will draw a second piece of paper from another container that will randomly assign the subject to an ME number. Test subjects participating in both scenarios 3a and 3b will be asked to draw two ME numbers (from separate containers), one for each scenario that they participate in. The ME number will determine which monitoring duration stratum the subject will be in."* (V2:51)

Subjects will be randomly assigned to the target Quat concentration level within each scenario.

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

None.

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

The hand wand sprayer applications for subjects spraying hard surfaces using the ADBAC treatment solution are following procedures according to typical practices. The typical procedures are holding the spray wands and spraying down hard surfaces, with nuances for each scenario as follows (a general list activities, spelling out 13 items, are presented in V2:57-59):

Outdoor spraying: *"Subjects will be told to spray the various outdoor surfaces, which will include vertical and horizontal surfaces, as they normally would. Subjects will not be allowed to rinse the treated surfaces with water as this could potentially remove residues from the subjects. At the end of the monitoring period, subjects will not clean out their spray equipment as this has the potential to remove residues from their hands."*

Indoor spraying (dry environments): *"Subjects will be told to spray the various indoor surfaces (floor, walls, ceilings, cabinets) as they normally would. Subjects will not be allowed to rinse the treated surfaces with water. At the end of the monitoring period, subjects will not clean out their spray equipment as this has the potential to remove residues from their hands."*

"Scenario 2b [electrostatic sprayers] *will take place an indoor environment designed to mimic indoor commercial or institutional spaces such as hospitals, classrooms, hotel rooms, day care centers, airplanes, metro-cars, ambulances, churches, lobbies, fitness centers, and offices. Rooms of various sizes, containing tables, chairs, and items such as lamps, computers, monitors, and toys or gym equipment will be included to represent surfaces that are treated. These items as well as cabinet exteriors, countertops, light switches, and door handles will be sprayed to simulate sanitizing for COVID-19."* (ESS Addendum:3)

Indoor spraying (wet environments): *"Subjects will be told to spray the various indoor surfaces (floors, walls, and equipment) as they normally would. At the end of the monitoring period, subjects spraying from point-of-use Venturi-injection units will simply turn off the wall-mounted valve. Subjects spraying from portable spray units will not clean out their spray tanks as this has the potential to remove residues from their hands."* (V2:20-21).

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

Hand wand spraying in mushroom houses, wood preservation sprays, cooling towers, HVAC systems, indoor agricultural growing facilities will not be simulated in this study. "*Since these specialized use sites typically are on labels with a broad range of other use sites, it is anticipated that these uses will be covered when assessing risks for uses based on one of the five* [six, including scenario 2b] *monitored scenarios*." (V2:22)

The AEATF II excluded monitoring subjects pouring the formulated product into the application equipment. The test substance in the formulated product will be added to the treatment solution by the researchers (not the test subjects) because formulation types can vary (i.e., liquid, powder, granule) and open pouring data are available from previous AEATF II exposure studies.

3. Is the proposed test material an appropriate surrogate?

The proposed active ingredient to be used in this study is the quaternary ammonium compound, commonly known as "Quats". Specifically, alkyl dimethyl benzyl ammonium chloride (ADBAC) C-14 carbon length side chain will be analyzed as the surrogate compound (CAS number 139-08-2). ADBAC has a low vapor pressure (3.5E-12 mmHg @ 25 °C) which is an appropriate choice for a surrogate test material. Two EPA-registered products containing Quats will be used this study, Maquat® 5.5-M (EPA Registration Number 10324-81) and Maquat® 7.5-M (EPA Registration Number 10324-81). The composition of the ADBAC Quat in both formulated products is 50% C_{14}, 40% C_{12}, and 10% C_{16}. (V2:34). The C_{14} chain of ADBAC was also used as the surrogate compound in previous AEATF II exposure studies (liquid pour, aerosol can, and immersion/dip/soak).

"GLP characterization of each lot of test substance used in this study will be done under a separate protocol prior to the start of monitoring to determine the C_{14}-ADBAC content.

Duplicate samples (approximately 20 ml each) of each lot of test substance used in this study will be retained by the analytical laboratory and shipped to Quality Associates, Inc. for archiving." (V2:38*)*

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 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 will be considered."* (V2:76). Note that under the proposed design given in Table 2 above, using the assumed geometric standard deviations tabulated in Table 3 above, the fold relative accuracy goals are estimated to be met for inhalation exposure and to be almost met (maximum fold relative accuracy 3.08) for dermal exposure. 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 Hand-Wand Sprayer Study Protocol (AEA14)

Title: **A Study for Measurement of Potential Dermal and Inhalation Exposure During Pressurized Hand-Wand Spraying of Antimicrobial Products (Volume 2)**

Date: March 19, 2020

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1. Societal Value of Proposed Research

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

"This study is being conducted to develop new data for evaluating potential dermal and inhalation exposures of consumers and/or professional workers who conduct manual pressurized hand-wand spraying of antimicrobials such as sanitizers, disinfectants, and fungicides/mildewcides using manually or mechanically-pressurized hand-wand spray equipment. The primary use sites for pressurized hand-wand spraying of antimicrobial products are sanitizing or disinfecting surfaces in industrial and institutional sites, and the primary users are occupational workers." (V2:10)

The addition of the electrostatic sprayers was a decision that was made post-submission of the AEATF II's hand-wand protocol and arose from this type of equipment being used to disinfect areas to deal with COVID-19. "*The use of electrostatic sprayers to sanitize and/or disinfect large areas is of key area of interest, both to industry and regulators, right now given the current situation with COVID-19. The EPA has received many inquiries about electrostatic spray applications and the efficacy and safety of this equipment type was brought up at the April 30, 2020 COVID-19 Review Panel EPA Science Advisory Board meeting. Since the AEATF II pressurized hand-wand spraying protocol was developed pre-COVID-19, at which time there was minimal use of electrostatic sprayers, the AEATF II has agreed to include electrostatic sprayers in the study.*

"Following a teleconference on May 11 2020 between the task force manager Has Shah, Study Director Leah Rosenheck, and AEA14 study team chair Kate Sande and representatives from the US EPA (Tim Leighton, Tim Dole, Alicia Denning, and Michelle Arling), the AEATF II agreed to add a separate monitoring scenario for electrostatic spraying to Scenario 2, indoor spraying, dry environments. The indoor, dry environment spraying with manually powered conventional hand-held tank and backpack sprayers and battery-powered backpack sprayer will remain as planned since this still represents how many (non-COVID19) indoor surface applications are made. Adding a separate scenario will allow the task force to generate dermal and inhalation unit exposures for electrostatic sprayers separate from conventional hand-wand sprayers." (ESS Addendum:2)

(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 use of sanitizers/disinfectants/algicides/etc. Currently EPA has evaluated various other types of "disinfectant" application methods such as trigger pump spray & wipe, ready-to-use (RTU) wipes for hard surface cleaning-type products, mopping, aerosol cans, however, hand-wand sprayers have the potential to result in different dermal and inhalation exposures based on the areas they are being used (e.g., house siding/driveways) and amounts applied. These data will fill a data gap. 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 for treating hard surfaces with various antimicrobial ingredients.

"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." (V2:16)

(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 occupational workers and consumers (for outdoor spraying scenario) who use antimicrobial products on surfaces.

(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?

As has been shown in previous AEATF II exposures studies for applying registered antimicrobial products, test subjects have been needed because these studies monitor the typical activities associated with these types of job functions. There are no acceptable methods or models that could be used to extrapolate exposure for this type of human activity.

(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 use an antimicrobial product by spraying with hand-wand sprayers. In this study, at least 18 subjects will be monitored in each of the six scenarios, (the study will have a total of 108 subjects monitored) to capture the expected variation in use 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?

"This study is being conducted to develop new data for evaluating potential dermal and inhalation exposures of consumers and/or professional workers who conduct manual pressurized hand-wand spraying of antimicrobials such as sanitizers, disinfectants, and fungicides/mildewcides using manually or mechanically-pressurized hand-wand spray equipment. The primary use sites for pressurized hand-wand spraying of antimicrobial products are sanitizing or disinfecting surfaces in industrial and institutional sites, and the primary users are occupational workers." (V2:10)

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."* (V2:76)

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 benchmark objective cited above can be achieved (or almost achieved, k=1.75 to 3.08) by the study as proposed. The AEATF II secondary objective of having 80% power to detect proportionality between exposure and concentration can also be achieved for most scenarios and EPA recommends making changes to Scenarios 1a and 2a to achieve the secondary objective (as noted above).

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 for each scenario has three groups of six MEs each for different combinations of target volumes and concentrations of active ingredient. Scenario 1a has eighteen MEs stratified into six groups of different amounts of active ingredient. Scenario 2b has eighteen MEs stratified into three groups of different amounts of active ingredient, although in the third group the amount of active ingredient differs slightly between workers that choose or do not choose the hand-held sprayer. Each of the other four scenarios has three groups of six MEs each for different amounts of active ingredient. Based on the data from the manually-pressured backpack sprayer greenhouse exposure study (MRID 43623202), the proposed sample size and study design is estimated to meet or almost meet the 3-fold relative accuracy goals for each scenario (i.e., k is estimated up to 3.08 for some scenarios).

(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.

"Once a test subject has signed the consent form, his/her Subject ID will be assigned. This will be accomplished by having the subject randomly draw a Subject ID number out of a container. The first 18 numbers (W01 through W18) identify the subjects who will be scheduled for monitoring, while the four remaining subjects (W19 to W22) will be held as alternates. In addition to drawing the Subject ID number, each subject, unless they have been assigned to be an alternate, will draw a second piece of paper from another container that will randomly assign the subject to an ME number. Test subjects participating in both scenarios 3a and 3b will be asked to draw two ME numbers (from separate containers), one for each scenario that they participate in. The ME number will determine which monitoring duration stratum the subject will be in." (V2:51)

(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 uses associated with hand-wand spraying and there is adequate justification for selecting test subjects from the consumer and occupational populations.

(f) Can the data be statistically analyzed?

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

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

"The AEATF II will not statistically analyze the monitoring data in order to investigate the relationship between exposure and other factors (e.g., environmental conditions or concentration of active ingredient)." (V2:76)

Each combination of scenario and exposure route will be separately analyzed by EPA. Since each scenario is stratified into three groups based on the combination of volume and concentration (six groups for scenario 1a), we will compare the group geometric means using analysis of variance. Most of the following analyses will use all 18 MEs in a scenario, and the results of those analyses will not be stratified by group, due to small sample sizes (6 MEs), unless useful patterns are found. For scenario 1a, we will use

analysis of variance to compare the geometric means between the hose-end and back-pack sprayer, but otherwise we will not stratify the analyses of scenario 1a by the sprayer type unless useful patterns are found. For scenario 2b, we will use analysis of variance to compare the geometric means between the hand-held, backpack, and cart-mounted sprayers, but otherwise we will not stratify the analyses of scenario 2b by the sprayer type unless useful patterns are found.

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 (pounds) of active ingredient handled (AaiH). 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 AaiH, has the same log-normal distribution for all 18 MEs. The fitted model will be used to estimate the arithmetic means, geometric means, and 95^{th} percentiles of the normalized exposure overall, and 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. 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. As previously recommended by the HRSB we will also evaluate models using the gamma distribution, with a much more flexible set of distributional shapes, instead of the log-normal distribution. These alternative models will be compared graphically using scatter plots of the predictions and will also be compared statistically using the Akaike Information Criterion.

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). If the width of the confidence interval is more than 1.4, then this implies that the post-hoc power to detect proportionality is less than the benchmark power of at least 80% calculated in Table 3 (except for dermal exposure in two scenarios where the estimated power was 75% and EPA recommends to make changes to the study design to increase the statistical power for Scenarios 1a and 2a).

The main statistical modeling will substitute values below the limit of quantitation (LOQ) by half the LOQ, but the results will be compared with alternative approaches for censored data such as the maximum likelihood method. 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 AaiH showing the fitted regression models, 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). We may evaluate the potential impacts of adding some other measured explanatory variables to the statistical models by examining plots of the residuals against those explanatory variables; however these analyses will be based on extra variables that can be regulated (e.g., temperature and humidity may affect droplets/exposure but these

variables cannot be controlled on the label). Finally we will evaluate the potential for bias and uncertainty in scenarios 3a and 3b if some subjects are in both scenarios. Bias might occur if those subjects "learn" from their previous ME and there will potentially be additional uncertainty caused by within-subject correlations. Using all the data from scenarios 3a and 3b, we will fit regression models for the logarithm of exposure against the logarithm of AaiH where the intercepts and slopes depend upon the scenario and there is a random subject effect as well as the random error term. We will also examine scatter plots of log exposure versus log AaiH where each point is labeled by the scenario and the subject ID.

(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. The error variance is unknown. For each scenario, the error variance was estimated using the geometric standard deviations (GSDs) calculated from the lognormal mixed model fitted to the similar Mixer/Loader/Applicator Manually-pressurized Backpack Sprayer greenhouse exposure study (MRID 43623202; V1:45). That study was determined by AEATF II to be the only study of the existing hand-spray exposure studies that "*meets current quality standards and could possibly be considered for use in a generic exposure database.*" (V1:47). For analyzing dermal exposure in scenarios 1a, 1b, 2a, 2b, and 3a, the greenhouse study GSD of 4.6403 was calculated for dermal exposure for subjects not wearing gloves and wearing a single layer of clothing, which represents the baseline PPE. For analyzing dermal exposure in scenario 3b, the greenhouse study GSD of 4.5681 was calculated for dermal exposure for subjects wearing gloves and a double layer of clothing, which represents the full PPE. For analyzing inhalation exposure in scenarios 1a, 1b, 2a, and 2b, the greenhouse study GSD of 2.6272 was calculated for inhalation exposure for subjects not wearing a respirator. For analyzing inhalation exposure in scenarios 3a and 3b, the same greenhouse study GSD of 2.6272 was calculated for inhalation exposure for subjects wearing a respirator, because the respirator adjustment used in the greenhouse study was the application of a constant protection factor (which has no impact on the GSD). The corresponding error variances are $(\ln(4.6403))^2$ (= 2.3555) for dermal exposure in scenarios 1a, 1b, 2a, 2b, and 3a, $(\ln(4.5681))^2$ (= 2.3077) for dermal exposure in scenario 3b, and $(\ln(2.6272))^2$ (= 0.9330) for inhalation exposure in scenarios 1a, 1b, 2a, 2b, 3a, and 3b. The statistical power is the probability that complete independence (a

log-log slope of zero) is rejected at the 5% significance level when there is complete proportionality (a log-log slope of one). EPA used a Monte Carlo simulation to calculate the power for each scenario assuming the null hypothesis of complete proportionality and using the target amounts of spray volume and concentration given in Table 2 above. For scenario 1a, the calculations needed to take into account the fact that the target amount of active ingredient is 10 times higher using the hose-end sprayer versus the manually-pressurized nozzle (see Table 1 above). For that scenario the Monte Carlo simulations assumed that each subject had a known probability p of selecting the hose-end sprayer and calculated the power for different values of p (0, 0.1, 0.2, …, and 1). For scenario 2b, the calculations needed to take into account the fact that the target amount of active ingredient is 50 percent higher using the backpack or cart sprayer versus the hand-held sprayer (see Table 2 above). For that scenario the Monte Carlo simulations assumed that each subject had a known probability p of selecting the hand-held sprayer and calculated the power for different values of p (0, 0.1, 0.2, …, and 1).

The estimated power for dermal exposure ranged from 0.75 to 0.96 across the six scenarios and choices of p. The estimated power for inhalation exposure ranged from 0.99 to 1.00 across the six scenarios and choices of p. (The true power cannot be exactly 1 but it was estimated from 50,000 simulations and rounded to the nearest hundredth). Thus, the estimated statistical power of each study scenario is at least 0.8, with the exceptions of a minimum estimated power of 0.75 for dermal exposure in scenario 1a and an estimated power of 0.75 for dermal exposure in scenario 2a. Although the estimated power is less than 0.8 in some cases for dermal exposure, this should not be a major concern because the true power depends on the unknown true GSD for the hand sprayer scenarios which could have been overestimated from the greenhouse exposure study. If instead the default GSD of 4.00 from the Governing Document is used, then the estimated power is 0.83 or higher in all cases. At this time, EPA is recommending changes to the protocol to increase the statistical power from 75% to at least 80% for Scenarios 1a and 2a.

EPA assumed a log-normal distribution for the normalized exposure and used a Monte Carlo simulation to estimate the fold relative accuracy of the estimated arithmetic mean and 95th percentile of the normalized exposure. Under the assumption of complete proportionality (a log-log slope of one), the normalized exposure has the same lognormal distribution for all 18 MEs in each scenario, regardless of the amount of active ingredient. All that matters for estimating the fold relative accuracy is the number of MEs and the GSD. Using the same GSDs as the power calculations, the estimated fold relative accuracy for the arithmetic mean is 3.08 for dermal exposure in scenarios 1a, 1b, 2a, 2b, and 3a, 3.02 for dermal exposure in scenario 3b, and 1.75 for inhalation exposure in all six scenarios. The estimated fold relative accuracy for the 95th percentile is 3.03 for dermal exposure in scenarios 1a, 1b, 2a, 2b, and 3a, 3.00 for dermal exposure in scenario 3b, and 2.01 for inhalation exposure in all six scenarios. Thus, the arithmetic mean and 95th percentile can be estimated within a factor of 3.08 with 95% confidence. Although the estimated fold relative accuracy slightly exceeds 3 for dermal exposure, this should not be a major concern because the true fold relative accuracy depends on the unknown

true GSD for the hand sprayer scenarios which could have been overestimated from the greenhouse exposure study. If instead the default GSD of 4.00 from the Governing Document is used, then the fold relative accuracy estimates are 2.61 for dermal exposure and 2.72 for inhalation exposure.

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 middle to high end of exposures that occur while consumers and occupational workers use hand sprayers to spray antimicrobials in each of the study design scenarios. EPA is confident that this design will provide data on hand sprayer exposures more accurately and reliably than currently available data.

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

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

2.2 How and to what will human subjects be exposed?

The test substance are Maquat® 5.5-M (EPA Registration Number 10324-81) which contains the following Quats: Alkyl (C14, 50%; C12, 40%; C16, 10%) dimethyl benzyl ammonium chloride (2.2%) Octyl decyl dimethyl ammonium chloride (1.64%) Didecyl dimethyl ammonium chloride (0.83%), and Dioctyl dimethyl ammonium chloride (0.83%); and Maquat® 7.5-M (EPA Registration Number 10324-81) which contains the following Quats: Alkyl (C14, 50%; C12, 40%; C16, 10%) dimethyl benzyl ammonium chloride (3.0%), Octyl decyl dimethyl ammonium chloride (2.3%), Didecyl dimethyl ammonium chloride (1.1%), and Dioctyl dimethyl ammonium chloride (1.1%) (V2:34).

Test subjects will be exposed to the diluted ADBAC and DDAC treatment solutions, as outlined in Table 2 above, ranging from 100 to 1160 ppm total Quats while spraying from various hand-wand (including electrostatic) sprayers "as they normally would do" for each of the scenarios (e.g., outdoors vs indoors).

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

"Both Maquat 5.5-M and Maquat 7.5-M are EPA-registered typical end-use products designed to be diluted in water prior to use. These products are used as cleaners, sanitizers, disinfectants, deodorizers, mildewstats, and virucides for food contact and non-food contact surfaces in homes, hospitals, and other commercial and industrial settings as well exterior residential surfaces such as vinyl, plastic, sealed concrete, and sealed stucco. Both products can be used on a wide range of hard surfaces such as floors, countertops, glassware, bathtubs, chairs, food storage areas, meat packing plant

surfaces, conveyors, and harvesting equipment. Application methods include, mop, rag, sponge, brush, immersion, mechanical spray device, or hand-pump/trigger device." (V2:41)

"Several quaternary ammonias have been used successfully in previous AEATF II studies as the analytes of interest and are selected for measurement based on their good stability, relative abundance in formulated products used by consumers and professionals, low mammalian toxicity, and the sensitivity of the analytical methods." (V2:42)

"The dermal removal efficiency of quaternary ammonium compounds has been shown to be quite high (~ 90%) for washing and wiping methods involving alcohol:water mixtures. As done in other AEATF II studies conducted with quaternary ammonia test substances, a 90% removal efficiency correction factor will be used to adjust the hand-wash residues found on the test subjects and an 89% correction factor will be used to adjust their face/neck wipe residues." (V2:42)

The maximum label rate for the non-food contact surfaces is 1275 ppm and 400 ppm for food contact surfaces.

The choice of the formulation type (i.e., both formulations are liquids) is irrelevant to this study because the pouring portion of the exposure is not being monitored. Different formulation types can be used as sanitizers/disinfectants/etc such as liquids, powders, and granules. These formulation types have been monitored separately for open pouring by the AEATF II.

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

"The sanitizing solutions used for indoor spraying in Scenario 2 will be prepared at approximately 600, 300, and 100 ppm total quat. This is below the maximum allowed rate for non-food contact sanitizing of 1,275 ppm, but given the potential for high residues, these concentrations are expected to result in detectable residues." "*For indoor spraying in Scenarios 3a and 3b, the target total quat concentrations used by the test subjects will be 400 ppm and 100 ppm. Four hundred ppm is the upper end of the label rate for sanitizing food contact surfaces without the need for a potable water rinse. One hundred ppm is below the lowest recommended concentration of 150 ppm for sanitizing food contact surfaces but was chosen to strengthen the statistical power of the dataset. Since the food contact rate (or less) is being used, surfaces sprayed during the study will not need to be rinsed after the sanitizing step."* (V2:39) In a revised submission, AEATF II increased the total Quat concentrations from the 100, 300, and 600 ppm to 215, 430, and 860 ppm (and Scenario 3b to 290, 580, and 1160 ppm) because *"using higher active ingredient concentrations in the study will result in higher pounds of active ingredient handled/sprayed which will improve accuracy when conducting registrant product-specific risk assessments which are done using the maximum label*

rate and a default upper-bound volume sprayed per day." (AEATF 2020). This increase over 400 ppm will require a potable water rinse (PWR) for food contact surfaces.

(c) What duration of exposure is proposed?

The selection of monitoring durations for each of the three scenarios are explained below:

"A rough estimation of duration of spraying is provided …[see Table 1 above]*; however, this may underestimate the total monitoring time since it does not take into account time for activities when the subject is not spraying such as moving from area to area pumping up the sprayer (for manual spray tanks and backpacks), making sprayer adjustments, any rest breaks, and time needed to fill/refill tanks."* (V2:43-44)

"Monitoring will be based on subjects applying a target amount of spray solution. The target volume of spray solution is based on generic assumptions regarding sprayer output (gallons per minute) for the various categories of sprayers and the typical duration of spraying for the use site (obtained from interviews with end-users)…" (V1:34)

The selection of monitoring durations was based on field observations made by AEATF researchers in various facilities as described in V1:26-28. The dermal and inhalation exposures are normalized by the amount of active ingredient handled (AaiH), and therefore, the AaiH in future risk assessments can be modified as necessary and the exposure data collected in this study extrapolated to other amounts (and the AaiH is related to the duration of application, flow rate, and treatment solution concentration).

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 tasks associated with spraying with a hand-wand sprayer. Dermal and inhalation exposure will be measured using whole-body dosimeters (WBD) (inner and outer), face/neck wipes, hand wipe/washes, head patches/hat, and two personal air monitors. 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 personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). An OSHA Versatile Sampler (OVS) "*…(SKC Catalog Number 226-30-16 containing a glass fiber filter and 270/140 mg sorbent beds, 13 mm diameter x 75 mm length)…"* will be used to collect inhalable particles. Additionally, "*Parallel Particle Impactor (PPI) (SKC Catalog # 225-3851) containing a 37 mm PVC filter and 37 mm support pad will be used to collect respirable residues."* (V2:63). Flow rates will be approximately 2 L/min for each of the samplers. (V2:63)

"Air temperature and relative humidity of the work area for the duration of exposure monitoring will be recorded with automated instrumentation at a minimum of 15-minute intervals for the duration of the work period. During the outdoor monitoring wind speed and direction will be collected. Environmental monitoring equipment will be calibrated or standardized according to field facility SOPs. The type and location of any HVAC system and whether it is operating will be documented in the raw data. A facilities maintenance engineer with HVAC training or an industrial hygienist will measure the airflow in the test room(s) and record the direction of airflow. The dimensions and layout of the room(s)/building(s)/surfaces(s) and the relative position of the test subjects with respect to them and the airflow direction will be documented in the raw data for each test site." (V2:61)

(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 Lead QAU while the analytical phase will be audited by the analytical facility QAU to ensure compliance with the FIFRA GLP regulations 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, and AEATF Sponsor Representative (40 CFR part 160.35 [4]). The analytical phase report will be audited by the analytical facility QAU, and 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 methods and SOPs and that the reported results accurately reflect the raw data 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[.]*"* (V2:79-80)

(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 Lead QAU while the analytical phase will be audited by the analytical facility QAU to ensure compliance with the FIFRA GLP regulations 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, and AEATF Sponsor Representative (40 CFR part 160.35 [4]). The analytical phase report will be audited by the analytical facility QAU, and 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 methods and SOPs and that the reported results accurately reflect the raw data 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[.]*"* (V2:79-80)

Correction for loss of residues on sampling matrices will be accounted for by using field fortified samples that are exposed to ambient conditions for the duration of exposure. These field recovery samples will be stored in the same way as the actual study samples, and will be analyzed concurrently with the actual exposure samples. Therefore, these field recovery results will correct for all phases of potential losses. Control (blank) samples for each matrix will also be processed with the field recovery samples. Field fortification levels (in triplicate) are proposed in the following table.

Matrix	**Target Field Fortification Level (C_{14}-ADBAC)**	**LOQ (C_{14}-ADBAC)**
OVS Tubes	3, 30, and 100 µg/tube	1 µg/tube
37 mm PVC Filter	0.5, 5, and 50 µg/tube	0.1 µg/filter
Hand Wash	100, and 1,000, and 10,000 µg/sample (Scenarios 1, 2, 3a)) 10 and 100 µg/sample (Scenario 3b)	1 µg/sample
Face/Neck Wipe	100 and 1,000 µg/sample	10 µg/sample
Inner Dosimeter	30, 3000, and 30,000 µg/sample	10 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 will be considered." (V2:76)

3. Subject Selection

3.1 Representativeness of Sample

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

"*Information collected from AEATF II members in a 2013-14 survey regarding products labeled for pressurized hand-wand spray applications revealed that the majority are intended for professional use only with just a few that would be used by both professionals and consumers, and none labeled solely for consumers use. The main categories of workers who apply antimicrobial products using pressurized hand-wand spray equipment are institutional/industrial/janitorial workers including sanitation crews, contractors/construction workers, agricultural workers, and pest*

control operators. The majority (approximately 60%) of use sites labeled for treatment by pressurized hand-wand spraying are indoor use sites (e.g., food handling and food processing facilities, livestock production, and mushroom houses) while approximately 20% are outdoors (such as outdoor wood surfaces, cooling towers, and exterior hard surfaces). Approximately 20% of the use sites could be either indoors or outdoors such as livestock housing, wood preservation, and mold control.

"*Although the majority of pressurized hand-wand spraying of antimicrobial products is done by occupational workers, there are some consumer pressurized hand-wand spray applications. Examples of potential use sites treated by consumers include indoor DIY treatments for mold remediation and outdoor treatment of building surfaces such as siding, shingles, and brick for fungal and mildew control. In this study both consumers and occupational workers will be monitored spraying exterior hard surfaces while occupational workers only will be monitored spraying indoors as this reflects the primary population using this application method. Occupational workers handle more chemical and spray for longer periods of time compared to consumers which will be reflected in the study design. This approach is consistent with previous AEATF II exposure monitoring studies*." (V1:13-14)

(b) From what populations will subjects be recruited?

"*The test site locations will be in metropolitan areas where a larger pool of potential subjects is available. This will increase the likelihood of getting diversity in subjects in terms of gender, age, and experience as well as level of training and expertise.*" (V2:45)

Scenarios 1a and 1b: "*Since both consumers and professionals may apply antimicrobials to exterior hard surfaces using hand-wand sprayers, subjects with home-use experience will be recruited for Scenario 1a while those with occupational experience will be recruited for Scenario 1b. Given that most homeowners do not purchase large commercial mechanically-pressurized sprayers designed to spray large volumes of solution, only people with occupational experience will be recruited for Scenario 1b (mechanically-pressurized sprayers). The monitoring of test subjects with occupational experience is consistent with the mop, wipe, aerosol, and liquid pour studies conducted by AEATF II which only monitored janitors even though consumers do many of those same activities.*" (V1:41)

Scenario 2a: "*People with occupational experience using pressurized hand-wand spray equipment to sanitize or treat for fungi/mold on indoor hard surfaces will be recruited. This will include people working for pest control companies, mold remediation companies, construction companies, handymen, and janitors. Potential subjects must either be currently employed in a position or have worked in such a position within the last 2 years where they use a manually-pressurized hand-held tank sprayer or back-pack sprayer to apply mold prevention/mold remediation products or sanitizers to*

interior surfaces in such areas as crawlspaces, attics, homes, and commercial buildings." (V1:41-42)

Scenario 2b: "*Only subjects who have experience using electrostatic sprayers will be recruited for this study. Given the rapid increased use of electrostatic sprayers as a tool to disinfect and sanitize surfaces as a response to COVID-19 in the food service, transportation, medical, hospitality, and personal care industries, no problems are anticipated to recruit 22 people (18 to be monitored and 4 alternates) with this experience*." (ESS Addendum:3)

Scenarios 3a and 3b: "*People with occupational experience using mechanically-pressurized hand-wand sprayers, central distribution spray systems and/or wall-mounted Venturi-injection systems to sanitize indoor hard non-porous surfaces will be recruited. The populations of interest are sanitation workers who work at food processing facilities (including meat/poultry processing, slaughter houses, creameries, dairies, breweries, and cheese-making), food/beverage handling facilities, livestock/poultry housing, animal transportation, and food storage locations. Potential subjects must either be currently employed in a position where they use a mechanically-pressurized hand-wand sprayer, central distribution spray system, and/or wall-mounted Venturi-injection system to apply a sanitizer or disinfectant as part of their sanitation tasks or have worked in such a position within the last 2 years.*" (V1:42)

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

"In order to obtain a subject pool that is familiar with the spraying tasks to be monitored, adult subjects with appropriate experience must first be identified. The inclusion and exclusion criteria listed in Section. XII.A detailed the specific experience criteria for each scenario. Finding a sufficient number of qualified test subjects for the indoor environmental cleaning (Scenario 3) is expected to be more difficult since this requires work experience with a specialized type of equipment that is generally only found in food processing facilities.

"In order to not exclude Spanish speakers, 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 Spanish-speakers." (V2:47).

"Volunteers will be recruited through the use of newspaper and radio ads in English and Spanish. If needed, on-line job posting sites and/or social media may also be used to recruit test subjects using IRB-approved materials." (V2:48).

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

"The AEATF II monitoring program, as described in the Governing Document (2011), intends to develop a database of exposure monitoring data that can be used to support

practical regulatory decisions about future exposures to antimicrobial active ingredients used in various products. Generic exposure data will be developed on a broad range of use patterns and associated application methods, as well as post application exposures, to support registration and re-registration by its member companies of such uses for antimicrobial ingredients. The data will be applicable to both occupational and consumer activities and methods used in the handling of antimicrobial products." (V2:16)

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, with EPA's recommendations incorporated.

The inclusion/exclusion criteria are listed in Volume 2, pages 26-30.The recommended revisions are shown below.

Inclusion Criteria

All scenarios

- Males or females at least 18 years old as verified by a government issued photo ID
- Willingness to sign the Informed Consent Form and the Subject Qualification Worksheet
- Speak and read English or Spanish
- Non-smoker or willing to refrain from smoking for the duration of the testing period

For the consumer outdoor scenario (1a):

- Self-identified as being in good health as defined as able to do the following tasks: lift and carry a hand pump spray tank containing up to 2 gallons of solution (~16 pounds) or a hose-end sprayer, walk the exterior of a large building while spraying various surfaces, including surface above shoulder height; spray up to 6 gallons (or 60 gallons with a hose-end sprayer).
- Have experience using a manually-pressurized hand-held tank sprayer (also called a manual pump-up sprayer) or a garden hose-end sprayer to sanitize/disinfect or remove mildew, mold, algae, or bacteria from exterior hard surfaces such as brick, siding, sidewalks, roof shingles, fences, or awnings at least one time within the last 12 months
- Willing to conduct the work without wearing gloves

For the occupational outdoor spraying scenario (1b):

- Self-identified as being in good health as defined as able to do the following tasks: maneuver/carry a hose, walk the exterior of a large

building, and spray various outdoor surfaces, including surfaces above shoulder height; spray up to 160 gallons
- Have employment experience within the last 2 years in a position that requires the use of a use a mechanically-pressurized hand-wand sprayer (on wheels or in the bed of a truck) to sanitize/disinfect or remove mildew/mold/bacteria from exterior hard surfaces (e.g., professional power washing, siding contractors, exterior home cleaning, mold removal, handyman, pest management professional)
- Willing to conduct the work without wearing gloves
- Willingness to wear a NIOSH-approved respirator (filtering facepiece or half-face respirator) while spraying in the study
- Certification of respirator fit testing within the past year as verified by a copy of the respirator fit test certificate or willingness to be fit tested for a respirator and complete an OSHA medical evaluation questionnaire as part of the respirator fit testing procedure
- ~~Willing to conduct the work without wearing gloves~~

For the occupational indoor surface spraying using manually-pressurized hand-held tank sprayers, piston-operated backpack sprayers, and battery-powered backpack sprayers scenario (2a):
- Self-identified as being in good health as defined as able to do the following tasks: lift, operate, and carry a 1-3 gallon capacity hand-held tank sprayer (~8 to 24 pounds) or a 4 gallon (~32 pounds) capacity piston-pump or battery-powered backpack sprayer and spray various indoor surfaces, including surfaces above shoulder height; spray up to 6 gallons
- Have occupational experience using a manually-pressurized hand-held tank sprayer (also called a manual pump-up sprayer) or a piston-pump or battery operated backpack sprayer for indoor mold remediation (or prevention) or to sanitize/disinfect indoor surfaces (including attics and crawlspaces).
- Either currently employed in such a position or was employed within the last 2 years in such a position
- Willing to conduct the work without wearing gloves

For the occupational indoor surface spraying using hand-held, backpack, and cart-mounted electrostatic sprayers scenario (2b):
- Self-identified as being in good health as defined as able to do the following tasks: operate and carry or move an electrostatic sprayer; spray various indoor surfaces, including surfaces above shoulder height; spray up to 3 gallons of diluted solution
- Have occupational experience using an electrostatic sprayer to sanitize/disinfect and/or decontaminate indoor surfaces
- Currently employed in a position where you use an electrostatic sprayer at least once a month

- Willing to spray without wearing gloves
- Willing to wear a NIOSH-approved respirator (N95 disposable filtering facepiece or half-face respirator) while spraying in the study
- Certification of respirator fit testing within the past year as verified by a copy of the respirator fit test certificate or willing to be fit tested for a respirator and complete an OSHA medical evaluation questionnaire as part of the respirator fit testing procedure
- Able and willing to fill out the OSHA medical evaluation questionnaire on a provided computer

For the occupational indoor environmental spraying scenario (3):

- Self-identified as being in good health as defined as able to do the following tasks: operate either a mechanically-pressurized sprayer, central distribution spray system, or point-of-use Venturi-injection spray system; walk around equipment and move hoses; and spray various indoor hard surfaces, including surfaces above shoulder height; spray up to 80 gallons.
- Have occupational experience using a mechanically-pressurized portable tank sprayer or a wall-mounted Venturi-injection system to sanitize/disinfect indoor hard surfaces in industrial sites such as food processing facilities (including meat/poultry processing, slaughter houses, creameries, dairies, breweries, and cheese-making), food/beverage handling facilities, livestock/poultry production, animal transportation, and food storage locations
- Either currently employed in such a position or was employed within the last 2 years in such a position
- Willingness to wear a NIOSH-approved respirator (filtering facepiece or half-face respirator) while spraying in the study
- Certification of respirator fit testing within the past year as verified by a copy of the respirator fit test certificate or willingness to be fit tested for a respirator and complete an OSHA medical evaluation questionnaire as part of the respirator fit testing procedure
- Able to fill out the OSHA medical evaluation questionnaire on a provided computer

For the occupational indoor environmental spraying scenario (3a):

- Willing to conduct the work without wearing gloves or water-proof pants and jackets

For the occupational indoor environmental spraying scenario (3b):

- Willing to conduct the work wearing a rain suit (pants and jacket) over a long-sleeved shirt and long pants, rubber boots, hard hat, and chemical-resistant gloves

Exclusion Criteria

For all scenarios:

- Skin conditions on the surface of the hands, forearms, face, or neck (e.g., psoriasis, eczema, cuts or abrasions) as declared by volunteer, or as determined by a visual inspection by the medical professional
- Pregnant, as declared by volunteer, or as shown by a urine pregnancy test
- Nursing/Lactating (as declared by volunteer)
- Allergies or sensitivities to chemical-based cleaning or disinfecting products, isopropyl alcohol (rubbing alcohol), and soaps (as declared by volunteer)
- Allergies or sensitivities to latex gloves
- Unwilling to be photographed or videotaped
- Is an employee or a spouse of an employee of any company represented by the AEATF II, the contract research organizations conducting the study, or the American Chemistry Council (as declared by volunteer)

For scenarios 1a, 2a:

- Unable to provide documentation of medical clearance/fit test if subject usually wears an elastomeric half-face respirator (type that is reusable with replaceable chemical cartridges or canisters) and wants to wear it during the study

For scenarios 1b, 2b, 3a, 3b:

- Unable to wear a respirator or there is insufficient information to make a determination or there are restrictions for using a respirator based on the OSHA medical evaluation questionnaire or other source
- Unable to pass a respirator fit test

For scenarios 1a, 1b, 2a, 2b:

- Participating in another scenario

(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. (V2:29)

(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 and radio, and potentially through online advertisements

and social media, 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 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 V2:44-46. Potential subjects will be recruited through newspaper and radio advertisements, and through online advertisements and social media if necessary. 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 a member of the research staff (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. Before completing the consent process and enrolling, a member of the research team will ask a standard set of questions to ensure that the potential subject comprehends the consent materials. Once comprehension is confirmed, the subject will proceed to sign the consent form and complete a Subject Qualification Worksheet.

(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?

"Compensation for the time and inconvenience spent on this study will be provided to the subjects in cash. The value for remuneration is based roughly on a half-day's wage and represents potential lost time from secondary sources of employment, travel time, and incidental expenses incurred with study participation.

"Potential subjects who attend the informed consent meeting whether they decide to participate or not will be paid $50 in cash for their time and inconvenience. Volunteers who want to take the consent form home to think about it and return at a later date to actually sign the form will not receive another $50 for the second visit.

"Subjects who enroll for scenarios 1b, 3a, and 3b and who have not been fit tested within the past year for a respirator (as evidenced by a respirator fit test certificate) will be compensated an additional $20 for completing the on-line medical

questionnaire. Subjects who pass the medical screen and come back to attend the respirator fit test will be compensated $100, even if they fail the respirator fit test. Subjects enrolled scenarios 1a, 1b, and 2 will be told that they will receive $150 for reporting to the study location on the scheduled day of the study, regardless of whether they participate in the study or not. Subjects enrolled in scenarios 3a and 3b will be told that they will receive $200 for reporting to the study location on the scheduled day of the study, regardless of whether they participate in the study or not. Subjects who enroll in both scenarios 3a and 3b and come to the study location on their scheduled day(s) will receive a total of $400. The higher remuneration for Scenario 3 subjects reflects the more specialized skill level required for this work task.

"In the case of the alternates, they will be compensated the same amount ($150 for scenarios 1a, 1b, and 2, or $200 for scenarios 3a and 3b) whether they are called in for monitoring or not. Alternates who are never called in for monitoring will be contacted by phone once monitoring is completed to set up a convenient location and time for the subject to receive his/her compensation in cash." (V2:50-51)

"*All subjects (those slated for monitoring and those who serve as alternates) in Scenario 2b will be compensated $50 for attending the consent meeting; $20 for completing the on-line medical questionnaire at the consent meeting; $100 for attending a respirator fit test; and $150 for reporting to the study site on the scheduled day of the study, regardless of whether they actually participate in the study or not*." (ESS Addendum:6)

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

Yes. The proposed payment amounts are fair and reasonable compensation for the subjects' time, factoring in their experience and inconvenience

(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 at the end of the consent meeting and when subjects leave the study site. Alternates will be contacted at the end of the study if they have not been invited to replace a test subject to arrange for payment.

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 (Maquat® 5.5-M and Maquat® 7.5-M active ingredients include Quats) are EPA-registered, with 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 eight types of risks:
"1. The risk associated with exposure to the test chemical
2. The risk associated with exposure to isopropyl alcohol
3. Physical risks associated with the spraying activities
4. The risk of heat related illness
5. Physical discomfort associated with wearing a personal air-sampling pump
6. Psychological risks associated with changing clothes and the pregnancy test
7. Risks associated with wearing a respirator
8. Risk of unanticipated release of confidential information" (V2:30)

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

The AEATF II cites the following on the toxicity of ADBAC:

"…when diluted in water, the acute oral, dermal, and inhalation toxicity as well as the eye and skin irritation potential are significantly reduced as seen on the Ready-to-Use Maquat® 86-M label (EPA Registration Number 10324-85) label. Maquat 86-M (signal word "Caution") contains 860 ppm of the same four quats that are in Maquat 5.5-M and Maquat 7.5-M, indicating that when these products are diluted to rates that will be used in this study (600 ppm and less), no personal protective equipment is needed. … as a standard study precaution, all test subjects will be required to wear eye protection which will be provided by the AEATF II. [Note: As per AEATF (2020), the total Quat concentration in the study has increased to a maximum of 1160 ppm]

EPA issued a Re-registration Eligibility Decision Document for ADBAC in 2006 (EPA, 2006). In 2006 EPA assessed dermal and inhalation risks for residential uses of ADBAC for a variety of use sites, including treatment of indoor hard surfaces (e.g., mopping, wiping, and low-pressure sprays) and open pouring liquids. Low-pressure spraying indoors in a residential setting resulted in unacceptable dermal risks; however, this assessment was based on a concentration of 0.156% which is higher than the highest concentration of 0.06% (equivalent to 600 ppm total quats) that will be used in this study. At a concentration of 600 ppm dermal risks for pressurized spraying are acceptable.

…the subjects participating in this study are required to wear a NIOSH-approved filtering face piece or half-face respirator when spraying indoors using mechanically-pressurized sprayers. Subjects who wish to wear their own filtering face piece or half-face respirator will be allowed to do so. Subjects who do not have their own respirator will be provided one by AEATF at no cost to the subject. The risk assessment also showed that subjects spraying outdoors and those spraying indoors with manually-pressurized sprayers do not require respiratory protection. At high concentrations products containing ADBAC may produce dermal, eye, and/or respiratory irritation, but this is not commonly seen at the diluted concentrations that will be used by participants in this study. Although not required when using the diluted product, as a study safety precaution all test subjects will be required to wear eye protection. Subjects in this study will not handle concentrated solutions of quaternary ammonia. Instead, they will be provided with solutions diluted to 0.06% total quats (600 ppm) or less which does not require any protective clothing. The use of eye protection along with wearing two layers of clothing will reduce the chance of dermal and ocular exposure.

Additionally, to minimize the potential for adverse reactions, subjects with open sores/skin conditions on their hands or face will not be allowed to participate. Any subject with known dermal allergy or sensitivity to cleaning and/or disinfecting products will be excluded from participating. Field personnel will be observing subjects and will intervene if evidence of dermal or ocular irritation occurs during the work activity." (V2:28-29)

Dermal. The DDAC risk assessment developed to support the Reregistration Eligibility Decision (RED) document provides for the selection of the toxicological endpoints for risk assessment purposes. The dermal toxicological endpoints indicate that low concentrations of DDAC (0.13% ai tested in a 21-day dermal toxicity study, MRID 45656601) display no dermal irritation effects and no systemic effects up to and including the limit dose of 1000 mg/kg/day. The proposed use of DDAC in this protocol by subjects exposed to a diluted treatment solution of 0.0108% DDAC or less will not trigger a dermal risk of concern. *"The highest proposed concentration of DDAC in the test solution to be sprayed by the test subjects is 108 ppm (600 ppm total quats of which DDAC accounts for 18%), equivalent to 0.0108%, considerably less concentrated than what was used in the dermal toxicity study that elicited no adverse effects."* (V1:67) The same conclusions for the dermal risk can be drawn from the higher concentration of DDAC now proposed at 1160 ppm total Quats (of which DDAC accounts for 18% or 209 ppm DDAC or 0.0209%, still considerably less concentrated than the dermal toxicity study that elicited no adverse effects.

The ADBAC risk assessment developed to support the Reregistration Eligibility Decision (RED) document provides for the selection of the toxicological endpoints for risk assessment purposes. Although ADBAC is considered less of a potent dermal irritant then DDAC, dermal irritation testing data at low concentrations in subchronic studies are not available. The available dermal toxicological endpoints indicate no systemic toxicity. However, dermal irritation has been observed in 21- and 90-day dermal toxicity studies

in guinea pigs and rats, respectively (MRIDs 41105801 and 41499601, respectively). The short-term dermal endpoint selected from the 21-day study is 333 µg/cm^2 (where the applied dose contained 0.8% ADBAC) and 80 µg/cm^2 in the 90-day study (where the applied dose contained 1.0% ADBAC). The potential exposure of subjects in this proposed study to a dilute treatment solution containing 0.024% concentration of ADBAC will not trigger a dermal risk of concern based on knowledge of the toxicological testing conducted with DDAC at low concentrations and use of ADBAC in prior AEATF II exposure studies (e.g., liquid pour at 0.2% ADBAC, aerosol can at 0.252% ADBAC and 0.378% DDAC). "*In the exposure monitoring study, the highest concentration of ADBAC that will be sprayed is 240 ppm (600 ppm total quats of which ADBAC accounts for 40%), equivalent to 0.024% ADBAC. This is over an order of magnitude less concentrated than the 0.8% ADBAC solution the guinea pigs were exposed to. Based on this, there are no concerns about potential dermal adverse effects from ADBAC."* (V1:67) In AEATF's revised submission, the highest concentration of total Quats that will be sprayed is 1160 ppm (1160 ppm total Quats of which ADBAC accounts for 40%), equivalent to 0.0464% ADBAC. This is still over an order of magnitude less concentrated than the 0.8% ADBAC solution the guinea pigs were exposed to. Additionally, the AEATF II conducted a dermal assessment using a film thickness approach where the dermal MOE at the highest ADBAC concentration was 277 with a Target MOE of 10. (V1:68)

Inhalation. Inhalation exposure for hand-wand spraying has been assessed by the AEATF II for each of the scenarios at each of the amount of active ingredient handled (AaiH) following EPA's standard procedures. (V1:68-72) Currently there is no route-specific inhalation toxicity study for ADBAC. The more potent inhalation toxicity for DDAC is being used as a default until chemical-specific data are provided. However, using the more potent DDAC toxicity data in this case is warranted as the treatment solution also contains DDAC. The DDAC LOAEC from a 28-day inhalation toxicity study in rats is 0.08 mg/m^3 based on ulceration of the nasal cavity, degeneration of the olfactory epithelium, increase in mucoid production and decreased body weight/weight gain in males. *"…the most recent EPA benchmark dose modeling (email to AEATF II from Laura Parsons, EPA Associate Branch Chief, Antimicrobials Division, dated July 23, 2019) instead of the LOAEL of 0.08 mg/m^3 found in the 2017 ADBAC Final Work Plan (US EPA, 2017). The BMDL10 for the quats is 0.18 mg/m^3 and is based bridging data from a 28-day inhalation toxicity study with DDAC. The Agency calculated a Human Equivalent Concentration (HEC) as follows: HEC = BMDL (0.18 mg/m3) * 6 hours rat exposure/8 hours human exposure (0.75) * RDDR (0.298) = 0.04 mg/m^3. The Agency indicated that since irritation is the main endpoint for DDAC, the reduction of the intraspecies uncertainty factor from 10X to 3X was appropriate; the uncertainty factor of 3x for interspecies variation is retained. In addition, it was noted that with the benchmark dose, the extra uncertainty factor of 3x for lack of NOAEC stated in the 2017 ADBAC and DDAC Final Workplans is no longer applicable since all the data points are considered in the benchmark dose analysis. As such, the revised target margin of exposure (MOE) is now 10."* (V1:68) The estimated inhalation MOEs for the subjects

spraying in the three scenarios (including a 10x protection factor for respirators where appropriate) range from 27 to 23,600 with a Target MOE of 10 (AEATF 2020).

(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 of available toxicity data on ADBAC and DDAC and the anticipated dermal and minimal inhalation exposure. The comparison indicates minimal dermal and inhalation risks. Please see part 4.1(c) (above) for details.

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

Individuals who may be at an increased risk for adverse effects are not eligible to become subjects in this study, including individuals known to be allergic or sensitivities to chemical-based cleaning or disinfecting products, isopropyl alcohol, soaps, or latex gloves, or as well as those with known skin conditions that could be exacerbated by study participation or with cuts/abrasions on areas that will be exposed during testing. (V2:29)

4.2 Risk Minimization

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

"[T]o minimize the potential for adverse reactions [and irritation], *subjects with open sores/skin conditions on their hands or face will not be allowed to participate. Any subject with known dermal allergy or sensitivity to cleaning and/or disinfecting products will be excluded from participating. Field personnel will be observing subjects and will intervene if evidence of dermal or ocular irritation occurs during the work activity."* (V2:32)

"The duration of these work tasks during the day of participation is expected to range from 5 to 50 minutes. Subjects will be allowed to take breaks as needed to minimize overheating and fatigue, and each subject will be closely observed by a study staff member. Additionally, there will be a third-party medical professional hired to be present during monitoring. Given that only experienced subjects will be recruited for this study and the short duration of the work tasks, it is anticipated that the activities being asked of the subjects are not unlike what they do on a normal workday (or for homeowner, what they do at their house on a periodic basis)." (V2:33)

"There is some risk of heat-related illness associated with wearing two layers of clothing while working. However, the length of time that any one subject is spraying is

less than one hour. Subjects will be allowed to take breaks as needed to minimize overheating and fatigue, water and sports drinks will be available, and each subject will be closely observed by a medical professional. AEATF SOP 11.B.1 (minimizing and handling heat related illness) will be followed." (V2:33)

"There could be some risk of embarrassment from disrobing to the subject's own underwear in the presence of another person. This risk is minimized by involving only a researcher of the same gender, keeping the amount of time that the subject is disrobed to a minimum, and ensuring that the dressing and undressing processes will occur in private (only the subject and the researcher)." (V2:33)

"Female subjects may be surprised by the outcome of the required pregnancy test. 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. See SOP AEATF II-11A.1 for a full description of the pregnancy testing procedures." (V2:33-34)

"Respirators can make breathing more difficult for the user, and not everyone is able to wear a respirator. Some conditions that could prevent someone from using a respirator include heart conditions, lung disease, and psychological conditions like claustrophobia. Subjects in scenarios 1b, **[2b,]** *3a, and 3b will be required to provide evidence of being fit tested for a respirator or will be fit tested. The OSHA requirement for respirator fit testing includes passing a written medical evaluation questionnaire, which screens those who have conditions that could make it unsafe for them to use a respirator. Requiring respirator fit testing will reduce the risks associated with wearing a respirator. Since many food processing sanitation workers normally wear respiratory protection, it is expected that many subjects in scenario 3 (environmental sanitizing/disinfecting) will be used to working while wearing a respirator. Monitoring environmental conditions for heat stress, observing the subjects closely, and allowing breaks as needed will also minimize the risks associated with wearing a respirator."* (V2:34)

"The information obtained from subjects taking part in this study will be used by the researchers, funders, and the sponsor, and will become part of one or more reports on the study. All reports (as well as all study-related records) will be kept as confidential as possible. The results of this study are not intended for publication; however, if any of the study-related data are published, subjects' identities will remain confidential. There is potential for a breach of confidentiality because photographs and video will be taken of the subjects during the study. However, efforts will be taken to conceal subjects' identities by not including their faces or editing so that facial features and any identifiable features, such as piercings or tattoos, are not recognizable or the photo/video will be deleted." (V2:34)

"All efforts will be taken to maintain the confidentiality of the pregnancy test results. A positive pregnancy test result will not be recorded, and will not be disclosed to anyone other than the test subject, the verifying employee, and/or the Study Director. Opaque containers will be available where the pregnancy tests are taken to allow for discrete disposal." (V2:34)

*"As a standard AEATF II study precaution, all subjects will be required to wear eye protection during the study. Eye protection will be supplied by AEATF II. In addition, subjects spraying outdoors with mechanically-pressurized sprayers (Scenario 1b)**, subjects spraying indoors using electrostatic sprayers (Scenario 2b),*** ~~*at high pressure (at or exceeding 60 psi)*~~ *and subjects spraying indoors with mechanically-pressurized sprayers (Scenarios 3a and 3b) will be required to wear a NISOH-approved filtering face-piece or half-face respirator.*

"For scenarios 1a, 1b, 2, and 3a, subjects will wear their own choice of footwear and socks; however, for scenario 3b (full PPE), rubber boots must be worn. Boots will be provided by the researchers if subjects do not have their own. Researchers will also provide new nitrile gloves, rain pants, and a rain jacket to each subject in Scenario 3b which will be worn during the entire monitoring interval. Hard hats will be provided to subjects in scenarios 3a and 3b." (V2:42)

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

"*If a subject does not wear the required clothing/PPE or acts in a manner that presents safety issues in the judgment of the research personnel or if he/she fails to follow the instructions of the researcher, the Study Director or the observer may terminate the subject's participation as per SOP AEATF II-11H.*" (V2:42)

"In the unlikely event that adverse effects are experienced, according to the SDS the most likely adverse effect is eye irritation. The symptoms of eye irritation are watering, irritation, and/or redness. This will be minimized by subjects handling only the diluted product and requiring that all test subjects wear eye protection while conducting work with the diluted sanitizer.

"If a subject reports eye irritation (or any other adverse effect) during the work period, he/she 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 needed, the medical professional will assist the subject in gently washing affected area with clean water. An eye wash station and soap and water will be available in case a subject experiences eye or skin irritation during the study. The medical professional will determine whether any medical treatment is necessary.

"The Study Director or designee will discuss the label safety warnings and heat stress with the subjects 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 an eye, skin, or breathing reaction 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 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 spraying activities or the hand and face/neck sampling. The medical professional will also check these same areas for possible irritation after monitoring is complete and samples have been collected. A member of the research team who is bilingual in English and Spanish will be present during this examination and during monitoring events involving subjects whose preferred language is Spanish.

"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 due to the study being conducted under controlled conditions and the relatively short monitoring durations. 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. A Spanish version will be posted for MEs that gave consent in Spanish.

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

"If subjects develop visible signs or report symptoms of distress such as pronounced fatigue, headache, cramps, feeling faint, increased pulse, muscle spasms, heavy sweating (or dry skin if previously sweating), extreme thirst, or rapid breathing, the subjects will be required to stop working immediately, and given their choice of water or a sports drink and a chair. The on-site medical professional will immediately be brought to the subject to give further medical management instructions and the Study Director will be contacted. AEATF II SOP 11C provides guidance on the handling of test subject illness and/or injury and will be followed. 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 index above 120 indoors or 110 outdoors), and for any post-study reports of illness, eye, skin, or respiratory reactions or unanticipated adverse effects.

"The Study Director will maintain a record of adverse health observations and reports, and follow the Study Sponsor, IRB, and EPA policies for medical event reporting as described in SOP 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." (V2:52-53)

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

See response to 4.2(b) above. The protocol calls for a trained medical professional to be on site for all monitoring events. The protocol also references two SOPs: SOP 11.B.1 for Management of Heat Stress (V4:138-149) and SOP 11.C.2 for Emergency Procedures (V4:150-157).

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

See the responses to 4.2(b) and 4.2(c). In addition to trained medical personnel on site during the study, researchers will be carefully observing subjects throughout their participation and will be looking for signs of fatigue, adverse effects from exposure to the test substance, and heat stress, and will raise concerns immediately to the Study Director or her designee, and the study's medical personnel.

(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 participation in the study you experience a skin reaction, eye reaction, or other physical injury that you believe is related to your participation in the study, you should seek medical treatment and alert the treating physician that you were participating in this research study. Also, call study staff immediately at the phone number on page 1 of this consent form."* (V2:184)

EPA expects that any adverse reactions would appear during or shortly after participation in the study, so a 24-hour follow up period is sufficient.

(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.

"*AEATF II SOP 11C provides guidance on the handling of test subject illness and/or injury and will be followed. 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.*" (V2:53)

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 sanitize and disinfect.

(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 for sanitizing and disinfecting. EPA will benefit from the submission of data that reduces uncertainty around the exposure experienced by consumers and workers using these products for various disinfecting and sanitizing tasks, 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, 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 these three disinfecting and sanitizing scenarios will likely meet 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?

Advarra 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?

Advarra IRB earned "Full Accreditation" from the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP).

(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. (V2:27)

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

"Volunteers will be recruited through the use of newspaper and radio ads in English and Spanish." (V2:48)

"Advertisements will contain a short description of the study and the scenario of interest, and a toll-free number where interested respondents can leave a voice message either in English or Spanish. These voice messages will be automatically forwarded to the Study Director or designated recruiter, or bilingual recruiter." (V2:48)

"Volunteers will be asked if they would like to have the consent meeting conducted in English or Spanish. For those who prefer Spanish, a bilingual researcher will assist during the consent meeting." (V2:48)

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. The Study Director will have at least one bilingual researcher on the staff to interact with subjects who speak Spanish. 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").

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). (V4:173)

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." (V4:171)

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

"At the consent meeting the potential subjects will be provided two copies of the Informed Consent Form (one to keep and one to sign). After the subjects have read the Informed Consent Form, the Study Director or bilingual researcher will go over the consent form to make sure that the potential subject understands it. The experimental study and the inclusion and exclusion criteria will be described to each potential subject 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. The label safety warnings will be discussed. Potential subjects will be told that they can withdraw from the study at any time without penalty or negative consequences. Potential subjects will be allowed to take these forms home with them to discuss the study with family and friends before deciding whether to sign the form.

"Copies of the appropriate label and SDS will be available at the consent meetings and provided to potential study volunteers upon request. A list of AEATF member companies will be available at the consent meetings should a potential subject have a question about employment with any of the entities listed in the eligibility criteria.

"If the eligible potential subject meets the inclusion criteria and is interested in enrolling in the study, he/she will be asked some questions to make sure that he/she understands what is being asked of him/her using a short list of standardized questions requiring an oral response (SOP AEATF II-11J).

"After confirming the subject understands what is being asked of him/her, the researcher will ask the subject to sign and date the Informed Consent Form and to answer the questions from the Subject Qualification Worksheet and then sign it. If the potential subject wants some time to think about the study, they will be allowed to leave and a follow-up appointment will be made. Once a consent form is signed, the subject is considered officially enrolled in the study." (V2:49)

(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 and the radio, and if necessary through online platforms and social media, 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."* (V4:171)

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."* (V2:184)

9. Respect for Subjects

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

"Subjects' names will not be revealed in the final report; instead information relating to each subject will be done using a Subject Identification code. All subjects' names and personal identifiers provided will be kept confidential to ensure their privacy. Photographs and video taken during the study will be taken in such a way or edited so that facial features are not recognizable or the photo/video will be deleted. Records correlating subject names to their identification codes will be retained separately from the study file in another file clearly marked 'CONFIDENTIAL'." (V2:35-36)

"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." (V2:58)

(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. If you withdraw from the study after coming to the test site on your scheduled date and time, whether you are monitored or not, you will still be paid for your time."* (V2:185)

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. There will be no penalty of any kind to you if you decide to withdraw from the study." (V2:181)*

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

"Any subject expressing a need or desire to withdraw from the research after the exposure monitoring begins for any reason will be paid their full compensation in addition to what was paid following the initial consent meeting (and after completing the medical evaluation and attending a respirator fit testing session, if applicable) and will be allowed to leave. A subject who has asked to withdraw from the study will be assisted in removing the air-sampling pump, hat, outer clothing, and inner dosimeter to avoid contamination, and that the subject will be instructed to wash his or her hands prior to leaving the study site. The hand and face/neck samples will be collected only with the subject's consent. If the subject was monitored for at least half of the target monitoring duration and has performed his/her work tasks as anticipated and all the samples were collected, it is likely that the samples will be analyzed; however, the Study Director will have the final responsibility on deciding whether these samples will be analyzed.

"If a subject withdraws from the research after the exposure monitoring begins and has performed the work task for less than half of the target monitoring duration, an alternate subject will be contacted and asked to take the place of the subject who withdraws. The monitoring of the alternate subject will be scheduled for a date and time that is convenient for the subject." (V2:36)

References

AEATF, 2020. Test substances and concentrations used in AEA14. June 17, 2020.

DeLaval Company, 2017. DeLaval Company is a member of the AEATF who provided technical input regarding the use of COP. DeLaval also arranged for site visits to two of their customers so that key study team members could observe cleaning and sanitizing at a frozen food processing plant (Windsor Foods, MS) and at a creamery (Petaluma Creamery, CA). The site visit to Windsor Foods on March 25, 2017, was done at midnight to observe the cleaning crew who came in after the work crew left for the night; on this particular night they provided a simulated COP tank cleaning with spare parts since the equipment had been dismantled and parts had been cleaned by COP the previous night.

NC State University, 2017. This is based on the information obtained by Leah Rosenheck (AEATF consultant) and Greg Baumann (Nisus Corp.) during a visit to the NC State University

Food Science Department Feldmeier Dairy Processing Lab in Raleigh, NC, on June 16, 2017 to observe the cleaning and sanitizing procedures at the University's milk and ice-cream production facility. The dairy processing facility supplies milk and ice-cream (Howling Cow Ice Cream brand) for the university dining halls and retail stores as well as the Central Prison in Raleigh (milk only!). The duration of cleaning was obtained from conversations with the employees and dairy manager as well as observing a worker manually cleaning equipment, taking apart equipment, and complete a cleaning/sanitizing cycle in a COP tank. Just as further verification, their visit to Sweetwater Farm Dairy (Sweetwater, TN) on March 9, 2017, provided consistent information.

Popendorf, W.; Selim, M.; Kross, B. (1992) Chemical Manufacturers Association Antimicrobial Exposure Assessment Study: Second Replacement to MRID 41761201: Lab Project Number: Q626. Unpublished study prepared by The University of Iowa. 316 p. MRID 42587501.

USEPA. 2017. Didecyl Dimethyl Ammonium Chloride (DDAC) Final Work Plan. Registration Review: Initial Docket, Case Number 3003. March 2017.

§ 26.1111 Criteria for IRB approval of research
AEATF II Pressurized Hand-Wand Study Protocol (AEA14)

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	V2:27-31
(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	V2:31-32
(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	V2:44
(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	V2:45-46
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	V2:45-46
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	n/a	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	V2:34
(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.	n/a	

§26.1116 General requirements for informed consent
AEATF II Pressurized Hand-Wand Study Protocol (AEA14)

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	V2:177-186
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	V2:177-186
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Y	V2:177-186
	(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	V2:177-186
	(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	V2:177-186
	(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	V2:177-186
	(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	V2:177-186
(b) When appropriate, one or more of the following elements	(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	V2:177-186
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Y	V2:177-186
	(3) Any additional costs to the subject that may result from participation in the research	Y	V2:177-186
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	Y	V2:177-186
	(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	V2:177-186
(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	V2:177-186

§26.1117 Documentation of informed consent
AEATF II Pressurized Hand-Wand Study Protocol (AEA14)

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	V2:48-50
(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	V2:48-50
(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 Pressurized Hand-Wand Study Protocol (AEA14)

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
(a) Copies of all of the records relevant to the research specified by § 26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and • reports of injuries to subjects.	 Y n/a Y n/a n/a	Volume 2, Volume 3
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.	Y	Volume 3
	§1115(a)(3): Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in §26.1109(f)(1).	n/a	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	Y	Volume 3
	§1115(a)(5): A list of IRB members in the same detail as described in § 26.1108(a)(2).	Y	Provided to EPA by Advarra
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a)(3) and (4).	Y	Provided to EPA by Advarra
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(c)(5).	n/a	
	§1115(a)(8): The rationale for an expedited reviewer's determination under §26.1110(b)(1)(i) that research appearing on the expedited review list described in §26.1110(a) is more than minimal risk.	n/a	
	§1115(a)(9): Documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of this subpart.	Y	Volume 2
(b) Copies of all of the records relevant to the information identified in	§1125(a)(1): The potential risks to human subjects	Y	Volume 2
	§1125(a)(2): The measures proposed to minimize risks to the human subjects;	Y	Volume 2
	§1125(a)(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	Volume 2
	§1125(a)(4): Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Volume 2
	§1125(a)(5): The balance of risks and benefits of the proposed research.	Y	Volume 2
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Volume 2

Requirement		Y/N	Comments
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	Volume 2
	§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	Volume 2
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	Volume 2
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.	Y	Volume 2
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research		n/a	
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.		n/a	