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 Immersion/Dip/Soak Scenario Design and Protocol for Exposure Monitoring

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We have reviewed the referenced protocol titled "A Study for Measurement of Potential Dermal and Inhalation Exposure During Antimicrobial Applications Involving Immersion, Dip, and Soak" (AEA12) submitted by the Antimicrobial Exposure Assessment Task Force II (AEATF II) from both scientific and ethics perspectives. This protocol proposes to evaluate potential dermal and inhalation exposure to consumers and/or occupational workers during the sanitizing of surfaces and equipment using an antimicrobial product in the following three scenarios: (1) bucket & sponge/rag, (2) 3-compartment sink, and (3) Clean-Out-of-Place (COP). Scientific aspects of the proposed research are assessed in terms of the recommendations of the EPA Guidelines Series 875 and of the EPA Human Studies Review Board. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board.

A. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 6. All elements of required documentation are provided in the submitted protocol package and supplementary documentation 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 immersion/dip/soak. The immersion/dip/soak treatment techniques for antimicrobial products that are used as sanitizers for hard surfaces (e.g., countertops/tables/etc.) and food processing equipment (e.g., cooking and eating utensils, and pieces of equipment such as fittings/impellers, etc.) can be sold to both occupational workers and consumers, but large-scale operations are typically in occupational settings. In this study, the AEATF II is sub-dividing these immersion/dip/soak application techniques into 3 exposure scenarios which are referred to herein as bucket & sponge/rag, 3-compartment sink, and Clean-Out-of-Place (COP). The subjects recruited for this study will be from the population with occupational experience with these application techniques. 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 scenarios as the following:
    - **Bucket & sponge/rag** – *"…placing a rag or sponge into a bucket of diluted antimicrobial solution, wringing out the rag/sponge, and wiping horizontal and vertical surfaces."* (V1:17)[1].
    - **3-compartment sink** - "*…three compartment sink system that is comprised of three sinks: the first to wash, the second to rinse, and the third to sanitize. … Although the focus of this study is on the task of immersing equipment and/or utensils into an antimicrobial solution, in the case of the food service industry, workers conduct a three step process to clean, rinse, and sanitize. Because of the limited size of the sinks, workers will run multiple batches of utensils through the three step process within a work shift. Since this is a sequential activity that is performed repeatedly, the entire process using the three-compartment sink will be monitored in the study. A quaternary ammonia-free dish washing detergent will be used in the wash sink. The diluted antimicrobial solution will be prepared in the third sink by research personnel, so the test subject will only be exposed to the diluted sanitizing solution in the third compartment sink and not during pouring/mixing. … Although this is a*

[1] This pagination convention is used throughout this review. "V1" refers Volume 1, "V2" refers to Volume 2, etc. Entries after the colon are page references; many page images bear more than one page number. In Volume 1, the cited page number is from the expression "Page n of 51" found at the bottom right-hand corner. Volume 2 page references are from the expression "Page n of 168" found at the bottom right-hand corner. Volume 3 page references are from the expression "Page n of 210" found at the bottom right-hand corner. Volume 4 page references are from the expression "Page n of 176" found at the bottom right-hand corner.

scripted study in a simulated environment, it is important that subjects clean articles that are actually soiled since this will impact the speed at which they move through the 3-step process. Therefore, a soiling procedure using commonly available food items such as oatmeal and/or instant mashed potatoes will be used to dirty the cookware and bakeware that will be provided to the test subjects. The monitored activities will include the washing, rinsing, and sanitizing steps, placement of the clean articles on to a drying rack, and opening of the sink stoppers to allow draining of the sinks once all articles have been cleaned and sanitized; however, the activity of cleaning the sinks with water and wiping the interior of the sinks has the potential to rinse off residues from the workers' hands and will not be monitored." (V1:17-18).

- **Clean-Out-of-Place (COP)** - *"…COP systems are used to clean pieces of equipment that cannot be cleaned by Clean-In-Place systems that clean the interior surfaces of equipment used in food processing facilities. Equipment that are cleaned using COP include removable articles such as fittings, clamps, product handling utensils, tank vents, pump rotors, impellers, blades, knives, casings, and hoses. COP generally occurs in large (100 to 500 gallon) stainless steel rectangular tanks specially designed for cleaning and sanitizing equipment parts. Once the equipment has been disassembled, manual dry cleaning or scraping may take place to remove debris from the equipment parts followed by placement into the COP tank. For this study, both the cleaning and the sanitization processes in COP tanks will be monitored; however, it will not be necessary to use dirty articles because, unlike with the 3-compartment sink, all the parts are placed together into one large tank and remain in the same tank throughout the cleaning, rinsing, and sanitizing processes. The upfront disassembling of the equipment and any manual pre-cleaning would not impact the contact potential with the sanitizing solution nor would it impact the amount of time spent doing the IDS activity. The monitored activity will include placing various pieces of equipment into the sanitization tank, adding water to clean the articles, overflowing (if it is the worker's typical practice), draining the wash water, rinsing of the articles (if typically done by the worker), filling the tank with water for the sanitizing step, allowing the articles to soak in the circulating sanitizing solution for at least the label recommended time, draining the tank, and finally removing the items and placing them on a rack or surface to air dry. The COP process is a very wet process and typically the water from the tank is drained through a large valve on the bottom of the tank onto the floor and down a drain."* (V1:18-19).

The study location and test sites are described in the protocol as follows: "*The geographic locations of the test sites will not be purposefully varied since exposure potential is not dependent on where the facility is located, but rather on the nature of the facilities, equipment used, articles sanitized, worker practices, and specific techniques used. … The bucket and rag/sponge and the 3-compartment sink sub-scenarios will be conducted at test sites located in the Orlando, Florida area. Three cafeterias/community centers/banquet facilities/restaurants or other rental site with kitchens containing a 3-compartment sink will be rented for the study. This will allow for three different sinks to be used in the study and for work activities to be done under typical use conditions. In addition to the kitchens, the locations should have other rooms containing tables, chairs, and other hard surfaces that can be wiped as part of the bucket and rag/sponge sub-*

scenario. The exact test sites and their locations will be provided in the final report. Since the test sites are commercial rental facilities, their availability will not be known until closer to the time that the study is scheduled. Facility identification and descriptions will be provided in the study report. Locating an appropriate place to conduct the COP use pattern is more challenging since conducting the study at an actual food processing plant would be difficult, if not impossible, given the disruption of normal work flow and numerous other regulatory and safety requirements under which these facilities operate. … Therefore the COP tank sub-scenario will take place at a COP tank manufacturing site in Madison, Wisconsin. This company is the leader in COP tank manufacturing and will provide three different tanks for the study. … A general description of the HVAC system and air flow will be documented. Ambient air temperature and relative humidity in the test room during all exposure monitoring events will be recorded." (V2: 35-36).

EPA intends to use these data developed by the AEATF II for the immersion/dip/soak application techniques to characterize typical occupational handlers' daily exposure to antimicrobial formulated products used as sanitizers in food processing facilities. Additionally, EPA will compare the results to the AEATF II's trigger pump spray and wipe scenario and use the higher exposures of the two based on the label being assessed. For example, if a label allows the spraying and wiping of countertops by consumers and the trigger pump spray and wipe scenario results in higher exposures than the bucket & sponge/rag, then the unit exposures of the former would be used to represent that label. Conversely, if dermal irritation was the risk driver and the bucket and sponge/rag indicated higher dermal exposure to the consumer, then this would be the scenario of interest. Additionally, some labels do not allow for the spraying of the product and restrict to application by sponge or cloth.

EPA believes that the AEATF II immersion/dip/soak scenarios are well defined (some revisions are provided below), and expects that the resulting data will meet the needs of regulatory agencies. The diversity of daily exposures under the immersion/dip/soak scenarios as defined in this proposal will adequately describe typical to high-end occupational daily exposures to the antimicrobial sanitizer applications. The use of occupational workers as test subjects is representative of the use pattern based on the equipment (e.g., 3-compartment sink and COP); but somewhat less known for the bucket and sponge/rag scenario -- perhaps that scenario will have lower unit exposures because workers are more experienced. EPA's regulatory approval process for sanitizers in the past has been based on the trigger pump spray and wipe; the availability to compare to the bucket & sponge/rag scenario will increase the risk characterization. The amount of active ingredient handled (AaiH) by the worker compared to the consumer will tend to drive risk decisions towards the worker exposure potential. Thus, the risk driver for regulatory decisions is the higher risks from the occupational scenario who apply more chemical per day and more frequently than consumers. The immersion/dip/soak exposure data will be used by EPA to extrapolate to the likely exposure expected from future events of sanitizing hard surfaces and equipment using treatment solutions containing antimicrobial products.

2. **Sampling Design:** The AEATF II has described in detail their sampling design for the three immersion/dip/soak scenarios 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 sanitizing of hard surfaces and food processing equipment.

The proposed sample size is a total of 54 monitoring events (MEs) evenly distributed among the three scenarios (i.e., 18 MEs per scenario). The plan is to use 18 individual test subjects for each scenario (use of same subject for multiple scenarios is allowed, V2:45) recruited from a population of occupational workers who had worked in the position within the last 2 to 3 years (V1:28). 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). To maintain the sample size as planned, EPA is recommending an increase in the range of ADBAC treatment solution concentrations to increase the statistical power for detecting proportionality between exposure and concentration (see detailed discussions below). Once the planned studies by the AEATF II have been completed, the adequacy of the sample sizes of completed studies will be revisited.

The study 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 bucket & sponge/rag scenario, the subjects will be provided 4 buckets that are typical of ones used to sanitize in restaurants/etc. and will be given the option to select the one they want to use. The following is a description of the planned diversity in the design of each scenario (Note: 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. Exposure data for pouring these formulation types are available from prior AEATF II exposure studies):

- **Bucket & sponge/rag** – The two pieces of equipment with both be varied (i.e., buckets & sponge/rag). Four bucket sizes will be provided, two pre-determined buckets that are 3 and 6-quart sanitizing Kleen-Pails meeting Hazard Analysis Critical Control Point (HACCP) guidelines and two "other" buckets from local retail stores (yet to be identified). Buckets will be filled by the researchers with the treatment solution between 50% to 90% capacity, the exact amounts to be selected by the subjects. Subjects will be able to choose between three sponges and three rags. Surfaces to wipe will be pre-determined by the researchers and will include vertical surfaces such as walls and horizontal surfaces such as countertops and tables. Surface area will be measured. Half the subjects will be assigned to each group of surface area to be wiped which will differ by 2-fold. Although the actual wiping action will be left up to the subjects, they will be instructed *"…to conduct a minimum of 5 immersion/wringing cycles with the sponge or rag"* (V1:24). Monitoring times will not be regulated (they will be based on the surface area to be cleaned) but are estimated to range between 20 to 60 minutes "*…to reflect the total amount of time that a busboy/busgirl or janitor would be doing this particular task during a*

workday." (V1:24). Concentrations of the ADBAC in the treatment solution are discussed separately below (see Table 1).

- **3-compartment sink** – Three different size/configuration sink setups will be selected and 6 MEs per setup will be randomly assigned to each setup. Sinks will be filled to a level requested by the subject, but at a minimum of 50%. A 2-fold number of soiled articles (dishware/etc.) will be cleaned/rinsed/sanitized by two equal groups of MEs (i.e., 9 MEs assigned to the lower amount of soiled dishware and 9 MEs assigned to the higher amount of soiled dishware; number of dishware articles not specified). Ecolab PanTastic detergent will be used for the cleaning portion of the process (AEATF II will confirm in the laboratory that it does not contain ADBAC) (V2:41). A variety of sponges (Commander Blue Scouring Pads, Scotch Brite Non-Scratch Scrub Sponge, and Scotch Brite No. 96 General Purpose Scouring Pad (V2:40)) will be provided for cleaning the dishware. Subjects will be instructed to work as they normally would do. The duration of the monitoring will be based on the time it takes to complete the task of cleaning the assigned amount of dishware; estimated to be 1 to 2 hours. (V1:25). Concentrations of the ADBAC in the treatment solution are discussed separately below (see Table 1).
- **Clean-Out-of-Place (COP)** - Three different size and/or dimension tanks will be selected and 6 MEs per tank will be randomly assigned. Tanks will be filled by the subjects as they normally would do. The subjects will be split into two groups of 9 MEs each. Each group will be assigned a set amount (2-fold difference) of equipment to be sanitized. No detergent will be used in the COP scenario. "*Unlike the 3-compartment sink sub-scenario, these articles need not be pre-soiled since all the parts are placed at the same time into the tank and remain in the same tank throughout the cleaning, rinsing, and sanitizing processes.*" (V2:42). One group of MEs will be able to sanitize the articles in one batch and the other group will need to sanitize the articles in two batches. The equipment to be sanitized will range in size from small pieces in wire baskets for immersion to larger items. During the automatic washing phase with tank jets, the subjects will be told to wait ~30 minutes in an area in the same room as the tank but not next to it to simulate typical activities associated with the COP operation (e.g., disassembling of other equipment). The total duration of each ME is expected to range from 1 to 1.5 hours for single batch and 2 to 3 hours for double batch. Concentrations of the ADBAC in the treatment solution are discussed separately below (see Table 1).

The AEATF II proposes to monitor 6 MEs per three concentrations of the test substance in each of the scenarios as outlined in Table 1 below. However, EPA has determined that based on the range of the concentrations proposed, for the 3-compartment sink and COP scenarios there is insufficient power to detect proportionality of concentration and exposure given the sample size. EPA proposes to increase the range of the concentration of the active ingredient for those two scenarios to increase the statistical power (the reader is referred to Section C.1 Statistical Design and Attachment 2, section 2.1(i)), below for additional details of EPA's recommendations).

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

- **Test subjects** – Test subjects will be recruited from occupational rather than residential populations. This has more of a potential relevance to the bucket & sponge/rag scenario then the other two scenarios as the other scenarios are atypical for consumers. *"Restricting the monitoring to only subjects with experience in these tasks may be a potential source of underestimating exposure as they may be more proficient at the task; however, it may also mean that they are more lax and apt to be less careful than someone who does the work activity for the first time. The use of occupational workers such as janitors or food service workers and not consumers for the bucket and rag/sponge sub-scenario may underestimate exposure. However, AEATF II does not foresee that this potential for underestimation would outweigh the sources that bias the study towards higher exposure."* (V1:16).
- **Limit of Quantitation (LOQ)** – *"It is important to recognize that some degree of overestimation bias is inherent in any study if the exposures measured on the samples collected from MEs are less than the limit of quantitation (LOQ). Based on the exposure pattern, the immersion/dip/soak application method is anticipated to result in low to no exposure to a number of body areas and for the air-samples. Thus, it is possible that some of the inner dosimeter samples and the air-samples will have non-quantifiable residues which will need to be estimated in an exposure analysis. For this study, the analytical method LOQ sets a practical lower limit on the amount of product that should be used for an ME and the standard approach is to assume ½ LOQ residues for calculating total exposure when there are non-quantifiable residues. However, because the LOQ will be relatively low, the resulting overestimation is not expected to be significant."* (V1:16).

  "The table below lists the target LOQs for C14-ADBAC in the different matrices.

Matrix	Target LOQ
OVS Tubes	1 ng/tube
Hand Wash*	1 µg/sample
Face/Neck Wipe	0.05 µg/sample
Forearm Wipe	0.05 µg/sample
Inner Dosimeter	3 µg/sample
Outer Dosimeter	3 µg/sample

  **500 ml per sample"* (V2:67).

- **Contamination from Prior Uses** – *"Another potential source of overestimation bias in the study design described in this document is the repeated use of one or more simulated work sites and the need to script the work activities to take place continuously over a specified period of time. The residue remaining in the test room(s) from prior uses represents a potential source of contamination for subsequent users. This will be minimized by cleaning and/or rinsing surfaces between MEs and allowing adequate time for surfaces to air dry."* (V1:16).

- **Scripted Activity** – *"Another potential source of overestimation bias is having the test subjects conduct the work activity continuously over a period of time in order to create a scripted monitored task for the study where in reality the worker may conduct the IDS work activity for much shorter periods of time intermittently throughout his/her work shift. The potential for workers to remove residues from their hands by hand-washing or by contact with other non-treated surfaces is not [feasible to] be captured in this type of a scripted study."* (V1:16).

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 as the surrogate compound (CAS number 139-08-2). ADBAC has a low vapor pressure (3.5E-12 mmHg @ 25 °C). The registered antimicrobial liquid formulated product in this study, Oasis 146 Multi-Quat Sanitizer (EPA Reg. No. 1677-198) contains a total of 7.5% Quats comprising 3% ADBAC and 4.5% other Quats. The composition of the 3% ADBAC Quat in the formulated product is 50% C_{14}, 40% C_{12}, and 10% C_{16}. (V2:28-29). The C_{14} chain of ADBAC was also used as the surrogate compound in previous AEATF II exposure studies (liquid pour and aerosol can).

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 scenarios for immersion/dip/soak use patterns. 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."* (V2:69). Note that under any of the proposed and recommended options given in Table 1 below, using the tabulated assumed GSDs, the fold relative accuracy goals are estimated to be met.

   Table 1 shows the AEATF II proposed concentrations of the test substance along with EPA recommended changes. For the bucket & sponge/rag scenario, EPA has determined

that based on the range of the concentrations proposed in the protocol, there is sufficient power (at least 80%) to detect proportionality of concentration and exposure given the sample size. However, for the 3-compartment sink and COP scenarios, EPA has determined that based on the range of the concentrations proposed in the protocol, there is insufficient power to detect proportionality of concentration and exposure given the sample size. For those two scenarios, EPA is providing two options to increase the range of the concentration of the active ingredient to increase the statistical power to an estimated 81%. The details of these power calculations are given below in Attachment 2, section 2.1(i).

The EPA recommendation for the 3-compartment sink and COP scenarios is to increase the statistical power in the study by increasing the range of the concentrations of the test substance in the treatment solution. In order to choose between options to increase the range of the test substance in the treatment solution one needs to consider the implications at both ends of the range. At the high end of the range one needs to consider the maximum allowable label application rate and at the low end of the range one needs to consider the desire to still obtain detectable residues on the sampling matrices. Option 1 is a viable option if the study site selection is not an active food serving location where the items sanitized (i.e., dishware, utensils, impellers, etc.) would be immediately be put into service and if at the end of the study the items are washed with a potable water rinse. If the conditions of Option 1 cannot be met, then Option 2 is expected to still result in detectable hand residues; residues for other body parts along with inhalation exposures are expected to be minimal, even all non-detect, and the lower concentrations might add to the uncertainty.

Table 1. Proposed and Recommended Options for ADBAC Concentrations.

Scenario	Assumed GSD[A]	Total ADBAC Concentration in ppm [Total QUAT Concentration in ppm]			Statistical Power
AEATF II Protocol's Proposal					
Bucket & sponge/rag	2	700 [1760]	350 [880]	175 [440]	0.90
3-compartment sink	4	160 [400]	80 [200]	40 [100]	0.37
COP	4				
EPA's Option 1					
Bucket & sponge/rag	2	No change proposed			0.90
3-compartment sink	4	400 [1000]	240 [600]	40 [100]	0.81
COP	4				
EPA's Option 2					
Bucket & sponge/rag	2	No change proposed			0.90
3-compartment sink	4	160 [400]	96 [240]	16 [40]	0.81
COP	4				

[A]Geometric Standard Deviation (GSD). The Bucket & sponge/rag scenario's dermal exposures are assumed to have similar GSDs to the AEATF II's RTU wipe scenario based on the similarity of the two scenarios. The AEATF II Governing Document's default geometric standard deviation (GSD) is assumed for the 3-compartment sink and COP scenarios.

2. **Proposed pattern of human exposure:** 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. The prepared treatment solution will be used by subjects according to typical sanitizing practices. 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 to their work as they work "*as they normally would do*". The researchers indicate the following:

   "The subjects will be informed as to exactly which surfaces are to be wiped with a bucket and rag/sponge, or which articles are to be washed and sanitized and where they can be put to dry.

   Subjects in the bucket and rag/sponge sub-scenario will be asked to choose the bucket size/type and rag or sponge type they want to use. Subjects will also be asked to specify how full they would like the bucket. Once the diluted sanitizing solution has been poured into the bucket, the subject can start work.

   Subjects in the 3-compartment sink sub-scenario will be asked to fill the wash and rinse sinks as they normally would. The subject will be provided with a quaternary ammonia-free detergent to use in the wash sink. A researcher will fill the sanitizing sink to the requested level with the sanitizing solution of the appropriate concentration. At this point the subject can start work.

   Subjects in the COP tank sub-scenario will be asked add the equipment parts and to fill the tank as they normally would for the wash cycle and to commence work. At the appropriate time a researcher will add sanitizer to the tank to create the appropriate concentration for the sanitizing step.

   Each subject will be asked to conduct their task as they typically would until they have completed their allocated surface area or articles to be sanitized; or the subject decides to withdraw from the study; or the research personnel terminates the monitoring." (V2:55-56).

   Subjects in the bucket & sponge/rag and 3-compartment sink scenarios will wear short-sleeved shirts, long pants, no gloves, and eye protection. Subjects in the COP scenario will wear long-sleeved shirts, long pants, gloves, and eye protection. (V2:13).

   The duration of each of the MEs will be based on how long it takes to complete the assigned tasks (e.g., clean the assigned surface area or sanitize the dishware or food processing equipment).

The EPA believes that the designs of the AEATF II immersion/dip/soak scenarios will represent the middle and upper portions of the daily exposure distribution expected for occupational workers applying sanitizers to hard surfaces and food processing equipment. The bucket & sponge/rag scenario will also be useful to estimate exposure to consumers who also use this technique in the home. The selection of occupational subjects who handle more treatment solution and clean more surface area with the sponge/rag than consumers is justified. The other two scenarios are atypical for consumers and if used in the home, are used on a much smaller scale.

3. **Endpoints and Measures:** The AEATF II proposes to measure dermal and inhalation exposures resulting from tasks associated with immersion/dip/soak. Dermal and inhalation exposure will be measured using whole-body dosimeters (WBD) (inner and outer), face/neck wipes, hand wipe/washes, forearm wipes (for bucket & sponge/rag and 3-compartment sink scenarios), and personal air monitors (V2:59-61). For the WBD, EPA is most interested in the inner dosimeters to assess potential exposure. The outer dosimeters will add to the existing data base on the development of protection factors for single layer of clothing. The potential for foot and head exposures are minimal and will not be monitored. The hand and face/neck wipe/wash is an appropriate method to determine exposure to the hands and face/neck. The use of forearm wipes is atypical for this body area but deemed acceptable for the two scenarios given that the lower arms will be immersed in the treatment solution (there is a need to avoid saturation of the WBD). The personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). An OSHA Versatile Sampler (OVS) will be used. *"The OVS tubes contain a glass fiber filter followed by two beds of XAD-2 sorbent in one glass tube (270/140 mg, SKC catalog number 226-30-16)."* (V2:59). Flow rates will be approximately 2 L/min for each of the samplers. (V2:54).

   "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. 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 and record the direction of airflow. The dimensions and layout of the room and the relative position of the test subjects with respect to the equipment being used and the airflow will be documented in the raw data for each test site." (V2:58).

   "The approximate volume of sanitizing solution used by each ME will be documented, including how many times the sanitizing sink is refilled during the ME and how many times the bucket is refilled with sanitizing solution." (V2: 57).

4. **QA/QC Plan:** The study will be conducted under the FIFRA GLP Standards (40CFR160) (V2:72). The AEATF II QA/QC plan for the immersion/dip/soak 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.

Matrix	Target Field Fortification Level (C_{14}-ADBAC)	LOQ (C_{14}-ADBAC)
OVS Tubes	3, 15, and 100 ng/tube	1 ng/tube
Hand Wash*	10, 100, and 1,000 µg/sample (bucket and rag/sponge and 3-compartment sink) 3, 30, and 300 µg/sample (COP tank)	1 µg/sample
Face/Neck Wipe	0.1, 1, and 10 µg/sample	0.05 µg/sample
Inner Dosimeter	10, 100, and 1,000 µg/sample	3 µg/sample

*Sample volume is 500 mL

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 immersion/dip/soak scenario will be separately analyzed. 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 concentration (ppm ADBAC). 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 ppm of ADBAC, has the same log-normal distribution for all 18 MEs. The fitted model will be used to estimate the arithmetic means, geometric means, and 95th percentiles of the normalized exposure for each group, together with bootstrap confidence intervals. The bootstrap confidence intervals will be used to assess the fold relative accuracy against a goal of 3-fold relative accuracy. 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 recently 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. 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 1, suggesting that the study was underpowered because the 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 ADBAC concentration 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). The graphs will also show the activity levels as defined in the next paragraph.

The statistical analysis plan will also include exploratory analyses of the impact of the 2-fold activity levels that are part of the study design. There are three groups of six MEs at different ADBAC concentrations. Within each group, three MEs will be assigned a lower activity level of 1 and the other three MEs will be assigned a two-fold higher activity level of 2. For the bucket & sponge/rag scenario, the activity level of 1 is for the smaller surface area to be cleaned and the activity level of 2 is for the larger surface area to be cleaned (approximately twice as large). For the 3-compartment sink, the activity level is 1 for the smaller number of articles cleaned and 2 for the larger number of articles cleaned (approximately twice as many). For the COP, the activity level is the number of loads (1 or 2). To investigate how the activity level and concentration are related to the exposure, we will fit linear models for the logarithm of the exposure with an intercept term, with a slope coefficient multiplied by the logarithm of the concentration (ppm ADBAC), and with another slope coefficient multiplied by the logarithm of the activity level (which is zero if the activity level equals 1). Of particular interest is the case where both slopes are close to 1, since that model implies that the exposure is proportional to the product of the concentration and the activity level, which in turn is approximately proportional to the AaiH. In a similar manner, for the bucket & sponge/rag scenario we will fit linear models for the logarithm of the exposure with an intercept term, with a slope coefficient multiplied by the logarithm of the concentration (ppm ADBAC), and with another slope coefficient multiplied by the logarithm of the surface area cleaned. Finally, we will fit linear models for the logarithm of the exposure with an intercept term and with a slope coefficient multiplied by the logarithm of the estimated AaiH, approximated by the product of the measured concentration and the approximate volume of sanitizing solution. The general intent of the various analyses proposed in this paragraph is to evaluate the potential for normalizing exposure by a surrogate of the AaiH instead of concentration. Unfortunately for the immersion/dip/soak scenarios, direct measurement of AaiH is not feasible.

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 (with modifications listed below)
- Quantification of the test materials
- Data collection, compilation and summary of test results

- Justification for selection of test substance and dilution rate (with modifications listed below)
- 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:

- EPA has determined that based on the range of the ADBAC concentrations proposed, for the 3-compartment sink and COP scenarios there is insufficient power to detect proportionality of concentration and exposure given the sample size. EPA proposes to increase the range of the concentration of the active ingredient for those two scenarios to increase the statistical power (the reader is referred to Section C.1 Statistical Design and Attachment 2, section 2.1(i)), below for additional details of EPA's recommendations).
- The protocol indicates that given the nature of the tasks, total volumes of treatment solutions used by each ME will only be approximated because the label use directions for these scenarios are typically expressed as concentrations and the exposures can be normalized by concentration rather than the amount of active ingredient handled (AaiH). "*Observe and record … including approximate volume of sanitizing solution used*." (V2:58) EPA is proposing to review the data once collected to determine the best approach to normalize the data and wants to re-emphasize that the researchers should make every attempt to record the volumes of treatment solution used during each monitoring event.
- The protocol recommends that volunteers are allowed to enroll in more than one of the three scenarios: *"It is likely that the bucket and rag/sponge and 3-compartment sink sub-scenarios will take place at the same test sites over the same time period. If this is the case, separate recruiting advertisements to solicit volunteers for each sub-scenario can be posted concurrently. It is possible that the same volunteer may respond to both ads since individuals experienced with using a 3-compartment sink may also have experience using a bucket and rag/sponge for sanitizing in food service establishments. The enrollment and monitoring of the same subject for multiple sub-scenarios is allowed. If this happens, the person would be assigned a separate Subject ID for each sub-scenario."* (V2: 45) If the same subject is used for two scenarios then the unit exposure estimates for the two scenarios will be correlated, so that estimates of several important summary statistics for the unit exposure of a person doing both tasks will be biased. For example, assuming the same active ingredient concentration is used for both tasks, the arithmetic mean unit exposure for both tasks combined is simply the sum of the arithmetic means for each task, but the 95th percentile unit exposure for both tasks combined cannot be properly estimated without accounting for the correlation between the exposures of the same worker doing both tasks. Precise estimates of this correlation

cannot be calculated if only a few of the workers do both tasks. EPA suggests that one of the following two approaches is considered: 1) no one can volunteer for more than one scenario; 2) all or almost all volunteers do both the bucket and sponge/rag and 3-compartment sink scenarios, but a different group of volunteers does the COP scenario. The first option avoids the correlation issue, but could lead to biased total exposure estimates for future workers who do multiple IDS activities. The second option should provide sufficient data to estimate correlations when the same worker uses a bucket and sponge/rag and a 3-compartment sink, so that reasonable unit exposure estimates can be calculated for all three individual scenarios and for a worker that uses a bucket and sponge/rag and 3-compartment sink in the same shift. The disadvantage of the second option is that it uses a smaller number of sampled workers to represent the entire population. Note that the protocol plans for both the bucket and sponge/rag and 3-compartment sink scenarios to be in the Orlando, Florida area, but the COP scenario to be located at a COP tank manufacturing site in Madison, Wisconsin. Thus, it is very unlikely that the same person will volunteer for the COP scenario as well as one of the other two scenarios.

- The study is designed to incorporate diversity and it captures many sources of variation in exposure from immersion/dip/soak activities (e.g., different bucket types/sizes, different sponges/rags, different sink sizes/configurations, different size COP tanks, differing amounts of items to be cleaned/sanitized, different workers, etc.); however, not all plausible sources of exposure variation have been accounted for in the design (e.g., different countertop textures, 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.
- As indicated by the HSRB in previous AEATF II protocol reviews (e.g., brush/roller study), the lack of justification and evidence for using only one subpopulation (e.g., consumer or professionals) does not detract from the data's scientific reliability but is a weakness when extrapolating exposure measurements to the other subpopulation (i.e., consumers or professionals). The same issue of using only one subpopulation applies to the IDS proposed study.

E. Summary Assessment of Ethical Aspects of the Proposed Research

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

1. **Societal Value of Proposed Research:** The purpose of this study is to "*develop new data for evaluating potential dermal and inhalation exposures of consumers and/or professional workers who conduct manual immersion/dipping/soaking (IDS) of articles, equipment, and/or utensils into solutions containing an antimicrobial and the immersion/dip/soak of a rag or sponge into a bucket containing an antimicrobial to sanitize hard surfaces.*" (V2:10) The data will be submitted to EPA to support registration and re-registration of antimicrobial pesticides. The existing data are not sufficient to answer the research questions. Additional dermal and inhalation exposure data are needed to accurately characterize the exposure potential application of

antimicrobial pesticides using these three methods. EPA will use this data in evaluating antimicrobial products applied using these methods.

2. **Subject Selection:** Sixty-six adult subjects will be recruited from two areas - the Orlando, Florida area (36 initially assigned for monitoring plus eight alternates) and the Madison, Wisconsin area (18 initially assigned for monitoring plus 4 alternates). The recruitment in Orlando will be conducted to enroll subjects in the bucket and rag/sponge, and the 3-compartment sink scenarios. The recruitment for the COP scenario will occur in Madison, Wisconsin as this area has a high number of food processing facilities, which employ COP as part of their industrial practices, and is therefore likely to have a sufficient number of qualified candidates.

   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 professional experience conducting the tasks to be monitored. The rationale for restricting subjects to those with work 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 a toll-free number where interested respondents can leave a message either in English or Spanish. The messages will be automatically forwarded to the Study Director or designated recruiter, and/or bilingual recruiter*." (V2:42) 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 cover whether the candidate has sufficient experience doing the task(s) to be monitored, and the candidate's age. 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 sub-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

For the bucket and rag/sponge sub-scenario:

- Self-identified as being in good health as defined as able to do the following tasks: lift and move a bucket containing sanitizer solution and weighing up to 16 pounds around a room and use a rag/sponge to clean hard surfaces for up to one hour
- **Have 2 months employment experience within the last 2 years** ~~Be currently employed or employed within the last 2 years~~ in a job where a bucket and rag/sponge was used at least once a month for sanitizing

For the 3-compartment sink sub-scenario:

- Self-identified as being in good health as defined as able to do the following tasks: stand and clean, rinse, and sanitize dirty cookware in a 3-compartment sink for up to 2 hours
- **Have 2 months employment experience within the last 2 years** ~~Be currently employed~~ in a position that requires the use of a 3-compartment sink to manually wash and sanitize cooking and/or eating/drinking utensils at least once a week ~~or have worked in such a position within the last 2 years~~

For the COP tank sub-scenario:

- Self-identified as being in good health as defined as able to do the following tasks: fill and operate a COP tank for up to 3 hours
- **Have 2 months employment experience within the last 3 years** ~~Be currently employed~~ in a position that requires the use of a COP tank at least once a month to clean and sanitize equipment parts ~~or have or have worked in such a position within the last 3 years~~

Exclusion Criteria (all sub-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) *(V2:21-22)*

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 (V4:138-140). 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.

Risks to Subjects: The proposed test product, Oasis 146 Multi-Quat Sanitizer, is an EPA-registered antimicrobial pesticide that contains the following quaternary ammonium antimicrobial compound: alkyl dimethyl benzyl ammonium chloride (3.00%); octyl decyl dimethyl ammonium chloride (2.25%); didecyl dimethyl ammonium chloride (1.35%); and dioctyl dimethyl ammonium chloride (0.90%). (V2:28). This product is representative of active ingredients that are commonly used in consumer and professional grade sanitizing and disinfecting products. Oasis 146 is registered for use in all three sub-scenarios to be monitored under this protocol. Oasis 146 is sold in a concentrated form, to be diluted prior to use. The label-approved dilution rates go up to 4 fluid ounces per gallon (fl oz per gal). For this study, the Oasis 146 will be diluted to concentrations ranging from 0.17 fl oz/gal to 3 fl oz/gal.

Risks to subjects include the risks associated with exposure to the antimicrobial pesticide Oasis 146 and to isopropyl alcohol, physical risks associated with the activities monitored under each sub-scenario, 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. The substances provided for use in each of the sub-scenarios will contain Oasis 146 diluted to concentrations at or below what is permitted under the EPA-approved label for the pesticide. At the proposed concentrations, Oasis 146 does not require users to wear any personal protective equipment. 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. Subjects will be wearing two layers of clothing and goggles/safety glasses to protect them from dermal and ocular exposure.

Subjects with job-related 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. It is not anticipated that participation in the

study would expose them to more risks associated with these activities than they would encounter on a daily basis at their job. Subjects will be permitted to take rests as needed, and the study director will provide chairs and cold drinks.

AEATF's SOP on managing heat stress (SOP AEATF II-11A.1) will be followed (V4:141-152). 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. They will monitor conditions that could lead to heat stress and stop the monitoring event if the heat index reaches 95 degrees. The study is planned for indoor, air-conditioned areas, so the likelihood of heat-related illness is low.

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

Information about subjects will be kept confidential by using numbers rather than names to identify subjects in study-related documents, keeping the key linking each subject's name and identifying number separate from other study records and in a locked cabinet, and removing any identifiable facial 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 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 the immersion/dipping/soaking activities."* (V2:26)

   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 on food contact and non-food contact surfaces."* (V2:26) 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. It is unlikely that as a result of subjects' participation in this research, they will experience additional risk beyond what they would ordinarily encounter when performing their jobs. With the recommendations of EPA incorporated, the risks to subjects have been thoughtfully and thoroughly minimized in the design of the research. The risks are reasonable in light of the likely benefits to society from new data supporting more accurate exposure assessments for antimicrobial

products used to disinfect and sanitize food and non-food surfaces through immersion, dipping, and soaking activities.

6. **Independent Ethics Review:** The protocol, informed consent form, subject qualification form, and recruitment materials were reviewed and approved by the Advarra IRB in July 2018. This research may not be initiated until IRB approval is granted following EPA and HSRB review.

   Advarra's 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 (V4:172-176). 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, (V4:176), and then sign the consent form and the Subject Qualification Worksheet. Each subject will be assigned as a subject or alternate and given instructions about participation.

8. **Respect for Subjects:** The protocol includes measures to protect subjects' privacy, including identifying subjects by number rather than name; maintaining the record linking name and number separately from the other study-related records and in a locked cabinet; not including the subjects' faces in any photos used in study reports; and

restricting access to records of the study to the study team, sponsor, EPA and the IRB. The protocol specifies that pregnancy testing will be conducted in a private location, the results will be verified by a female employee, and provision will be made for discrete disposal of the test. The process of dressing and undressing in the clothing required for the study will be conducted in a private location with a member of the study team of the same gender as the subject.

The proposed compensation for subjects is adequate to compensate them for inconvenience, missed employment opportunity, and travel to and from the test location. All volunteers will receive $20 for the consent meeting regardless of whether they enroll in the study. Subjects and alternates for the bucket and rag/sponge sub-scenario and the 3-compartment sink scenario will receive $100 for the study day. Subjects and alternates for the COP sub-scenario will receive $200 for the study day; this higher amount is based on the higher level of skill required of the subjects performing this task. This proposed compensation is not so high as to constitute undue inducement to participate or so low as to draw only economically disadvantaged participants.

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

F. Compliance with Applicable Ethical Standards

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

A detailed evaluation of how this proposal addresses applicable standards of ethical conduct is included in Attachments 2-6 to this review.

EPA Ethics Comments

Before the research is conducted, the documents should be revised as follows and resubmitted for review and approval by the reviewing IRB. This list of comments does not include all typographical and spelling edits, or minor suggestions about wording or language placement:

General comments

1. Specify the amount of experience candidates must have for each sub-scenario. The protocol calls for subjects to be currently or recently employed in a job where the task is conducted, but does not state how much time in the job is necessary (e.g., “Be currently employed or employed within the last 2 years in a job where a bucket and rag/sponge was used at least once a month for sanitizing” (V2:21). Because AEATF is proposing to minimize risks by recruiting people with occupational experience performing the tasks to be monitored, the minimum amount of experience must be

specified, e.g., "**Have at least 2 months experience** ~~Be currently employed or employed~~ within the last 2 years in a job where a bucket and rag/sponge was used at least once a month for sanitizing." These edits should be made consistently throughout the protocol, consent forms, recruitment materials, and subject qualification questionnaires.

2. Add to the inclusion criteria for all scenarios the following "**Non-smoker or willing to refrain from smoking for the duration of the test day**."
3. Specify which inclusion and exclusion criteria apply to all 3 sub-scenarios.
4. Clarify that a subject withdrawing will be assisted in removing the outer clothing and dosimeters to avoid contamination and that the subject will be instructed to wash his or her hands and forearms prior to leaving the study site.
5. Revise the protocol to include the potential for confidentiality to be breached through photos taken of the subjects: "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 your facial features and any identifiable features, such as piercings or tattoos, are not recognizable or deleted.**" (V2:26)
6. Explain under what circumstances data from a subject withdrawing will be included in the study results and under what circumstances an alternate subject will be asked to perform a monitoring event. (V2:28)
7. At consent meetings for each of the sub-scenarios, the person conducting should discuss the Oasis 146 Multi-Quat label safety warnings with the subjects. This should be in addition to the discussion of the label safety warnings with subjects immediately prior to the monitoring event.
8. After the consent form review and prior to obtaining consent, ensure that all subjects answer questions to ensure their comprehension of the materials. The current protocol language is unclear and could be read as only asking questions of those who do not want to take the forms home to think about it further. Please edit as follows: "*If the eligible potential subject meets the inclusion criteria and is interested in enrolling in the study* ~~*and does not want to take the forms home to think about it further*~~*, 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).*" (V2:46).
9. Include a statement that a list of all of the members of the AEATF-II task force and the ACC will be available during the consent process in the event any subject has a question related to employment with any of the entities listed in the eligibility criteria.
10. Revise the consent forms for all 3 sub-scenarios as follows: "The sanitizer used in this study is Oasis 146 Multi-Quat Sanitizer that is made by Ecolab and registered **as an antimicrobial pesticide** by the US EPA."

11. Revise the protocol to clarify whether the subjects will handle their drink containers, or whether a member of the research team will hold the drink and allow the subject to drink through a straw during the monitoring event. If subjects are to hold the container, explain whether holding a drink container would affect the amount of the test substance on subjects' hands?

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. EPA has reviewed the protocol and is presenting the protocol 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 April 15, 2013, provides in pertinent part:

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

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

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

Attachments:
1. EPA Scenario Review: AEATF-II Immersion/Dip/Soak Scenario
2. EPA Protocol Review: AEATF II Immersion/Dip/Soak 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 Immersion/Dip/Soak Scenario

Title: **IMMERSION/DIP/SOAK SCENARIO: RATIONALE FOR STUDY DESIGN**

Date: August 2, 2018

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

1. Scope of Scenario Design

(a) Is the scenario adequately defined?

"The purpose of the immersion/dip/soak monitoring study is to develop measurements of potential exposures to antimicrobials used to sanitize/disinfect/treat objects by immersion, dipping, or soaking. These data will consist of dermal and inhalation exposure measurements derived from monitoring human test subjects under conditions constructed to broadly represent those expected under actual use conditions. The general approach used by AEATF II to obtain such data is to conduct scripted simulated-condition exposure monitoring studies for scenarios of interest. For each scenario, a set of monitoring events (ME) is constructed. Each ME simulates one set of possible conditions consistent with the scenario using a person who is monitored for dermal and inhalation exposure. For this study, three sets of 18 MEs will be collected, one for each sub-scenario. Each set of MEs is constructed so as to span a diverse set of conditions expected to impact exposure for that application. The exposure results from this monitoring study must be applicable to different active ingredients and to the use of varying amounts of a product that could lead to potential exposure. … For the immersion/dip/soak scenario (as is true for all AEATF II scenarios) only a small number of expensive experimentally-obtained monitoring events are possible. Each ME represents the exposure from a single handler-day, but collectively a set of MEs can be used to predict exposure for future handler-days involving other products. Each of the three IDS sub-scenarios in this study could involve more handling conditions than any small number of MEs can practically include in a single study. For example, there are many possible active ingredients; concentrations of ai in diluted sanitizing solutions; tanks and other equipment used to treat articles; number, type, and size/configuration of articles to be sanitized/disinfected/treated; workers and their associated behaviors; and environmental conditions that can be involved. All of these might impact dermal and/or inhalation exposure potential to varying degrees. In view of this limitation, a practical goal for this study is that 18 MEs for each IDS sub-scenario will be collected involving some planned diversity in handling conditions that are biased towards higher exposure elements. As a result, the diverse sample of MEs for each sub-scenario is

expected to at least cover the middle and upper portions of the exposure distribution, and to capture the higher end range of exposures that is expected to exist." (V1:14-16)

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

Bucket & sponge/rag – "*…placing a rag or sponge into a bucket of diluted antimicrobial solution, wringing out the rag/sponge, and wiping horizontal and vertical surfaces."* (V1:17).

3-compartment sink - "*…three compartment sink system that is comprised of three sinks: the first to wash, the second to rinse, and the third to sanitize. … Although the focus of this study is on the task of immersing equipment and/or utensils into an antimicrobial solution, in the case of the food service industry, workers conduct a three step process to clean, rinse, and sanitize. Because of the limited size of the sinks, workers will run multiple batches of utensils through the three step process within a work shift. Since this is a sequential activity that is performed repeatedly, the entire process using the three-compartment sink will be monitored in the study. A quaternary ammonia-free dish washing detergent will be used in the wash sink. The diluted antimicrobial solution will be prepared in the third sink by research personnel, so the test subject will only be exposed to the diluted sanitizing solution in the third compartment sink and not during pouring/mixing. … Although this is a scripted study in a simulated environment, it is important that subjects clean articles that are actually soiled since this will impact the speed at which they move through the 3-step process. Therefore, a soiling procedure using commonly available food items such as oatmeal and/or instant mashed potatoes will be used to dirty the cookware and bakeware that will be provided to the test subjects. The monitored activities will include the washing, rinsing, and sanitizing steps, placement of the clean articles on to a drying rack, and opening of the sink stoppers to allow draining of the sinks once all articles have been cleaned and sanitized; however, the activity of cleaning the sinks with water and wiping the interior of the sinks has the potential to rinse off residues from the workers' hands and will not be monitored."* (V1:17-18).

Clean-Out-of-place (COP) - *"…COP systems are used to clean pieces of equipment that cannot be cleaned by Clean-In-Place systems that clean the interior surfaces of equipment used in food processing facilities. Equipment that are cleaned using COP include removable articles such as fittings, clamps, product handling utensils, tank vents, pump rotors, impellers, blades, knives, casings, and hoses. COP generally occurs in large (100 to 500 gallon) stainless steel rectangular tanks specially designed for cleaning and sanitizing equipment parts. Once the equipment has been disassembled, manual dry cleaning or scraping may take place to remove debris from the equipment parts followed by placement into the COP tank. For this study, both the cleaning and the sanitization processes in COP tanks will be monitored; however, it will not be necessary to use dirty articles because, unlike with the 3-compartment sink, all the parts are placed together into one large tank and remain in the same tank throughout the cleaning, rinsing, and sanitizing processes. The upfront disassembling of the equipment and any manual pre-cleaning would not impact the contact potential with the sanitizing solution nor would it impact the amount of time spent doing the IDS activity. The monitored activity will include placing various pieces of equipment into*

the sanitization tank, adding water to clean the articles, overflowing (if it is the worker's typical practice), draining the wash water, rinsing of the articles (if typically done by the worker), filling the tank with water for the sanitizing step, allowing the articles to soak in the circulating sanitizing solution for at least the label recommended time, draining the tank, and finally removing the items and placing them on a rack or surface to air dry. The COP process is a very wet process and typically the water from the tank is drained through a large valve on the bottom of the tank onto the floor and down a drain." (V1:18-19).

The scenario is limited to the use of the 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. Exposure data for pouring these formulation types are available from prior AEATF II exposure studies.

The AEATF II immersion/dip/soak scenario design appropriately proposes to diversify the sampling characteristics by selecting different subjects for each monitoring event and allowing them to clean as they normally would do, conducting the study during multiple application dates, providing various equipment (buckets, sink and tank sizes, sponges and rags), varying the area to be sanitized, varying the amount of items to be sanitized, as well as varying the active ingredient concentration in the treatment solution. The test subjects will be drawn from the occupational population to represent janitors/professionals who apply more sanitizing solution from buckets & sponge/rag than homeowners (the other two scenarios are atypical consumer uses).

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

There are no exposure data available involving immersion/dip/soak. The closest data available for the bucket & sponge/rag scenario are the data for the trigger pump spray and wipe and the data for the ready-to-use (RTU) wipes collected by the AEATF II in previous studies. The proposed study will fill these data gaps for the sanitizer uses.

2. Rationale for Scenario Sampling Design

(a) Are the variables in the immersion/dip/soak scenario design likely to capture diverse exposures at the high-end?

The design choices in the immersion/dip/soak scenario include: (1) using 3 different exposure scenarios to capture the various activities associated with sanitizing solution treatments; (2) selection of the type of equipment (e.g., bucket, sponge/rag) by the subject from an assortment provided by the researchers; (3) variation provided in the volume of treatment solution, surface area treated, and number of items cleaned; (4) variation in the active ingredient concentration; and (5) diversity among test subjects. Additional descriptions of these key variables are provided 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. For example, in the bucket & sponge/rag scenario, the subjects will be provided 4 buckets that are typical of ones used to sanitize in restaurants/etc. and will be given the option to select the one they want to use. The following is a description of the planned diversity in the design of each scenario:

Bucket & sponge/rag – The two pieces of equipment will both be varied (i.e., buckets & sponge/rag). Four bucket sizes will be provided, two pre-determined buckets that are 3 and 6-quart sanitizing Kleen-Pails meeting Hazard Analysis Critical Control Point (HACCP) guidelines and two "other" buckets from local retail stores (yet to be identified). Buckets will be filled by the researchers with the treatment solution between 50% to 90% capacity, the exact amount to be selected by subjects. Subjects will be able to choose between three sponges and three rags. Surfaces to wipe will be pre-determined by the researchers and will include vertical surfaces such as walls and horizontal surfaces such as countertops and tables. Surface area will be measured. Half the subjects will be assigned to each group of surface area to be wiped which will differ by 2-fold. Although the actual wiping action will be left up to the subjects, they will be instructed *"…to conduct a minimum of 5 immersion/wringing cycles with the sponge or rag"* (V1:24). Monitoring times will not be regulated (they will be based on the surface area to be cleaned) but are estimated to range between 20 to 60 minutes "*…to reflect the total amount of time that a busboy/busgirl or janitor would be doing this particular task during a workday*." (V1:24). Concentrations of the ADBAC in the treatment solution are discussed separately (see Table 1).

3-compartment sink – Three different size/configuration sink setups will be selected and 6 MEs per setup will be randomly assigned to each setup. Sinks will be filled to a level requested by the subject, but at a minimum of 50%. A 2-fold number of soiled articles (dishware/etc.) will be cleaned/rinsed/sanitized by two equal groups of MEs (i.e., 9 MEs assigned to the lower amount of soiled dishware and 9 MEs assigned to the higher amount of soiled dishware; number of dishware articles not specified). Ecolab PanTastic detergent will be used for the cleaning portion of the process (AEATF II will confirm in the laboratory that it does not contain ADBAC) (V2:41). A variety of sponges (Commander Blue Scouring Pads, Scotch Brite Non-Scratch Scrub Sponge, and Scotch Brite No. 96 General Purpose Scouring Pad (V2:40)) will be provided for cleaning the dishware. Subjects will be instructed to work as they normally would do. The duration of the monitoring will be based on the time it takes to complete the task of cleaning the assigned amount of dishware; estimated to be 1 to 2 hours. (V1:25). Concentrations of the ADBAC in the treatment solution are discussed separately (see Table 1).

Clean-Out-of-Place (COP) - Three different size and/or dimension tanks will be selected and 6 MEs per tank will be randomly assigned. Tanks will be filled by the subjects as they normally would do. The subjects will be split into two groups of 9 MEs each. Each group will be assigned a set amount (2-fold difference) of equipment to be sanitized. No detergent will be used in the COP scenario. "*Unlike the 3-compartment sink sub-scenario, these articles need not be pre-soiled since all the parts are placed at the same time into the tank and remain in the same tank throughout the cleaning, rinsing, and sanitizing processes.*" (V2:42). One group of MEs will be able to sanitize the articles in one batch and the other group will need to sanitize the articles in two batches. The equipment to be sanitized will range in size from small pieces in wire baskets for immersion to larger items. During the automatic washing phase with tank jets, the subjects will be told to wait ~30 minutes in an area in the same room as the tank but not next to it to simulate typical activities associated with the COP operation (e.g., disassembling of other equipment). The total duration of each ME is expected to range from 1 to 1.5 hours for single batch and 2 to 3 hours for double batch. Concentrations of the ADBAC in the treatment solution are discussed separately (see Table 1).

Test Subjects. *"Another important meta-characteristic that will be formally diversified is the test subject, i.e., the person volunteering to perform the various sanitizing tasks. People with experience in IDS will be recruited from the local area in which the test site is located. … Although both consumers and professionals use this method* [bucket & sponge/rag] *of application and there is no obvious reason to believe there would be differences in exposures attributed to technique, only subjects who have occupational experience with this application method will be recruited for the study. Additionally, because greater quantities of product are handled by professionals, professional handler exposure is anticipated to be higher. … The experience criteria for potential test subjects will be that they are currently employed or were employed within the last 2 years in a position (e.g., busboys/busgirls, cleaning staff, janitors, housekeepers, sanitation workers) where they used a bucket and rag/sponge at least once a month for cleaning and/or sanitizing hard surfaces.*

People with experience doing manual dishwashing using a 3-compartment sink in the food service industry will be recruited for this sub-scenario. Potential subjects must either be currently employed in a position where they use a 3-compartment sink to wash and sanitize cooking and/or eating utensils or have worked in such a position within the last 2 years.

People with experience using a COP tank in a food processing facility (such as meat processing, dairy or cheese processing, pet food processing, and breweries) will be recruited for this sub-scenario. It is expected to be more difficult to find qualified people in the food processing industry so the timeframe of recent experience was expanded from 2 to 3 years to help broaden the pool of potential subjects. Thus potential test subjects must either be currently employed in a position where they use a COP tank to wash and sanitize equipment parts or have worked in such a position within the last 3 years." (V1:27-28).

Active Ingredient Concentration. The proposed approach is for each scenario to test 6 MEs with each of three ADBAC concentrations, as shown in Table 1. For the bucket and sponge/rag scenario, the proposed concentrations are 700, 350, and 175 ppm ADBAC. For the 3-compartment sink and COP scenarios, the proposed concentrations are 160, 80, and 40 ppm ADBAC. EPA recommends no changes for the bucket and sponge/rag scenario, but recommends a wider range of concentrations for the 3-compartment sink and COP scenarios in order to have sufficient statistical power to detect proportionality between (expected) exposure and concentration. i.e., log-log-linearity with a slope of one. In Option 1, the recommended concentrations are 400, 240, and 40 ppm ADBAC. In Option 2, the recommended concentrations are 160, 96, and 16 ppm ADBAC.

An important consideration for these scenarios is the choice of normalizing factor, specifically whether the exposure data should be normalized by the amount of active ingredient handled (AaiH) or by the concentration. *"To be most useful to regulators, the data need to be normalized by some measurable parameter that reflects the potential contact with the active ingredient. Unlike most occupational exposure studies, the normalizing factor for this study may not be the amount of active ingredient handled (AaiH), typically expressed as pounds of ai handled, but rather concentration of active ingredient (e.g., ppm or % active ingredient) in the antimicrobial solution. The label use directions for immersion/dip/soak of antimicrobials are typically expressed as parts per million (ppm); for this reason, it is possible that the concentration of active ingredient may be the most appropriate normalizing factor."* (V1:15). *The approximate volume of sanitizing solution used by each ME will be documented, including how many times the sanitizing sink is refilled during the ME and how many times the bucket is refilled with sanitizing solution. Although the total volume of sanitizing solution used will not be factored into the exposure calculation, it provides ancillary information on the work practice."* (V2: 57). Since the total volumes used will only be approximated and since the label use directions for these scenarios are typically expressed as concentrations, EPA primarily proposes to normalize the exposures by concentration rather than AaiH. Nonetheless, the researchers should make every attempt to record the volumes of treatment solution used during each monitoring event.

Table 1 shows the AEATF II proposed concentrations of the test substance along with EPA recommended changes. For the bucket & sponge/rag scenario, EPA has determined that based on the range of the concentrations proposed in the protocol, there is sufficient power (at least 80%) to detect proportionality of concentration and (expected) exposure given the sample size. However, for the 3-compartment sink and COP scenarios, EPA has determined that based on the range of the concentrations proposed in the protocol, there is insufficient power to detect proportionality of concentration and (expected) exposure given the sample size. For those two scenarios, EPA is providing two options to increase the range of the concentration of

the active ingredient to increase the statistical power to an estimated 81%. The details of these power calculations are given below in Attachment 2, section 2.1(i).

The EPA recommendation for the 3-compartment sink and COP scenarios is to increase the statistical power in the study by increasing the range of the concentrations of the test substance in the treatment solution. In order to choose between options to increase the range of the test substance in the treatment solution one needs to consider the implications at both ends of the range. At the high end of the range one needs to consider the maximum allowable label application rate and at the low end of the range one needs to consider the desire to obtain detectable residues on the sampling matrices. In the bucket & sponge/rag scenario, the AEATF has proposed to use a maximum of 1,760 ppm total Quat (i.e., 3 fluid ounces of formulated product per gallon of water) which will yield 700 ppm ADBAC. Note: the maximum label rate for this product is 4 oz/gal for this same use. As indicated on the Oasis label, the maximum label rate for the food processing equipment and food contact use for the restaurant and bar rinse for sanitizing eating and drinking utensils (i.e., 3-compartment sink and COP scenarios) is the 400 ppm total Quat (160 ppm ADBAC) without a potable water rinse (water rinses are specified prior to the sanitizing step). (V2:84-85).

Option 1 is a viable option if the study site selection is not an active food serving location where the items sanitized (i.e., dishware, utensils, impellers, etc.) would be immediately be put into service and if at the end of the study the items are washed with a potable water rinse. If the conditions of Option 1 cannot be met, then Option 2 is expected to still result in detectable hand residues; residues for other body parts along with inhalation exposures are expected to be minimal, even all non-detect, and the lower concentrations might add to the uncertainty.

Table 1. Proposed and Recommended Options for ADBAC Concentrations.

Scenario	Assumed GSD[A]	Total ADBAC Concentration in ppm [Total QUAT Concentration in ppm]			Statistical Power
AEATF II Protocol's Proposal					
Bucket & sponge/rag	2	700 [1760]	350 [880]	175 [440]	0.90
3-compartment sink	4	160 [400]	80 [200]	40 [100]	0.37
COP	4				
EPA's Option 1					
Bucket & sponge/rag	2	No change proposed			0.90
3-compartment sink	4	400 [1000]	240 [600]	40 [100]	0.81
COP	4				
EPA's Option 2					
Bucket & sponge/rag	2	No change proposed			0.90

3-compartment sink	4	160 [400]	96 [240]	16 [40]	0.81
COP	4				

[A]Geometric Standard Deviation (GSD). The Bucket & sponge/rag scenario's dermal exposures are assumed to have similar GSDs to the AEATF II's RTU wipe scenario based on the similarity of the two scenarios. The AEATF II Governing Document's default geometric standard deviation(GSD) is assumed for the 3-compartment sink and COP scenarios.

(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." (V2:47).*
- Subjects will be randomly assigned to the target Quat concentration level within each scenario;
- Subjects in the bucket and sponge/rag scenario will be randomly assigned to the surface area to be treated;
- Subjects will be randomly assigned to the size/configuration of the 3-compartment sink choices;
- Subjects will be randomly assigned to the amounts of articles to be treated in the 3-compartment sink scenario;
- Subjects will be randomly assigned to the size of the COP tank choices;
- Subjects will be randomly assigned to the number of articles to be cleaned/sanitized in the COP scenario (i.e., either 1 batch or 2 batches of articles).

(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 immersion/dip/soak applications for subjects sanitizing hard surfaces and food processing equipment using the treatment solution are following procedures according to typical practices. The typical procedures are wiping down hard surfaces and immersing food contact items into the treatment solution by dipping/soaking.

"Subjects in the bucket and rag/sponge sub-scenario will be asked to choose the bucket size/type and rag or sponge type they want to use. Subjects will also be asked to specify how full they would like the bucket. Once the diluted sanitizing solution has been poured into the bucket, the subject can start work.

Subjects in the 3-compartment sink sub-scenario will be asked to fill the wash and rinse sinks as they normally would. The subject will be provided with a quaternary ammonia-free detergent to use in the wash sink. A researcher will fill the sanitizing sink to the requested level with the sanitizing solution of the appropriate concentration. At this point the subject can start work.

Subjects in the COP tank sub-scenario will be asked [to] *add the equipment parts and to fill the tank as they normally would for the wash cycle and to commence work. At the appropriate time a researcher will add sanitizer to the tank to create the appropriate concentration for the sanitizing step.*

Each subject will be asked to conduct their task as they typically would until they have completed their allocated surface area or articles to be sanitized; or the subject decides to withdraw from the study; or the research personnel terminates the monitoring." (V2:55-56).

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

The proposed study has purposely excluded using residential (consumer) test subjects. The AEATF II selected occupational workers over residential/consumer test subjects because consumers treat less surface area than occupational workers while sanitizing hard surfaces (bucket scenario) and it is atypical for consumers to participate in the other two scenarios.

The AEATF II excluded the subjects from pouring the formulated product. 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. The registered antimicrobial liquid formulated product in this study, Oasis 146 Multi-Quat Sanitizer (EPA Reg. No. 1677-198) contains a total of 7.5% Quats comprising 3% ADBAC and 4.5% other Quats. The composition of the 3% ADBAC Quat in the formulated product is 50% C_{14}, 40% C_{12}, and 10% C_{16}. (V2:28-29).

"*Oasis 146 is an EPA-registered formulated product designed to be diluted in water prior to use. It is used as a sanitizer, disinfectant, and deodorizer in homes, hospitals, and other commercial and industrial areas. It can be used on a wide range of hard, non-porous surfaces and on food contact surfaces. Application methods include mop, rag, sponge,*

soaking, mechanical or hand-pump spray device. This product is currently registered for all of the sub-scenarios in this study. ADBAC has been used in previous AEATF II studies as the analyte and is selected for measurement based on its good stability, its relative abundance in formulated products labeled for IDS uses, low mammalian toxicity, and the sensitivity of its analytical methods." (V2:33).

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."* (V2:69). Note that under any of the proposed and recommended options given in Table 1 above, using the tabulated assumed GSDs, the fold relative accuracy goals are estimated to be met. 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 Immersion/Dip/Soak Study Protocol (AEA12)

Title: **A Study for Measurement of Potential Dermal and Inhalation Exposure During Antimicrobial Applications Involving Immersion, Dip, and Soak** (Volume 2)

Date: August 2, 2018

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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 immersion/dipping/soaking (IDS) of articles, equipment, and/or utensils into solutions containing an antimicrobial and the immersion/dip/soak of a rag or sponge into a bucket containing an antimicrobial to sanitize hard surfaces. The terms "immersion", "dip", and "soak" are used interchangeably to describe the application process in which an article (e.g., equipment/equipment part, cooking/eating utensils, barber/salon equipment, surgical instruments) is placed into a container (e.g., bucket, tank, sink, or other holding device) containing an antimicrobial solution for purposes of sanitizing, disinfecting, or protecting the article. The terms "immersion", "dip", and "soak" are also used interchangeably to describe the placement a rag or sponge into a bucket containing a sanitizing solution where the treated surface is the hard surface (e.g., countertops), not the rag or sponge itself." (V2:10).

(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. Currently EPA has evaluated trigger pump spray & wipe and ready-to-use (RTU) wipes for hard surface cleaning-type products, but some labels do not allow sprays, nor are the products RTU wipes. 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 and immersing items (e.g., food processing equipment and dishware) to be sanitized.

"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." (V2:12).

(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/or consumers (for the bucket and sponge/rag scenario) who use sanitizers to clean/sanitize hard surfaces and food processing equipment, etc.

(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. There is the potential to model a film-thickness of water on the hands, but not for other body parts or inhalation exposure. Even the film-thickness approach would not estimate dermal hand exposure, with accuracy, over the duration of the 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 a sanitizing solution during the immersion/dip/soak (IDS) applications. In this study, at least 18 subjects will be monitored in each of the three scenarios associated with IDS 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 immersion/dipping/soaking (IDS) of articles, equipment, and/or utensils into solutions containing an antimicrobial and the immersion/dip/soak of a rag or sponge into a bucket containing an antimicrobial to sanitize hard surfaces." (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."* (V2:69).

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

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

The objective cited above can be achieved by the study as proposed. However, in order to meet the AEATF II secondary objective of having 80% power to detect proportionality between exposure and concentration, EPA has provided recommendations to change the range of the treatment solution concentrations as noted within this review.

2.1 Statistical Design

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

The benchmark objective in the AEATF II exposure studies is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time. A statistical rationale for the choice of sample size is presented in item 2.1(i) below. The proposed sample size and study design for each scenario has six groups of 3 MEs each for different concentrations of active ingredient. Based on the data from the AEATF II ready-to-use wipe study, the proposed sample size and study design is estimated to meet the 3-fold relative accuracy goals for the bucket and sponge/rag scenario. Based on the Governing Document default assumption of a geometric standard deviation of 4, the proposed sample size and study design is estimated to meet the 3-fold relative accuracy goals for the 3-compartment sink and COP scenarios.

"A total of 66 test subjects will be recruited for this study. Twenty-two subjects are required for each sub-scenario. This includes the planned 18 subjects to be monitored and 4 alternates for each sub-scenario. The 4 alternates will be recruited in case a subject withdraws from the study or fails to complete the assigned work tasks or otherwise does not complete the monitoring event." (V2:44).

(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. The ME number will determine which quat concentration group and which equipment/task diversity group the subject will be in." (V2:47).

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

Yes, the proposed research includes developing unit exposures for the uses associated with immersion/dip/soak scenario and there is adequate justification for selecting test subjects from the occupational population. Occupational workers would be expected to clean more surface area than the typical consumer using a hard surface sanitizer. It would be atypical for a consumer to use a 3-compartment sink or COP tank to sanitize dishware and/or food processing equipment.

(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)." (V2:69).

Each immersion/dip/soak scenario will be separately analyzed. 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 concentration (ppm ADBAC). 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 ppm of ADBAC, 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 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 recently 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. 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 1, suggesting that the study was underpowered because the 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 ADBAC concentration 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). The graphs will also show the activity levels as defined in the next paragraph.

The statistical analysis plan will also include exploratory analyses of the impact of the 2-fold activity levels that are part of the study design. There are three groups of six MEs at different ADBAC concentrations. Within each group, three MEs will be assigned a lower activity level of 1 and the other three MEs will be assigned a two-fold higher activity level of 2. For the bucket & sponge/rag scenario, the activity level of 1 is for the smaller surface area to be cleaned and the activity level of 2 is for the larger surface area to be cleaned (approximately twice as large). For the 3-compartment sink, the activity level is 1 for the smaller number of articles cleaned and 2 for the larger number of articles cleaned (approximately twice as many). For the COP, the activity level is the number of loads (1 or 2). To investigate how the activity level and concentration are related to the exposure, we will fit linear models for the logarithm of the exposure with an intercept term, with a slope coefficient multiplied by the logarithm of the concentration (ppm ADBAC), and with another slope coefficient multiplied by the logarithm of the activity level (which is zero if the activity level equals 1). Of particular interest is the case where both slopes are close to 1, since that model implies that the exposure is proportional to the product of the concentration and the activity level, which in turn is approximately proportional to the AaiH. In a similar manner, for the bucket & sponge/rag scenario we will fit linear models for the logarithm of the exposure with an intercept term, with a slope coefficient multiplied by the logarithm of the concentration (ppm ADBAC), and with another slope coefficient multiplied by the logarithm of the surface area cleaned. Finally, we will fit linear models for the logarithm of the exposure with an intercept term and with a slope coefficient multiplied by the logarithm of the estimated AaiH, approximated by the product of the measured concentration and the approximate volume of sanitizing solution. The general intent of the various analyses proposed in this paragraph is to evaluate the potential for normalizing exposure by a surrogate of the AaiH instead of concentration.

(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 concentration of active ingredient, and a normally distributed error term. The error variance is unknown. For the bucket and sponge/rag scenario, the error variance was estimated using the geometric standard deviation (GSD) of 2.0 calculated from the lognormal mixed model fitted to the somewhat similar Long Dermal exposure data collected in the AEATF ready-to-use wipe study (AEA02). The GSD of 2.0 gives an estimated error variance of $(\ln(2))^2$ = 0.4805. For the 3-compartment sink and COP scenarios, in the absence of similar studies, the error variance was estimated using the Governing Document default assumed GSD of 4.0. The GSD of 4.0 gives an estimated error variance of $(\ln(4))^2$ = 1.9218. 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 an exact power calculation to calculate the power for different designs assuming 6 MEs for each of 3 concentrations.

For the bucket and sponge/rag scenario, the proposed concentrations are 700, 350, and 175 ppm ADBAC, giving an estimated power of 0.90. For the 3-compartment sink and COP scenarios, the proposed concentrations are 160, 80, and 40 ppm ADBAC, giving an estimated power of 0.37, which does not meet the desired power of at least 0.80. EPA recommends no changes for the bucket and sponge/rag scenario, but recommends a wider range of concentrations for the 3-compartment sink and COP scenarios in order to have sufficient statistical power to detect proportionality between (expected) exposure and concentration. i.e., log-log-linearity with a slope of one. In Option 1, the recommended concentrations are 400, 240, and 40 ppm ADBAC, giving an estimated power of 0.81. In Option 2, the recommended concentrations are 160, 96, and 16 ppm ADBAC, also giving an estimated power of 0.81. Both options produce the same estimated power since the concentrations are in the ratio 10:6:1.

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 unit exposure. Under the assumption of complete proportionality (a log-log slope of one) and assuming the same GSDs as the power calculations, the estimated fold relative accuracies for the bucket and sponge/rag scenario are 1.43 for the arithmetic mean and 1.65 for the 95th percentile. The estimated fold relative accuracies for the 3-compartment sink and COP scenarios are 2.63 for the arithmetic mean and 2.75 for the 95th percentile; since a slope of 1 is assumed, the fold relative accuracy estimates are the same for the proposed concentrations and for Options 1 and 2. This means that the arithmetic mean and 95th percentile can be estimated within a factor of 3 with 95% confidence.

Even though the study is not a completely randomized study, based on these calculations, EPA believes that the proposed study, modified to use the revised concentration values given in Table 1, is likely to characterize reliably the middle to high end of exposures that occur while individuals conduct manual immersion/dipping/soaking (IDS) of articles, equipment, and/or utensils into sanitizing solutions containing an antimicrobial. EPA is confident that this design will provide data on IDS 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 is Oasis 146 Multi-Quat Sanitizer (EPA Reg. No. 1677-198) and contains the following Quats: Alkyl (C14, 50%; C12, 40%; C16, 10%) dimethyl benzyl ammonium chloride (3.00%); Octyl decyl dimethyl ammonium chloride (2.25%); Didecyl dimethyl ammonium chloride (DDAC) (1.35%); and Dioctyl dimethyl ammonium chloride (0.90%). (V2:28).

Each test subject will be exposed to the diluted ADBAC and DDAC in the treatment solution while immersing either their bare hands (bucket and 3-compartment sink scenarios) or glove-protected hands (COP scenario) into the treatment solution and conducting the cleaning/sanitizing activities as they normally would do.

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

"*Oasis 146 is an EPA-registered formulated product designed to be diluted in water prior to use. It is used as a sanitizer, disinfectant, and deodorizer in homes, hospitals, and other commercial and industrial areas. It can be used on a wide range of hard, non-porous surfaces and on food contact surfaces. Application methods include mop, rag, sponge, soaking, mechanical or hand-pump spray device. This product is currently registered for all of the sub-scenarios in this study. ADBAC has been used in previous AEATF II studies as the analyte and is selected for measurement based on its good stability, its relative abundance in formulated products labeled for IDS uses, low mammalian toxicity, and the sensitivity of its analytical methods."* (V2:33).

The choice of the formulation type (i.e., Oasis is a liquid formulation) is irrelevant to this study because the pouring portion of the exposure is not being monitored. Different formulation types can be used as sanitizers 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?

"In order to have a range in the concentration of active ingredient handled during the study, three different concentrations of diluted Oasis 146 will be used in each sub-scenario. Subjects will be randomly assigned to each concentration level so each concentration will include 6 MEs.

The bucket and rag/sponge sub-scenario will be done using the label maximum allowed rate for general disinfection which is 3 fluid ounces of Oasis 146 per gallon of water, equivalent to 1,760 ppm or 0.176% active ingredient (total quats) and at two lower rates, 880 and 440 ppm total quats. The rate of 3 fl oz/gallon is allowed for general disinfection of hard, non-porous surfaces such as walls, floors, sink tops, garbage pails, restrooms, and finished woodwork. The label states that food contact surfaces require a rinse after disinfection at rates above 400 ppm. However, for this study, no surfaces will be rinsed after wiping in order to monitor the potential for worst-case dermal exposure. There will be 6 monitoring events per concentration." (V2:29-30).

The table below shows the proposed concentrations of the test substance; 6 MEs per concentration are proposed. However, EPA has determined that for the 3-compartment sink and COP scenarios, based on the range of the concentrations proposed, there is insufficient power to detect proportionality of (expected) exposure and concentration given the sample size. EPA proposes to increase the range of the concentrations of the active ingredient for those scenarios to increase the statistical power (the reader is referred to Section C.1 Statistical Design for additional details of EPA's recommendations).

Scenario	**Total ADBAC Concentration in ppm [Total QUAT Concentration in ppm]**		
Bucket & sponge/rag	700 [1760]	350 [880]	175 [440]
3-compartment sink	160 [400]	80 [200]	40 [100]
COP			

(c) What duration of exposure is proposed?

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

Bucket & sponge/rag - *"Since wiping to clean and/or sanitize surfaces in homes nowadays is typically done using ready-to-use products such as a trigger-spray cleaner or impregnated wipes, it is likely that these times reflect the use of a spray and wipe, not a bucket and rag/sponge. Because of the trend to use sanitizing wipes and trigger spray bottles and disposable towels both in commercial settings as well as homes combined with the higher physical demands (bending, kneeling, and lifting) associated with using a bucket and rag/sponge, it is unlikely that someone will be spending more than an hour a day doing this activity.*

In a prior AEATF II study (AEA02 which involved a trigger spray and wiping and RTU wiping of indoor surfaces), monitoring time was purposely diversified by creating six strata that ranged from 30 to 210 minutes (3.5 hours). Monitoring time ranged from 31 to 209 minutes, and all test subjects had experience in the janitorial industry. Because subjects in this study will be immersing their hands into the sanitizing solution to wet and wring the rag/sponge, the actual amount of time spent wiping is not as critical as ensuring that there be a minimum number of immersions (five) into the bucket. As such, the target monitoring time for the bucket and sponge/rag sub-scenario is anticipated to range from 20 minutes to 1 hour. There will be two ranges of surface areas (approximately 2-fold different) to be wiped to provide some variation in work intensity and duration. The use of a bucket and rag/sponge to sanitize both food-contact and non-food contact surfaces is typically an intermittent task done periodically throughout the workday. An hour would represent about 12% of a professional worker's total work shift which probably represents an upper-bound amount of time spent dipping hands into buckets and treating surfaces with sanitizers and disinfectants since workers also perform other tasks such as cleaning equipment and floors, loading and unloading the dishwasher, manual dishwashing, busing tables, and stocking supplies.

The question of how long a worker spends using a bucket of sanitizer during a work shift was posed to Ecolab, a company that sells sanitizers and disinfectants to the food service industry (August 1, 2017). Representatives from the Full Service Restaurant division agreed that the food service worker durations were appropriate as outlined in the IDS study protocol for both a bucket and rag and 3-compartment sink sanitizer scenarios. They concluded that the durations are likely a worst case

scenario for an individual worker, and the actual durations spent conducting these activities during a work shift are likely much less.

For the bucket and rag scenario the Ecolab representatives indicated that the greatest time spent applying a sanitizing solution with a bucket with a rag is during preparation at the beginning of a work shift and clean-up at the end of the shift. A single worker would spend short periods of time (2 minutes or less at a time) wiping a surface as they move between preparation of different food types. During a shift, various workers wipe tables, work stations, and countertops and this is not an activity designated to just a single worker. Workers do not spend more than 30 minutes wiping down surfaces at the end of the shift because they are eager to complete their work. Realistically they spend 10-15 minutes wiping surfaces at the end of the shift." (V1:43-44).

3-Compartment Sink – "*Because dishwashing employees perform other duties and routinely use automatic dishwashing machines, the actual time spent manually washing oversized articles in a 3-compartment sink is a relatively small part of a worker's daily shift. It is common for items requiring manually washing to collect for a while before a worker fills the three compartments and washes/sanitizes a batch of dirty items. Information from site visits with an Ecolab sales representative to four restaurants (one sit-down national chain restaurant; one national chain fast food; one hotel/light dining; and a large luxury resort hotel with several restaurants and banquet facilities) in Asheville, North Carolina in 2016 indicated that at the majority of facilities a batch of cookware or other utensils would be washed two or three times during a typical work shift, with each batch taking approximately 15 to 20 minutes.*

Key observations at these dining facilities were as follows:
1. All locations used Oasis 146 Sanitizer to sanitize utensils
2. At all locations the Oasis 146 Sanitizer 2.5 gallon jug was connected via a flexible hose to a dispensing mechanism on the wall above the 3-compartment sink which would automatically add sanitizer to the sanitizing sink with the water flow. The target concentration is between 150 and 400 ppm.
3. The sanitizing sink is drained and the solution replaced approximately every 2 hours, depending on the frequency of use; one location indicated that the sanitizing solution could be replaced every 20-30 minutes if they were very busy.
4. Workers wore long pants, closed-toe shoes/boots, and short sleeve shirts. Gloves are typically not worn. In some case, nitrile gloves with grips are available for certain types of large, bulky equipment that need to be cleaned; but this seemed to be the exception. At three locations employees were required to wear aprons. These aprons cover the chest, stomach, and upper legs. At two locations the aprons are made of fabric; at one location the aprons were white thin plastic and disposable.
5. All locations had automatic dishwashing and sanitizing machines that do the bulk of the dishes. The 3-comparment sinks are used for the large and bulky items that either don't fit in the dishwasher or would not be properly cleaned in an automatic dishwasher. Items that are hand washed and sanitized include pots, trays, pans, bakeware, food containers, mixer blades, ice-cream making equipment parts, and beverage dispensers.
6. Soft nylon scouring pads are commonly used to clean the cookware; depending on the surface to be cleaned, steel wool may also be used. Most used Commander Blue or Scotch Brite scouring pads.
7. Typically items are placed into the wash sink to soak before being cleaned. Most workers wash several items consecutively, placing them into the rinse sink. Then several items are moved from the rinse sink to the sanitizing sink to soak for at least one minute. There can be multiple items resting in the sanitizing sink.

8. Three of the four locations indicated that a person would spend about 15 to 20 minutes manually washing cookware several times during an 8 – 12 hour work shift. At the large resort hotel it is possible, but rare, that a worker would spend a whole work shift washing/sanitizing at the 3-compartment sink; however, it is more typical to spend around 30 minutes and then switch to another work task.
9. At the end of the shift, the dishwasher would open the plugs (using a lever below the sink), drain the sinks, and then rinse the sinks with water.

Based on this, the target monitoring time for an ME in this sub-scenario will be 1 to 2 hours. This time is sufficiently long to represent the typical to upper-end amount of time that manual dishwashing is performed in a typical restaurant setting during a work shift.

The question of how long a worker spends using a 3-compartment sink during a work shift was posed to Ecolab, a company that sells sanitizers and disinfectants to the food service industry (August 1, 2017). Representatives from Ecolab's Full Service Restaurant division agreed that the food service worker durations were appropriate as outlined in the IDS study protocol for both the bucket and rag and 3-compartment sink sanitizer sub-scenarios. They both concluded that the durations likely reflect the upper-bound amounts of time an individual worker would spend at the tasks, and that the actual durations spent conducting these activities during a work shift are likely much less. They indicated that workers would spend no more than 1-2 total hours per shift cleaning dishes in a 3-compartment sink." (V1:35-36).

Clean-Out-Of-Place (COP) – "*Typically COP cleaning takes 1.5 to 2 hours per day and generally it is done only once during a work shift (NC State University, 2017) or once every other day (DeLaval Company, 2017) depending on the cleaning regime. The 1.5 to 2 hours includes the time needed to fill the tank with equipment parts, although depending on how difficult it is to disassemble the machinery this time may increase. It also includes about 30 to 45 minutes of wash time during which the detergent and water are being circulated by the jets in the tank. The sanitation step can take anywhere from 10 minutes to an hour although many workers will let the equipment sit in the sanitizing solution longer while doing other tasks. Workers do not stand over the COP tank; instead once the water has reached the correct level and either the detergent or sanitizer has been added, the worker will turn off the water supply, turn on the jets, and walk away. The worker is doing other tasks during this time such as disassembling equipment, cleaning floors, and running CIP in certain equipment. Unlike IDS in food service, the operator does not need to physically be present at the tank during the washing and sanitizing steps.*" (V1:46)

"Information obtained from DeLaval Company (a leading producer of dairy and farming machinery) who provides chemicals, equipment, and technical support to food processing facilities throughout the United States indicated that during the cleaning and sanitation shift a worker will be performing sanitation for 10 to 20% of their time. The rest of their time would be spent taking equipment apart (or putting it together), scrubbing equipment, rinsing equipment, inspecting it, etc." (V1:47).

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 immersion/dip/soak. Dermal and inhalation exposure will be measured using whole-body dosimeters (WBD) (inner and outer), face/neck wipes, hand wipe/washes, forearm wipes (for bucket

and sponge/rag and 3-compartment sink scenarios), and personal air monitors (V2:59-61). For the WBD, EPA is most interested in the inner dosimeters to assess potential exposure. The outer dosimeters will add to the existing data base on the development of protection factors for single layer of clothing. The potential for foot and head exposures are minimal and will not be monitored. The hand and face/neck wipe/wash is an appropriate method to determine exposure to the hands and face/neck. The forearm wipes are atypical for this body area but deemed acceptable for the two scenarios give that the lower arms will be immersed in the treatment solution (there is a need to avoid saturation of the WBD). The personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). An OSHA Versatile Sampler (OVS) will be used. *"The OVS tubes contain a glass fiber filter followed by two beds of XAD-2 sorbent in one glass tube (270/140 mg, SKC catalog number 226-30-16)."* (V2:59). Flow rates will be approximately 2 L/min for each of the samplers. (V2:54).

"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. 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 and record the direction of airflow. The dimensions and layout of the room and the relative position of the test subjects with respect to the equipment being used and the airflow will be documented in the raw data for each test site." (V2:58).

(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[.]*"* (V2:72-73).

(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[.]*"* (V2:72-73).

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, 15, and 100 ng/tube	1 ng/tube
Hand Wash	10, 100, and 1,000 µg/sample (bucket and rag/sponge and 3-compartment sink) 3, 30, and 300 µg/sample (COP tank)	1 µg/sample
Face/Neck Wipe	0.1, 1, and 10 µg/sample	0.05 µg/sample
Inner Dosimeter	10, 100, and 1,000 µg/sample	3 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." (V2:69).

3. Subject Selection

3.1 Representativeness of Sample

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

Test subjects will be recruited from occupational rather than residential populations. The choice between the two populations has more of a potential relevance to the bucket & sponge/rag scenario then the other two scenarios as the other scenarios are atypical for consumers. "*Although both consumers and professionals use this method* [bucket & sponge/rag] *of application and there is no obvious reason to believe there would be differences in exposures attributed to technique, only subjects who have occupational experience with this application method will be recruited for the study. Additionally, because greater quantities of product are handled by professionals, professional handler exposure is anticipated to be higher.*" (V1:27). Although the immersion/dip/soak treatment techniques for antimicrobial products that are used as sanitizers for food processing equipment (e.g., cooking and eating utensils, and pieces of equipment such as fittings/impellers, etc.) can be used by both occupational workers and consumers, the large-scale operations for the 3-compartment sink and COP scenarios are typically occupational settings. Subjects for all 3 sub-scenarios will be recruited from the occupational population.

(b) From what populations will subjects be recruited?

"The experience criteria for potential test subjects will be that they are currently employed or were employed within the last 2 years in a position (e.g., busboys/busgirls, cleaning staff, janitors, housekeepers, sanitation workers) where they used a bucket and rag/sponge at least once a month for cleaning and/or sanitizing hard surfaces.

People with experience doing manual dishwashing using a 3-compartment sink in the food service industry will be recruited for this sub-scenario. Potential subjects must either be currently employed in a position where they use a 3-compartment sink to wash and sanitize cooking and/or eating utensils or have worked in such a position within the last 2 years.

People with experience using a COP tank in a food processing facility (such as meat processing, dairy or cheese processing, pet food processing, and breweries) will be recruited for this sub-scenario. It is expected to be more difficult to find qualified people in the food processing industry so the timeframe of recent experience was expanded from 2 to 3 years to help broaden the pool of potential subjects. Thus potential test subjects must either be currently employed in a position where they use a COP tank to wash and sanitize equipment parts or have worked in such a position within the last 3 years." (V1:28).

EPA suggests amending the protocol to require that subjects have a minimum amount of experience conducting the task(s) to be monitored.

(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 various IDS tasks to be monitored, adult subjects with appropriate experience must first be identified. … Orlando, Florida is a large metropolitan area and is expected to yield plenty of people with sufficient experience for the bucket and rag/sponge and the 3-compartment sink sub-scenarios. Finding a sufficient number of qualified test subjects for the COP tank sub-scenario 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. However, given the number of dairies and cheese processing facilities in and around Madison, Wisconsin, it is anticipated that there is a sufficiently large population base from which to recruit subjects.

In order to adequately capture the ethnic diversity in the study locations, 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." (V2:44).

"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." (V2:44).

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

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

decisions about future exposures to antimicrobial active ingredients used in various products." (V2:12).

"The AEATF II program, as described in the Governing Document (2011), intends to develop a database of exposure monitoring data that can be used to support practical regulatory decisions about future exposures for different active ingredients in various product applications. The database addresses a variety of exposure scenarios for which no or limited data currently exist. The immersion/dip/soak scenario is an important component of the AEATF II program. As noted in Section 4, there are no existing monitoring data for this scenario. For this reason, the AEATF II is generating new exposure monitoring data that will be used to assess potential exposure and risks from this use pattern.

The purpose of the immersion/dip/soak monitoring study is to develop measurements of potential exposures to antimicrobials used to sanitize/disinfect/treat objects by immersion, dipping, or soaking. These data will consist of dermal and inhalation exposure measurements derived from monitoring human test subjects under conditions constructed to broadly represent those expected under actual use conditions.

The general approach used by AEATF II to obtain such data is to conduct scripted simulated-condition exposure monitoring studies for scenarios of interest. For each scenario, a set of monitoring events (ME) is constructed. Each ME simulates one set of possible conditions consistent with the scenario using a person who is monitored for dermal and inhalation exposure. For this study, three sets of 18 MEs will be collected, one for each sub-scenario. Each set of MEs is constructed so as to span a diverse set of conditions expected to impact exposure for that application." (V1:14-15).

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 21-22. The recommended revisions are shown below.

Inclusion Criteria

All sub-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 test day**

For the bucket and rag/sponge sub-scenario:

- Self-identified as being in good health as defined as able to do the following tasks: lift and move a bucket containing sanitizer solution and weighing up to 16 pounds around a room and use a rag/sponge to clean hard surfaces for up to one hour
- **Have 2 months employment experience within the last 2 years** ~~Be currently employed or employed within the last 2 years~~ in a job where a bucket and rag/sponge was used at least once a month for sanitizing

For the 3-compartment sink sub-scenario:

- Self-identified as being in good health as defined as able to do the following tasks: stand and clean, rinse, and sanitize dirty cookware in a 3-compartment sink for up to 2 hours
- **Have 2 months employment experience within the last 2 years** ~~Be currently employed~~ in a position that requires the use of a 3-compartment sink to manually wash and sanitize cooking and/or eating/drinking utensils at least once a week ~~or have worked in such a position within the last 2 years~~

For the COP tank sub-scenario:

- Self-identified as being in good health as defined as able to do the following tasks: fill and operate a COP tank for up to 3 hours
- **Have 2 months employment experience within the last 3 years** ~~Be currently employed~~ in a position that requires the use of a COP tank at least once a month to clean and sanitize equipment parts ~~or have or have worked in such a position within the last 3 years~~

Exclusion Criteria (all sub-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) *(V2:21-22)*

(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. (V2:22)

(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 subjects. Potential subjects who attend the informed consent meeting whether they decide to participate or not will be paid $20 in cash for their time and inconvenience. Volunteers who return at a later date to actually sign the form will not receive another $20 for that visit. Enrolled subjects in the 3-compartment sink and bucket and rag/sponge sub-scenarios who report to the study site on their assigned day, will receive $100 in cash for their time and inconvenience when they leave the study site, whether they are monitored or not. For subjects in the COP tank sub-scenario, the compensation amount will be $200 due to the higher skill-level required. In the case of the alternates, they will be compensated $100 ($200 for COP tank sub-scenario) 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." (V2:49-50)

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

Yes. The proposed payment amount is fair and reasonable compensation for the subjects' time, factoring in their experience 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 (Oasis 146, active ingredient ADBAC) is EPA-registered, with an essentially complete supporting database. Additional discussion is provided below on the comparison of the hazard and anticipated exposures for the test subjects in this study.

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

The AEATF II identified six types of risks:
"1. The risk associated with exposure to the surrogate chemical
2. The risk associated with exposure to isopropyl alcohol
3. Physical risks associated with the immersion/dip/soak 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. Risk of unanticipated release of confidential information" (V2:22-23)

(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:

"…at the use rate dilution of 4 fluid ounces (fl oz) or less per gallon of water the acute oral, dermal, and inhalation toxicity and eye and skin irritation potential are significantly reduced (see the Oasis 146 Secondary/Use Dilution Container Label on the last page of the Oasis 146 Master Label in Appendix A). At the diluted rate (4 fl oz/gallon or less) no personal protective equipment are needed; however, there is still potential for eye irritation. As a study precaution, all test subjects will be required to wear eye protection which will be provided by the AEATF II. The highest dilution rate of Oasis 146 that will be used in this study is 3 fl oz per gallon of water.

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 trigger pump sprays) and open pouring liquids. Other than wiping, these use patterns resulted in acceptable dermal and inhalation margins of exposure. Consumers wiping surfaces in a residential setting resulted in unacceptable dermal risks; however, this assessment was based on an ADBAC concentration of 0.3%

which is higher than the highest concentration of 0.176% that will be used in this study. At a concentration of 0.176% dermal risks for wiping are acceptable. Appendix D contains excerpts from EPA's 2006 risk assessment as well as a current risk assessment specific for test subjects participating in this study.

EPA did not conduct occupational use assessments since personal protective equipment are required when handling the concentrate and this was considered protective of skin irritation (EPA, 2006). EPA noted that when ADBAC is diluted, the personal protective equipment are not required. Occupational inhalation risk assessments conducted for treatment of indoor hard surfaces (e.g., mopping, wiping, and trigger pump sprays) and immersion/flooding/circulation showed acceptable risks. The maximum amount of product that will be handled during a monitoring event in this study will be well within the range of the daily amount of active ingredient assumed by EPA in their risk assessments. ADBAC will be going through a new registration review process with EPA (ADBAC Final Work Plan, 2017).

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 by the use dilution container label, 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 ADBAC. Instead, they will be provided with solutions diluted to 0.176% or less (3 fl oz/gallon water) which is what is used in restaurants and other commercial food service locations for sanitizing food contact utensils and does not require any protective clothing.

To minimize the potential for adverse reactions, subjects with open sores/skin conditions on their hands, forearms, or face will not be allowed to participate. Field personnel will be observing subjects and will intervene if evidence of dermal or ocular irritation occurs. Any subject with known dermal allergy or sensitivity to cleaning and/or disinfecting products will be excluded from participating." (V2:23-24)

EPA's assessment of the comparison of the estimated exposures for the subjects participating in this study to the available toxicity data includes the dermal and inhalation routes for both the DDAC and ADBAC components in the diluted treatment solution (the subjects are not exposed to the higher concentrations in the formulated product itself). The maximum concentration proposed is 3 fluid ounces formulated product/gallon of water. This is equivalent to 1760 ppm total Quat of which 700 ppm (0.07%) is ADBAC and 1060 ppm (0.106%) is DDAC. The dermal and inhalation assessments are as follows:

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 0.106% DDAC or less will not trigger a dermal risk of concern.

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 ug/cm^2 (where the applied dose contained 0.8% ADBAC) and 80 ug/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 0.07% 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).

Inhalation. Inhalation exposure for the three immersion/dip/soak scenarios are expected to be minimal/non-detect (and given the buffer in the risk calculations below, the exposures can be higher than the LOQ without trigger a risk of concern). The air concentration of ADBAC at the LOQ (1 ng/sample) for the longest exposure duration expected, 3 hours for COP, using the 2 L/min sampling pump flow rate, would be 0.0000028 mg/m^3. The air concentration at the LOQ (1 ng/sample) for the longest exposure duration expected, 3 hours for COP, using the 2 L/min sampling pump flow rate, the ADBAC air concentration would be 0.0000028 mg/m^3 (the DDAC air concentration in this example would be expected to be the same). 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. This LOAEC has been converted to a human equivalent concentration (HEC) of 0.018 mg/m^3 with a target MOE of 100 (uncertainty factors of 3x inter-species extrapolation, 10x intra-species variation, and 3x NOAEC to LOAEC conversion). The reader is referred to the Registration Review Final Work Plan for DDAC for more details (EPA 2017). The margin of exposure (MOE) is the ratio of the HEC (mg/m^3) divided by the inhalation exposure (mg/m^3) which is 0.018 mg/m3 / 0.0000028 mg/m^3 = 6,400 which is greater than the target MOE of 100 indicating that the risk is not of concern. Although there is some uncertainty in these calculations based on estimating the exposure to subjects at the LOQ, there is extra margin of exposure built-in based on the MOE of 6,400.

(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. (V2:22)

4.2 Risk Minimization

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

"To minimize the potential for adverse reactions, subjects with open sores/skin conditions on their hands, forearms, or face will not be allowed to participate. Field personnel will be observing subjects and will intervene if evidence of dermal or ocular irritation occurs. Any subject with known dermal allergy or sensitivity to cleaning and/or disinfecting products will be excluded from participating." (V2:24)

"The potential for irritation will be minimized by excluding those subjects with visible abrasions or eczema on exposed skin or who have known sensitivities to rubbing alcohol." (V2:25)

"The duration of these work tasks during the day of participation is expected to range from 20 minutes for the bucket and rag/sponge sub-scenario up to 3 hours for the COP tank sub-scenario. 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 experienced workers will be recruited for this study, it is anticipated that the activities being asked of them are not unlike those they do on a daily basis." (V2:25)

"There is some risk of heat-related illness associated with wearing two layers of clothing while working. However, this will be minimized by conducting the study indoors where the temperature is controlled. Additionally, the COP tank sub-scenario will take place in the winter time in Wisconsin making heat stress an unlikely event. 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." (V2:25)

"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)." (V2:25)

"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." (V2:26)

"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 your facial features and any identifiable features, such as piercings or tattoos, are not recognizable or deleted. *" (V2:26)*

"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." (V2:26)

EPA has recommending adding a statement that subjects' identities will be protected in videos and pictures by editing them in a way that renders facial features and any other identifiable features, such as piercings or tattoos, are not recognizable.

(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.*" (V2:33)

"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 Oasis 146 Multi-Quat 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 IDS activities or the hand and face/neck sampling. For subjects in the bucket and rag/sponge and the 3-compartment sink sub-scenarios, their forearms will also be examined. 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 indoors under controlled conditions. 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 stress index above 95), 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." (V2:50)

(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 (V4:141-152) and SOP 11.C.2 for Emergency Procedures (V4:153-157).

(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 your participation in the study you experience a skin reaction, respiratory irritation, eye reaction, or other physical injury that you believe is due to your participation in the study you should seek medical treatment and call the Study Director, Leah Rosenheck, immediately at [redacted]."* (V2:129)

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. As the informed consent form states: *"If you get injured or experience a medical problem while participating in this study, a medical professional will be present to assist. If you need to be taken to an emergency room or medical facility, the Study Director and medical professional will accompany you there. The AEATF II will pay for reasonable and appropriate medical treatment for a study-related injury or illness that is not paid for by your own insurance or insurance provided by your employer."* (V2:129)

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 sub-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. (V2:21)

(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." (V2:44)

"Advertisements will contain a short description of the study and the sub-scenario of interest, and a toll-free number where interested respondents can leave a voice message in either English or Spanish. These voice messages will be automatically forwarded to the Study Director or designated recruiter, or bilingual recruiter." (V2:45)

"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." (V2:45)

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). (V4:176)

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." (V4:174)

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

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

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

Recruiting will take place through advertisements in newspapers 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."* (V4:174)

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."* (V2:129)

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 are deleted. Records correlating subject names to their identification codes will be retained separately from the study file in another file clearly marked "CONFIDENTIAL"." (V2:27)

"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."* (V2:130)

During the preparations on the day of the monitoring event, subjects will also be reminded: *"The research team will review with you what will happen during the study and you'll have another chance to ask questions. We will remind you that you may change your mind about being in the study at any time before or after the study begins. All you need to do is tell us you've changed your mind. There will be no penalty of any kind to you if you decide to withdraw from the study." (V2:136-137)*

(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 the $20 that was paid following the initial consent meeting and will be allowed to leave. If a subject withdraws while being monitored, the outer dosimeters, long underwear, and air sampling pumps will be removed, and the

hand, forearm, and face/neck samples will be collected only with the subject's consent. The Study Director will determine whether these samples will be analyzed." (V2:27-28)

References

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.

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 Immersion/Dip/Soak Study Protocol (AEA12): August 2, 2018

Criterion	Y/N	Comment/Page Reference
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	n/a	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	Y	
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	Y	

§26.1116 General requirements for informed consent
AEATF II Immersion/Dip/Soak Study Protocol (AEA12): August 2, 2018

Criterion		Y/N	Comments
No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative		Y	
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		Y	
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		Y	
No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence		Y	
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	Y	
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Y	
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	n/a	
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Y	
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	Y	
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	Y	
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	Y	
(b) When appropriate, one or more of the following elements of information shall also be provided to each subject	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	Y	
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Y	
	(3) Any additional costs to the subject that may result from participation in the research	Y	
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	Y	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	n/a	
	(6) The approximate number of subjects involved in the study	Y	
(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		Y	

§26.1117 Documentation of informed consent
AEATF II Immersion/Dip/Soak Study Protocol (AEA12): August 2, 2018

Criterion	Y/N	Comments
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.	Y	
(b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or	Y	
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	n/a	

§26.1125 Prior submission of proposed human research for EPA review
AEATF II Immersion/Dip/Soak Study Protocol (AEA12): August 2, 2018

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

	Requirement		Y/N	Comments
All information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	
	(3) Records of continuing review activities.		n/a	
	(4) Copies of all correspondence between the IRB and the investigators.		Y	
	(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y	
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		Y	
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	
The following Information, to the extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	
		(2) The measures proposed to minimize risks to the human subjects;	Y	
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	
		(5) The balance of risks and benefits of the proposed research.	Y	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	
	§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	
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.		Y	