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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 10, 2008

MEMORANDUM

SUBJECT: Science and Ethics Review of AEATF Scenario Design and Protocol for Exposure Monitoring in Wipe Scenarios

FROM: John M. Carley
Human Research Ethics Review Officer

Timothy Leighton
Antimicrobials Division

Cassi Walls, Ph.D.
Antimicrobials Division

TO: Norm Cook, Chief
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division

REF: Selim, S. (2008) A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using Trigger Spray and Wipe or Ready to Use Wipes for Cleaning Indoor Surfaces. Unpublished protocol dated January 16, 2008, prepared by Golden Pacific Laboratories for the Antimicrobial Exposure Assessment Task Force II under Sponsor ID AEA02 and GPL Study No. 070264. 140 p., plus 346 p. supplement containing IRB correspondence.

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

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.

In addition to the final protocol and its appendices A through L (pp. 33-171)[1], Volume 3 of the AEATF submitted package includes the following supporting documents—all considered in this review:

- Transmittal Letter (pp. 4-5)
- 40 CFR 26.1125 Checklist (p. 7)
- Mopping Application Scenario: Rationale for Study Design (pp. 9-31)
- IIRB Approval Letter (pp. 173-174)
- IIRB-approved English consent materials (pp. 175, 177-186)
- IIRB-approved Spanish consent materials (pp. 176, 187-198)
- Product Label for test material (p. 89)
- MSDS for test material (pp. 104-105)
- Recruiting materials (pp. 107-112)

Volume 4 of the submitted package includes the following additional supporting documents—also considered in this review:

- Correspondence between the investigator and IIRB (pp. 5, 146, 171-195)
- Protocol and appendices as initially submitted to IIRB (pp. 7-145)
- Wipe scenario design as initially submitted to IIRB (pp. 14148-170)
- Protocol as revised 1/16/08 and resubmitted to IIRB, with appendices unchanged from initial submission (pp. 197-335)
- IIRB approval letter of January 22, 2008 (pp. 337-338)
- Minutes of 1/22/08 IIRB Meeting and IIRB Membership List (pp. 340-346)

B. Summary Assessment of the Scenario Design

Supporting details are in attachment 1

1. **Scenario Design:** The Antimicrobials Division (AD) assesses potential occupational and consumer exposure from various antimicrobial products that are applied by a multitude of application techniques including wiping. AEATF-II defines a wiping application scenario as the wipe-based application of a label-specified end-use formulation containing an antimicrobial chemical.

[1] Most page images in the submitted volumes bear more than one page number. All page references in this review to Volume 3 are to "page N of 198", and all page references to Volume 4 are to "page N of 346."

The act of wiping—moving a hand-held rag over a hard surface to clean/disinfect it—can be accomplished in many ways. Wipe methods include spray-and-wipe, ready-to-use wipes (RTU), and bucket-dipped rag or sponge wipes. From this array of choices the regulatory consensus was to monitor all three techniques. Two of them are proposed in this protocol: (1) spray-and-wipe, and (2) RTU wipe. The third method of wiping, using a sponge or rag dipped into a bucket of treatment solution, will be monitored by the AEATF under the soak/immersion/dip scenario.

EPA intends to use the data developed by the AEATF II for the two wipe scenarios to describe a typical handler's daily exposure to the antimicrobial wipe solution. The data must be generic enough to be useful for estimating exposures using various types of wipes (i.e., spray-and-wipe, RTU wipe), different hard surfaces (i.e., walls, table tops, bathrooms, etc.), room configurations, types of buildings (i.e., homes, schools, medical facilities, commercial office buildings, etc.), handlers (i.e., professional and consumer), and antimicrobial active ingredients. AD plans to use the data generated from the proposed wipe study generically to estimate dermal and inhalation exposures and risks for other antimicrobial ingredients where wipe application is consistent with product labeling use directions. Antimicrobial products have been grouped by EPA into the 12 Use Categories presented below. Although wiping of hard surfaces may occur in many Use Categories, most wipe applications are expected to occur in Use Categories II, III, IV, and V.

I	Agricultural premises and equipment
II	Food handling/storage establishments/premises and equipment
III	Commercial/institutional/industrial premises and equipment
IV	Residential and public access premises
V	Medical premises and equipment
VI	Human drinking water systems
VII	Material preservatives
VIII	Industrial processes
IX	Antifouling coatings
X	Wood preservatives
XI	Swimming pools
XII	Aquatic areas

The EPA believes that the AEATF wipe scenarios are well defined and we expect that resulting data will meet the needs of EPA and other regulatory agencies. The diversity of daily exposures under the two wiping scenarios addressed by this proposal will thus adequately describe a typical handler's daily exposure to the antimicrobial treatment solution.

2. **Sampling Design:** The AEATF has described in detail their sampling design for the wipe scenarios and has incorporated random elements where feasible. The AEATF proposes to monitor dermal and inhalation exposures using passive dosimetry techniques to measure exposure to human subjects wiping horizontal and vertical hard surfaces above floor level. Specifically, the wiping to be monitored will occur in

individual offices, bathrooms, kitchen areas, hallways, dining areas. The proposed sample size is the default scheme outlined in the AEATF-II Governing Document, involving of 3 clusters (sites) with 6 subjects at each. This is believed adequate to provide data to meet EPA's needs.

In the spray-and-wipe scenario workers will use a 32-ounce trigger-pump spray bottle with a nozzle adjustable to produce a fine spray, referred to in the protocol as an All Purpose Cleaner (APC). The standard APC spray bottle (size/volume, trigger pump configuration, and fine mist) has been purposively selected to represent the type and size most commonly used by janitors and consumers.

The spray-and-wipe scenario does not include diluting the concentrate or pouring the solution into the trigger pump sprayer. Mixer/loader exposure will be monitored in a separate study. This separation of tasks into multiple scenarios will allow regulatory agencies to assess exposure associated with either professional products that use automatic dispensers or RTU trigger-pump sprayers or products requiring mixing of the antimicrobial solution.

In the RTU wipe scenario workers will use wipes pre-saturated with antimicrobial solution, taken one-at-a-time from a roll of wipes in a plastic housing.

The study location has been purposively selected to be Fresno County, CA. EPA believes that the application of an antimicrobial product in an indoor environment will not vary substantially from one city to another, and therefore that the selection of Fresno County is reasonable. Fresno is close to the laboratory conducting the study, it is large enough to have a substantial population of professional janitors, and it contains many suitable vacant buildings. Conducting all monitoring in a single geographic area will save resources and will not adversely effect the results of the research.

Each of the two wipe scenario designs calls for three clusters of MEs, each at a different site. The designs specify further that each site must be a different type of building, that monitoring at different sites must be separated by at least one week, and that each selected building must include appropriate surfaces for wiping.

Within Fresno County, three sites will be selected using a stratified random sampling approach. A list of all available vacant buildings in Fresno County will be compiled, and stratified into three classes of buildings: office building, retail space, or meeting facility. Properties in each of the three categories will be "investigated independently and in random order until a single acceptable facility is found for each category." The acceptance criteria are that the building:

- Is available for 1-month rental
- Has a functional HVAC system
- Has operating electrical service

- Meets minimum surface area requirement with acceptable diversity in available surfaces (e.g., hallways, bathrooms, stairs, empty rooms)
- Does not require cleaning or maintenance before use

The result is a "random sample of one facility from the population of all acceptable facilities of each type in Fresno County." The two distinct wiping scenarios will be monitored independently at the same sites—i.e., a total of three buildings will be selected, and both spray-and-wipe and RTU wipe monitoring will be conducted in each building.

Each of the two wipe scenarios calls for monitoring 6 subjects at each of three sites. Two additional subjects will be enrolled for each scenario/site in case some subjects withdraw or fail to meet all eligibility criteria, making a total of 48 subjects to be enrolled in the study. Subjects will be professional janitors, selected randomly from among those who respond to flyers posted in randomly selected janitorial service companies in the Fresno area, and who meet the eligibility criteria for participation. Enrolled subjects will be randomly assigned to one of the two scenarios and to wiping tasks of differing durations at one of the three test sites.

AEATF-II proposes to recruit only professional janitors as subjects. The selection of janitors as subjects is justified in the protocol. Enrolled subjects will be listed in random sequence, and assigned to purposively predefined task durations ranging from 30 to 120 minutes. The amount of DDAC applied/handled will vary among the subjects depending on the duration of the task to which each is assigned. The first subject to be assigned will be assigned to the task of the longest duration, but may not be able to fulfill the design duration. Additional subjects will be assigned, each in turn to the longest task duration for which monitoring data have not yet been collected, until all the task durations are complete.

In order to make the most effective use of a limited number of monitoring events, the overall sampling design is purposive. No feasible opportunities to incorporate random elements in the sampling design, however, have been overlooked.

3. **Choice of Surrogate Material:** The choice of DDAC as the antimicrobial material for this scenario is appropriate. It is widely used, readily available, and there is a reliable and sensitive analytical method available for it.

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

Supporting details are in attachment 2

1. **Statistical design:** AEATF-II proposes for each of the wipe scenarios the default design of 3 clusters of 6 monitoring events (MEs) each, as discussed in the Governing Document. No characteristics of this scenario have been identified which would justify a departure from this norm.

2. **Proposed pattern of human exposure:** The AEATF proposes to select professional applicators (i.e., janitors) as subjects for the wiping scenarios. The test subjects will use SANI-CARE LEMON QUAT to conduct wiping activities using a spray & wipe or RTU wipes over a range of time durations extending from 30 to 120 minutes in 15 minute increments. In the spray & wipe scenario, workers will spray a fine mist of dilute material in water with a trigger pump sprayer, followed by a hand wiping using a commercially available cotton hand towel. In the RTU wipe scenario, workers will wipe down hard surfaces using a pre-moistened wipe pulled from a plastic container. In both scenarios workers will be instructed to work as they would normally work. Surface wiped will range from 1000 to 4000 ft^2, depending on work speed and task duration.

   SANI-CARE LEMON QUAT which contains the active ingredients didecyl dimethyl ammonium chloride (DDAC) at a concentration of 2.54% and n-alkyl dimethyl benzyl ammonium chloride (ADBAC) at a concentration of 1.69% will be used as a diluted treatment solution (1:64) per label directions in the spray & wipe scenario. The concentration of the test material will be constant for all subjects. Variation in exposures will result from differing exposure durations. Thus, the total amount of ai handled will vary by the wiping duration (e.g., 30 to 120 minutes).

   EPA believes that the AEATF wiping study will represent typical worker activities applying the test substance to hard surfaces under both the spray & wipe and the RTU wipe scenarios. The selection of janitorial subjects, test material, and mopping activities is adequately described and justified in the protocol.

3. **Endpoints and Measures:** The AEATF proposes to measure dermal and inhalation exposures resulting from wiping activities of hard surfaces. Dermal and inhalation exposure will be measured using whole-body dosimeters (inner and outer), hand/face washes, and personal air monitors. The Agencies are most interested in the inner dosimeters to assess potential exposure and/or dose. The outer dosimeters will add to the existing data base on the development of protection factors for single layer of clothing. The personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). The sampling train will consist of OVS tubes with glass filters backed by XAD sorbent. Because the air sampling will not size particles, the Agencies will assume all of the residues are inhalable and/or respirable (which tends to overestimate inhalation exposure). The sampling pumps will be calibrated prior to use.

   The output of treatment solution for each spray bottle will be measured prior to the study using tap water by measuring the volume output from 10 trigger pulls. Additionally the amount of treatment solution used by each subject during the monitoring event will be recorded by weight before and after each use. The surface area wiped will also be recorded.

   The RTU wipe scenario will consist of a roll of wipes in a plastic housing. The roll of wipes will be provided to the subjects pre-saturated (i.e., RTU). The researchers

will collect 10 wipes from each roll prior to the study and determine the amount of DDAC per wipe. During the study, the number of wipes per monitoring event will be recorded allowing for an estimate of the amount of DDAC applied. The surface area wiped will also be recorded.

Environmental parameters of the work area such as air temperature, and relative humidity will also be documented. The HVAC system will be described and the air turnover rates will be measured or estimated.

4. **QA/QC Plan:** The AEATF QA/QC plan for the wiping 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, travel recovery analyses, storage stability studies, break-through analyses, and method validation.

   Primary components of the field recovery analyses include: two fortification levels per matrix, triplicate samples per fortification level, exposed to ambient conditions for the maximum duration of exposure, and WBD not covered during exposure duration. Field recovery samples will be fortified in the field, transported and stored in the same way as the actual study samples, and analyzed concurrently with the actual exposure samples. Correction for loss in field recoveries will correct for all phases of potential losses.

   Travel fortifications will also be used as insurance if low recoveries are obtained in the field recoveries. However, travel recoveries will not be analyzed if acceptable recoveries are observed in the field recovery samples.

   Storage stability samples have been run prior to the development of the protocol and indicate stability over the six-month period assessed.

5. **Statistical Analysis Plan:** The results of physical sample analysis will be provided in the final report. The AEATF II will not statistically analyze the monitoring data. However, the wipe monitoring data will be imported into the AEATF database (BHED®) where they will be available to regulatory agencies for later statistical analyses. The study documentation will report a confidence-interval-based approach to determine the relative accuracy for the arithmetic mean and 95th percentile of exposure normalized by amount of ai handled. The report will further provide the intraclass correlation for clusters (ICC) and its confidence interval, using a variance components model. In addition, the effects of ignoring clusters in the estimation of means and percentiles will be determined by comparing the estimates of a no-cluster model to those of the random effects model.

D. Compliance with applicable Scientific standards

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

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

Additionally, the AEATF 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).

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

- The type of wipe to be used in the spray & wipe scenario is inadequately specified.

- The efficiency of residue removal through the hand-wash and face/neck wipe methods must be addressed, as well as the possibility of an adjustment in resulting data to compensate for potential incomplete residue removal.

E. Summary Assessment of Ethical Aspects of the Proposed Research

Supporting details are in Attachment 2.

1. **Societal Value of Proposed Research:** The purpose of the proposed wiping application monitoring study is to develop more accurate information on worker exposures to antimicrobials as they clean indoor surfaces using either a spray & wipe technique or ready-to-use wipes. Because many millions of Americans apply antimicrobial products in these ways, the research question is important; it cannot be answered with confidence without new monitoring data meeting contemporary standards of quality and reliability.

2. **Subject Selection:** Forty-eight adult subjects will be recruited from the janitorial/ cleaning service population of Fresno County. Participants will self-identify in response to flyers soliciting interest, posted in the workplaces of janitorial services companies. Participants will be screened in random sequence from among responders, and in that sense will be representative of the population of janitorial service workers in the Fresno area. There is no reason to think that janitorial service

workers in Fresno are not representative of janitorial service workers in any other area of the United States.

Inclusion/exclusion criteria are complete and appropriate. Pregnant or nursing women and employees or relatives of employees of the investigators are excluded from participation.

No potential subjects are from a vulnerable population. Recruitment materials and interactions with potential subjects will be conducted in both English and Spanish. To minimize the potential for coercion or undue influence from their employers, subjects will not be recruited directly through contract janitorial service companies. Flyers will encourage interested workers to contact the investigators directly.

Subjects who participate fully will be paid $100/day. Alternate subjects who are enrolled but are not actually monitored will be paid $50 for their trouble.

3. **Risks to Subjects:** The proposed test material is EPA-registered for the use proposed, is of low toxicity to mammals, and will be used in full compliance with the approved label. Risks to subjects include risks of a reaction to the test material or the solvents used to obtain residues from hands and face/neck; of discomfort and possibly heat-related illness associated with wearing two layers of clothing while doing physically demanding work; of a cardiovascular adverse event attributable to physical exertion; of discomfort or inconvenience from wearing the air sampling device; of embarrassment from disrobing in the presence of a research technician; of an unexpected result of pregnancy testing. All identified risks are characterized as of low probability.

   Risks are minimized by exclusion of candidates known to be sensitive to quaternary ammonium compounds or in poor health or with broken skin on hands, face, or neck; testing in a controlled-temperature environment; alerting subjects to signs and symptoms of heat stress; monitoring heat index with associated stopping rules; limited time of exposure with rest periods at 30-min intervals, or more frequently if requested; close observation of subjects; training of experienced technicians to minimize embarrassment; incorporation of procedures to keep results of pregnancy testing private and to permit discrete withdrawal; provision of appropriate work clothing and PPE.

4. **Benefits:** This research offers no direct benefits to the subjects, but subjects may request their individual results, from which they may learn that their work practices produce more or less exposure than average. The principal benefit of this research is likely to be reliable data about the dermal and inhalation exposure of workers and the general population wiping indoor surfaces with antimicrobials, usable by EPA and other regulatory agencies to support exposure assessments for a wide variety of antimicrobial products.

5. **Risk/Benefit Balance:** Risks to subjects have been thoughtfully and thoroughly minimized in the design of the research. The low residual risk is reasonable in light of the likely benefits to society from new data supporting more accurate applicator exposure assessments for a wide range of antimicrobial products used for mopping.

6. **Independent Ethics Review:** The proposed research has been reviewed and approved by the Independent Investigational Review Board, Inc., (IIRB) of Plantation FL. The submitted materials include a full record of correspondence between the investigators and the IIRB.

7. **Informed Consent:** Informed consent will be obtained from each prospective subject and appropriately documented. Literacy in English or Spanish is a criterion for inclusion.

   Both English and Spanish-language recruiting flyers will be available, and will encourage interested workers to contact either the study Field Coordinator or Spanish-speaking coordinator directly. A Spanish translator will be available at recruitment meetings. Consent forms are available in both languages.

   The protocol and consent form indicate that the Principal Investigator, who is not fluent in Spanish, will be relied on to inform candidates, who will also be provided product labels and MSDSs, both of which are available only in English. These procedures may not be adequate to ensure comprehension by candidates whose language of choice is Spanish.

8. **Respect for Subjects:** Subject identifying information will be recorded only once; all subsequent data records and reports will refer to individual subjects only by an arbitrary code. Provision is made for discrete handling of pregnancy testing, required of female subjects on the day of testing. Candidates and subjects will be repeatedly reminded that they are free to decline to participate or to withdraw at any time for any reason, without penalty. Medical care for research-related injuries will be provided at no cost to the subjects.

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, and because the research will be conducted in California, the provisions of California Code of Regulations Title 3, Section 6710 apply as well. A detailed evaluation of how this proposal addresses applicable standards of ethical conduct is included in Attachment 2.

The following specific deficiencies should be corrected before the research is initiated:

- Better provision is needed to ensure that Spanish-speaking candidates are fully informed and fully comprehend what they have been told.

- References in the consent forms to "normal business hours" should be replaced by references expressed in California local time, and care must be taken to ensure that a Spanish-speaking responder can be reached at any telephone number cited as a source for further information.

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

> EPA shall not rely on data from any research 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.

Attachments:

1. Summary Review of Mopping Scenario Design dated 14 Jan 08
2. Summary Review of AEATF-II Protocol AEA02 dated 16 Jan 08
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 Mop Application Scenario/Protocol

Title: **MOPPING APPLICATION SCENARIO: RATIONALE FOR STUDY DESIGN** (Pages 9-31 in AEATF-II Volume 3)

Date: 14 January 2008

Sponsor: American Chemistry Council
Antimicrobial Exposure Assessment Task Force II
c/o Has Shah, Ph.D.
1300 Wilson Blvd
Arlington VA 22209

1. Scope of Scenario Design

(a) Is the scenario adequately defined?

Preliminary versions of the wipe protocol have been reviewed by EPA/PMRA/CDPR to determine the appropriate wiping scenarios for regulatory purposes (i.e., to assess exposure accurately assess exposure as accurately as possible, but to ensure any error does not underestimate exposure). Many varied antimicrobial products can be applied by wipes vary greatly from typical consumer applications in home furnishings/bathrooms/windows/etc to commercial applications in hotels, hospitals, schools, or restaurants, to applications in agricultural premises. Wipe choices include spray and wipe, ready-to-use wipes, and bucket-dipped rag and/or sponge wipes. From this array of choices, the regulatory consensus was to monitor all three of these choices, two of the choices in this wipe protocol. This wipe protocol will include spray & wipes as well as the RTU wipes. The actual wipes to be used in the trigger pump scenario are imprecisely described; this should be corrected before execution. Paper towels are also used in this type of task but differences in exposure are not expected because rags/sponges/paper towels are all expected to be saturated. The third choice for wiping, use of a sponge or cloth rag dipped into a bucket of treatment solution will be monitored by the AEATF at a later date under the soak/immersion/dip scenario as outlined in the Governing Document.

Activities included in the wiping scenario are wiping horizontal and vertical surfaces that are above the floor level. "Further, buildings are preferred if they provide diverse indoor room sizes and area configurations, e.g., individual offices, bathrooms, kitchen areas, hallways, dining areas". (V3:53)[2] The actual activity of the subject while wiping "…will

[2] This pagination convention is used throughout this review. "V3" refers Volume 3 of the AEATF submission—the "primary documents" volume for the wipe scenario design and protocol. "V4" refers to Volume 4 of the AEATF submission—the "secondary documents" for the wipe scenario design and protocol. Entries after the colon are page references; many page images bear more than one page number. In volume 3 the cited page number is always from the expression "p. N of 198". Volume 4 page references are always from the expression "p. N of 346."

be conducted by each participant as they would normally work. Each subject will not re-wipe any surface during a given monitoring event (ME). Past observation indicates a wide variety of application methods (oval, side to side, back and forth motion)." (V3:51) The scenario does not include the pouring of the concentrate into the trigger pump sprayer. The mixer/loader portion of the exposure will be conducted in a separate mixing/loading study. This separation of tasks has been selected to allow for the regulatory agencies to assess professional products that use automatic dispensers and/or RTU trigger pump sprayers as opposed to open pouring. The RTU wipes will be provided to the subjects already saturated.

The AEATF proposes to recruit only professional janitors. Janitors have been selected to provide longer wiping periods then are typical for consumers so that there is a greater likelihood for detectable residues on sampling matrices. Although shorter durations typical of consumer wiping (AEJV survey indicates an average ~5 minutes) are believed to result in detectable residues on the hands, other parts of the body are more likely to provide measurable residues only when longer exposure durations are sampled. Nonetheless, the upper range of consumer wiping durations indicated in the Antimicrobial Exposure Joint Venture (AEJV) survey (i.e., 60 minutes) is within the range of professional wiping durations (i.e., 30 to 120 minutes) proposed. Thus the scenario design will result in exposure data directly usable to estimate consumer as well as professional exposures.

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

The CMA study is the only source of exposure data for wiping scenarios. The CMA data for wiping includes 6 monitoring events and is characterized by poor recoveries. Based on these data limitations, the Antimicrobial Division is requiring dermal and inhalation exposure data in many of its assessments to fill this data gap.

2. Rationale for Scenario Sampling Design

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

The design choices in the wipe scenario to provide diversity in sampling include (1) application equipment; (2) multiple indoor sites in one geographic location; (3) varying the amount of active ingredient handled by the subjects; and (4) using different workers for each monitoring event.

Application equipment. "The All Purpose Cleaner (APC) trigger sprayer to be used in this study is supplied by Buckeye International. It is used as standard janitorial and home consumer equipment in the US. The size of the spray bottle is 32 ounces, which is the most common size in use. The adjustable nozzle will be set to a fine spray that would normally be used to apply antimicrobials to surfaces prior to wiping. APC sprayers are the most-used surface disinfectant method in many commercial and home settings." (V3:49)

Sites. Three sites (i.e., buildings) in Fresno County, CA, will be selected for this study. The choice of one geographical location of Fresno County assumes indoor wiping will not differ substantially from one geographic location to another. This assumption is supported by the previous CMA study ("…variability in dermal and inhalation exposures across workers was most primarily influenced by the application method and by implication, each individual worker's implementation of that application method (i.e., their work practices and behavior), rather than the location or setting in which the application method is performed.") (V3:17) Moreover, the available training material for janitorial practices is supported by national organizations (e.g., International Sanitary Supply Association (ISSA)), not regional differences. The choice of sampling vacant buildings allows the researchers "…to be free from personal interferences with non-subjects… It also allows the focus to be on wiping only as opposed to the broad range of janitorial activities a subject might engage in…" (V3:18). Finally, the geographic area selected in close to the laboratory conducting the study and will save resources.

Amount of AI Handled. The amount of active ingredient handled will be varied among monitoring events by varying the wiping durations. The AEATF cites existing survey data from ISSA and the Antimicrobial Exposure Joint Venture (AEJV). The ISSA indicates professional applicators wipe an average of 213 minutes per day. The AEJV indicates that consumers average ~5 minutes per event. The wipe protocol will monitor wiping for 30 to 120 minutes in increments of approximately 15 minutes. (V3:51) This will encompass 1000 to 4000 ft^2 of surface area depending on working speed and task duration.

Varying Subjects. The goal of the study is to monitor professional applicators, so the selection of janitors is appropriate to the goal of the study. Each monitoring event will use a separate individual to maximize diversity. "Each surrogate worker provides his/her unique set of behaviors to the wiping task. Use of the same worker for all monitoring events would over-represent a single type of behavior. As a result, diversification of worker behavior among MEs is accomplished by simply requiring that each ME be based on a different surrogate worker." (V3:23) The use of professional applicators is a reasonable surrogate for the range of potential users that may wipe with an antimicrobial product such as consumers, building staff/maintenance workers, school janitors, for-hire janitorial firms, etc.

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

"Surrogate worker selection: This process results in a simple random sample of qualifying subjects from the volunteer pool. Note, however, that is not the same as a random sample from the existing population of professional janitorial workers. By definition, volunteers are self-selected and could have different characteristics than non-volunteers. Such distinctions have no relevance in this case, however. There is no particular need to obtain a random sample from the Fresno janitorial population. This existing population is not the target population for the study. The MEs are synthetic constructs that attempt to predict aspects of a future handler-day population. It is

purposive by definition. Thus, a random sample of just one ME component (e.g. subject) from a subpopulation (e.g. Fresno County) provides no statistical advantage. In fact, a random sample of subjects from the volunteer pool is not the only possibility. For example, a more diverse sample of surrogate workers from this pool could also be acceptable if a clear diversifying characteristic were available for all workers. Lacking this, the wiping application study uses the reasonable default option of a random sample from the volunteer pool." (V3:23)

"A stratified random sampling approach will be used to locate acceptable facilities. (V3:19)

"The properties within each of these three categories (office, retail or meeting) will be investigated independently and in random order until a single acceptable facility is found for each category."

"Each ME will be randomly assigned to a different task duration interval." (V3:21)

"Individuals who express a desire to participate in the study within a fixed period of time will be contacted and screened in random order. Surrogate workers are randomly assigned to MEs. "(V3:23)

48 subjects are recruited randomly from the pool of qualifying volunteers. These 48 subjects are randomly divided into six groups of eight subjects each. (V3:54)

"The eight subjects in each site are ordered randomly. The first subject is then assigned to the ME in the longest wiping duration stratum (i.e., stratum F, 105-120 minutes). No other assignments of subjects to MEs are made until the subject completes the monitoring task in this stratum. When the ME is complete, the next subject in order is assigned to the next longest stratum (E, 90-105 minutes). As long as each subject achieves the target wiping duration, the process is continued down to the shortest duration stratum (A, 30-45 minutes) and six MEs have been obtained, one for each of the six strata. If this process proceeds as expected, the last two subjects are never used for MEs." (V3:54)

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

No feasible opportunities to incorporate additional random elements in the sampling design are apparent.

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

The wipe protocol proposes to monitor two distinct wipe application techniques. The two wipe methods include a spray & wipe and a RTU wipe. The spray & wipe scenario will consist of a worker spraying a fine mist onto a hard surface with a trigger pump sprayer, followed by hand wiping with a commercially available cotton towel. The RTU wipe scenario consists of the worker using a pre-moistened wipe pulled from a plastic

container to wipe hard surfaces. The workers will be instructed to work as they would normally work.

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

The study is designed to monitor professional janitors, so any different behaviors a consumer might exhibit while wiping will be excluded. Given that wiping is not a specialized task, exclusion of consumers from the sampling design is not a limiting factor.

The types of wipes available to applicators range from RTU wipes to some type of cloth, sponge, or paper towel. RTU wipes on the market all appear to be similar (i.e., cloth-based). Other types of wipes such as bucket and sponge/rag will not be included in this particular wipe protocol. The bucket and sponge/rag exposure scenario will be monitored under the scenario of immersion/dip/soak as outlined in the AEATF Governing Document.

The wipe protocol does not monitor the activity of diluting a concentrated product prior to use in the spray & wipe scenario. The exposures associated with pouring a liquid concentrate will be monitored in a separate mixing/loading scenario as outlined in the AEATF Governing Document.

3. Is the proposed test material an appropriate surrogate?

The test substance, DDAC, is an appropriate choice for the development of surrogate exposure data because it is stable, is characterized by a low vapor pressure (estimated to be 2E-11 mmHg), diluted solutions are not dermally irritating, no systemic toxicity was seen in a 90-day dermal rat study, the product is registered for the intended use (i.e., wiping), and DDAC has been demonstrated to have a low analytical limit of detection.

"The test material, Sani-Care Lemon Quat, an EPA approved product, containing didecyl dimethyl ammonium chloride (DDAC), CAS No. 7173-51-5, and n-alkyl dimethyl benzyl ammonium chloride (ADBAC), CAS No. 68424-85-1 will be applied at a target rate not to exceed the maximum label-recommended rate. The test material will be used in this study in accordance with the product label." (V3:40)

"Sani-Care Lemon Quat is a professional use product, and the product label specifies the PPE requirements as protective eyewear." (V3:41)

"Based on its safety profile, DDAC and ADBAC have been approved for use in many formulations, and are extensively used in many janitorial products. The test material, Sani-Care Lemon Quat has also been tested for acute effects and has been approved by the EPA. The EPA has recently re-registered both DDAC and ADBAC and issued REDs for both (EPA, 2006 a,b). Additionally, the safety of the test material has been established through long term professional use of the product. The product will be used according to its label. The Sani-Care Lemon Quat concentrated formulation will be handled only by

researchers and the diluted material (1:64) in a ready-to-use form will be provided to the subjects." (V3:44)

"The freezer storage stability of DDAC on the different matrices to be used in this study has been completed showing that DDAC is stable on the different matrices when stored in a freezer for 6 months (GPL, 2005)." (V3:48)

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

AEATF-II proposes for the wipe scenarios the default design of three clusters of six monitoring events (MEs) each, as discussed in the Governing Document. No characteristics of these scenarios have been identified which would justify a departure from this norm.

"For the wiping application scenario (as is true for all AEATF II scenarios) only a small number of expensive experimentally-obtained monitoring events (MEs) are possible." (V3:15)

"… a practical goal for this study is that the small sample of wiping application MEs be biased towards increased diversity of handling conditions. As a result, the diverse sample of MEs is expected to at least cover the middle portion of the future exposure distribution, cover the upper portion of the future exposure distribution, and capture the range of exposure variation that is expected to exist." (V3:16)

"For the wipe application study, random nested (or cluster) sampling is used as the reference model for the combination of purposive and random diversity selection actually used." (V3:24)

"Benchmark objectives specify accuracy goals that must be achieved within the reference sampling model when sample size is adequate. In this study, 'sample size' means the number of clusters (NC) and the number of MEs per cluster (NM). For the wipe application study, the benchmark objective is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time." (V3:5)

EPA Protocol Review: AEATF-II Mop Application Scenario/Protocol

Title: A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using Trigger Spray and Wipe or Ready to Use Wipes for Cleaning Indoor Surfaces

Date: 16 January 2008

Principal Investigator and sub-investigators:

Sami Selim, Ph.D.
Megan T. Boatwright
Tami I. Belcher

Participating Laboratories:

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

Grayson Research, LLC
211 N Main Street
Creedmoor NC 27522

Sponsor: American Chemistry Council
Antimicrobial Exposure Assessment Task Force II
c/o Has Shah, Ph.D.
1300 Wilson Blvd
Arlington VA 22209

Reviewing IRB: Independent Investigational Review Board
6738 West Sunrise Blvd Suite 102
Plantation FL 33313

1. Societal Value of Proposed Research

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

"The primary purpose of the wiping application monitoring study is to develop more accurate information on worker exposures to antimicrobials . . . to support exposure assessments for wiping application." (V3:15)

"This study is being conducted to determine potential dermal and inhalation exposures associated with wiping indoor surfaces with an antimicrobial pesticide product." (V3:38)

"A practical goal for this study is that the small sample of wiping application MEs be biased towards increasing diversity of handling conditions. . . . The diverse sample of MEs is expected to at least cover the middle portion of the future exposure distribution, cover the upper portion of the future exposure distribution, and capture the range of exposure variation that is expected to exist." (V3:16)

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

"This study is being conducted to determine potential dermal and inhalation exposures associated with wiping indoor surfaces with an antimicrobial pesticide product." (V3:38)

"Since 1992 the EPA has conducted professional and consumer mixer/loader and applicator exposure and risk assessments relying primarily on the exposure data in PHED. . . . However, PHED does not include any data directly relevant to wiping application methods." (V3:12)

"The CMA study represents the only existing data in the case of the wiping scenario. . . Based on EPA's review, CMA's study data met some regulatory agency requirements, but was lacking in other areas." (V3:13)

"Currently, US EPA relies upon the results of the CMA study conducted more than 15 years ago to characterize exposure from mopping using an antimicrobial (Popendorf et al. 1992). That study has a total of 6 measurements of whole body exposure at levels above the Limit of Quantification (LOQ). Analytical methods, exposure dosimetry methods and regulatory needs have changed significantly since that time. EPA has requested confirmatory exposure monitoring data for a number of antimicrobial use scenarios in Registration Eligibility Decision (RED) documents issued over the last 2 years. There appears to be no publicly available data with which to make a credible estimate of exposure for persons using either a trigger spray and wipe or ready-to-use wipes. Thus, the rationale for conducting this study is to measure dermal and inhalation exposure in a large enough group of typical users to adequately estimate central tendency and variability for this use of antimicrobial pesticides." (V3:41)

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

EPA will consider the data from this study in assessing exposures of occupational or residential applicators using a trigger spray and wipe or RTU wipes to apply an antimicrobial pesticide to indoor hard surfaces

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

Due to the limitations of existing data, the research question cannot be answered with confidence relying on existing data.

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

"Human subjects are required in this study because they will normally be exposed to the test material when performing their daily activities. There are no acceptable methods or models that could be used to extrapolate subjects' exposure." (V3:42)

2. Study Design

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

"The primary purpose of the wiping application monitoring study is to develop more accurate information on worker exposures to antimicrobials. These data will consist of dermal and inhalation exposure estimates derived from monitoring subjects under conditions constructed to broadly represent those expected for the future application of arbitrary antimicrobial pesticides. AEATF II anticipates the resulting database will contain sufficient data to support exposure assessments for wiping application." (V3:15)

"This study is being conducted to determine potential dermal and inhalation exposures associated with wiping indoor surfaces with an antimicrobial pesticide product." (V3:38)"

"The primary objective of this study is to monitor exposure to subjects who wipe horizontal and vertical surfaces with a liquid antimicrobial pesticide product. Each monitored applicator will apply product using either a trigger-spray-and-wipe or ready-to-use (RTU) wipes and will generally involve work periods of 30 to 120 minutes." (V3:40)

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

"...large deviations from the benchmark goals may affect the regulatory usefulness of the data. If large deviations from the benchmark goals are observed 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 clusters might be considered." (V3:78)

2.1 Statistical Design

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

"The goal is to use these data to characterize some 'population' aspect of the future exposure to arbitrary antimicrobial pesticides. Hence, this study is more closely aligned with the random sampling situation (1)…." "There is assumed random sampling from a population and the goal is to estimate some characteristic of that population. . . ." (V3:24)

"For each scenario in the wiping application study, random nested (or cluster) sampling is used as the reference model for the combination of purposive and random diversity selection. . . . " (V3:24)

"…the benchmark objective is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time." (V3:25).

Monte Carlo simulations were used to identify the most economical number of clusters (3) and subjects per cluster (6) consistent with achieving design levels of precision in the results (V3:28-29)

(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?

Candidates selected randomly from among respondents to recruiting flyers will be assigned randomly to one or another ME, pre-defined in terms of its duration and location. (V3:23)

MEs with longer durations will be executed first; a subject who is unable to continue wiping for the designed duration of the ME will be reassigned to a shorter ME, and the next subject in random order will be assigned to the uncompleted longer ME. (V3:54)

(e) Can the data be statistically analyzed?

The results of the analysis from the sampling will be provided in the final report. (V3:81).

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

"The AEATF II will not statistically analyze the monitoring data in order to characterize exposure or investigate the relationship between exposure and other factors (e.g., room size, level of residual organic matter, environmental conditions including temperature, humidity, air turnover rate, etc.) However, regulators and other users of the constructed database (BHED) may choose to conduct such analyses. The extent of AEATF II's data analyses will be limited to the statistical characterization of data adequacy for inclusion in BHED scenario monographs. Two specific types of analyses will be performed (these analyses are discussed in more detail in the AEATF II's Governing Document (AEATF, 2008a):

"1. Evaluation of benchmark adequacy. A confidence interval based approach will be used to determine the realized relative accuracy for the arithmetic mean and 95th percentile of exposure normalized by amount of ai handled.

"2. Cluster effects. The intraclass correlation for clusters (ICC) and its confidence interval will be estimated using a variance components model. In addition, the effects, if any, of ignoring clusters in the estimation of means and percentiles will be determined by comparing the estimates of a no-cluster model to those of the random effects model.

"We note that the analysis in (1) above may suggest that the realized accuracy bounds differ from the benchmark targets to some extent. This does not invalidate the study since small deviations would be expected and are of little practical concern. However large deviations from the benchmark goals may affect the regulatory usefulness of the data. If large deviations from benchmark goals are observed 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 clusters might be considered." (V3:77-78)

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

Yes.

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

Because of its Purposive Diversity Sampling Design, the study will support only limited inferences. EPA believes, nonetheless, that it is likely to characterize reliably the exposures of professional janitors in the Fresno area, that those exposures are likely to be similar for other professional janitors elsewhere, and that the exposures of professional janitors wiping for extended durations can inform assessments of the likely exposure of others wiping with similar methods for shorter durations. EPA is confident that this design will provide data on wiping exposures more accurate and reliable than currently available data.

2.2 How and to what will human subjects be exposed?

The test subjects will be exposed to SANI-CARE LEMON QUAT (EPA Reg. No. 47371-131-559) which contains active ingredients 2.54% didecyl dimethyl ammonium chloride (DDAC) and 1.69% n-alkyl dimethyl benzyl ammonium chloride (ADBAC). (V3:47).

Test subjects will be exposed during wiping activities. Two distinct wiping scenarios are to be monitored, including a spray and wipe method and a RTU wipe method. The spray and wipe method will use a 32 ounce spray bottle with an adjustable nozzle using a fine spray. This trigger pump spray bottle is referred to as an "All Purpose Cleaner (APC trigger sprayer… supplied by Buckeye International". After using the trigger pump sprayer subjects will wipe surfaces with cotton rags. The RTU wipes are pre-saturated with antimicrobial solution, and will be prepared by the researchers. Test subjects will not pour the concentrate. Exposure while pouring the concentrate will be monitored in a separate study. (V3:11, 49-50 and 64).

"…represent typical consumer and professional worker methods of applying the test substance to indoor horizontal and vertical surfaces above floor level". (V3:51)

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

"The test substance for these studies is the formulated product, LEMON QUAT, containing didecyl dimethyl ammonium chloride (DDAC) and n-Alkyl dimethyl benzyl ammonium chlorides (ADBAC). The quaternary ammonium antimicrobials are commonly known as "quats". DDAC is the active ingredient selected for measurement, based on its stability, abundance in the formulation, and sensitivity of its analytical method." (V3:47)

"LEMON QUAT is an end use product registered with the EPA for use on smooth surfaces in indoor environments. LEMON QUAT contains didecyl dimethyl ammonium chloride (DDAC) and n-Alkyl dimethyl benzyl ammonium chlorides (ADBAC). DDAC was selected as the analyte based primarily upon its abundance (3x the largest ADBAC homologue), and on its stability, and the sensitivity of its analytical method. The quats ADBAC and DDAC have complete toxicology databases with low mammalian toxicity. Virtually all quat antimicrobial products contain more than a single quat, i.e., a readily available product containing only DDAC was not apparent.

"The analytical method for DDAC on the proposed monitoring matrices at very low concentrations has been validated (GPL, 2004). Additionally, DDAC is a single quat (as opposed to ADBAC, the other active ingredient in LEMON QUAT which is an homologous series of quats) and has the requisite degree of stability under field, storage and transit conditions. The freezer storage stability of DDAC on the different matrices to be used in this study has been completed showing that DDAC is stable on the different matrices when stored in a freezer for 6 months (GPL, 2005).

"The very sensitive and selective analytical method developed for the analysis of DDAC on different study matrices will allow for the detection and quantification of extremely low levels of active ingredient in the collected samples. This will allow for shorter exposure time, thus minimizing the risk to research study subjects.

"Additionally, Sani-Care Lemon Quat has been deemed suitable by the Sponsor and EPA as a surrogate compound for generating exposure data for other antimicrobial pesticides." (V3:48)

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

Concentration of test materials is constant for all subjects, as is equipment. Variation in exposure results from monitoring events (MEs) of differing durations. MEs of predefined duration will bracket the range of typical time spent wiping indoor surfaces per day by professional cleaners and consumers, taking into account the limit of quantitation associated with the analytical method. (V3:20-21)

DDAC was selected because of its relatively high concentration (2.54%), its stability, and the sensitivity of the analytical method. (V3:47)

The SANI-CARE LEMON QUAT product will be diluted 1:64 with tap water as per label directions. (V3:50)

The same dilute concentration will be used by all MEs. The total amount of ai handled will vary by the duration of wiping.

(c) What duration of exposure is proposed?

"Wiping duration will range between 30 and 120 minutes. This interval is partitioned into six mopping duration strata as follows:

A. 30 minutes to less than 45 minutes
B. 45 minutes to less than 60 minutes
C. 60 minutes to less than 75 minutes
D. 75 minutes to less than 90 minutes
E. 90 minutes to less than 105 minutes
F. 105 minutes to 120 minutes

At each site, a single ME is targeted for each stratum. . . . As long as the subject is within the correct stratum, it is unnecessary to control the duration more precisely. However, the subject's actual wiping duration will be recorded to the nearest minute." (V3:54)

Any test subjects not able to wipe for the given duration are allowed to stop and as long as the duration was a minimum of 30 minutes the dosimeters will be analyzed. Durations of less then 30 minutes will not be analyzed. (V3:55)

Table 1 Justification for Duration of Task and Area Treated Estimated Cleaning Times for Healthcare – Mop/Wipe Operations (V3:22) provides estimates of exposure durations from the International Sanitary Supply Association (ISSA).

2.3 Endpoints and Measures

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

Residues of the surrogate chemical on inner and outer passive dosimeters, on hands and face/neck, and in personal air samplers. (V3:70-72)

"Light level, air temperature, and relative humidity of the work area for the duration of exposure monitoring will be documented with automated instrumentation logging. . . . HVAC will be described in detail and the air turnover rate will be measured or estimated." (V3:69)

Dermal and inhalation exposures will be measured using inner and outer dosimeters consisting of 100% cotton long underwear/long johns, long pants, long-sleeved shirts, 100% cotton socks, hand wash, face wash, and personal air sampling pumps (OVS tube with glass filter and XAD2 sorbent tubes run at 2 L/min. (V3:65-66). SOP citations for monitoring methods provided V3:70-72.

"….each [personal air monitors] pump will be calibrated to a nominal sample flow rate of approximately 2 L/min… Flow rates will be measured before and after each exposure monitoring period…" (V3:67)

The validated method (GPL-MTH-052) will be tested. "Each analytical set will include two laboratory fortified samples, a solvent blank and a control" (V3:76)

"The single pull output of each trigger sprayer used in the study will be determined by a calibration run (using tap water and 10 pulls) and the results will be documented in the raw data." (V3:50)

Storage stability of DDAC-fortified matrices was measured (V3:77).

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

The AEATF SOPs provide specific procedures to ensure accurate measurements such as calibration of application solution dispensing (i.e., SOP 10F (V6:70 of 100) and inhalation monitoring devices (i.e., SOPs 10A and 10G (V6:58 and 74 of 100)). "….each [personal air monitors] pump will be calibrated to a nominal sample flow rate of approximately 2 L/min… Flow rates will be measured before and after each exposure monitoring period . . . . per SOP AEATF II – 10F and – 10G" (V3:67-68).

"[air temp, humidity] monitoring equipment will be calibrated or standardized." (V3:69)

(c) What QA methods are proposed?

Section 10.2.3 Air Sampling for Ambient Pre-existing DDAC discusses sampling for background air concentrations of DDAC (V3:68)

Field recovery evaluation procedures provided in SOP 8E. Fortification levels (two levels provided) for each matrix (i.e., dosimeter) listed in table format with the lower fortification levels 4x the LOQ (V3:72). Triplicate samples at each of the two fortification levels (V3:73)

"This study will be conducted according to FIFRA GLP Standards (40 CFR 160)." (V3:81)

(d) How will uncertainty be addressed? Will point estimates be accompanied by measures of uncertainty?

"...large deviations from the benchmark goals may affect the regulatory usefulness of the data. If large deviations from the benchmark goals are observed 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 clusters might be considered." (V3:78)

3. Subject Selection

3.1 Representativeness of Sample

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

The target population is the distribution of future handler/days of applicators applying antimicrobial pesticides in the wiping scenario.

"The community of individuals that use wipes to clean/disinfect surfaces is enormous and includes millions of workers and at least 100 million residents in the U.S. alone" (V3:46)

(b) From what populations will subjects be recruited?

"Adult subjects will be recruited from the janitorial/cleaning service population of Fresno County. The most-recent US Census indicates that 40% of the population in Fresno, CA metropolitan area is Hispanic. The proportion of Hispanics in service industries, e.g., janitorial services, may be even higher than the general population. Therefore, to adequately represent the ethnic diversity in the Fresno area, recruitment

materials and all interactions with potential subjects will be conducted in both English and Spanish." (V3:56)

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

Expected participants will self-identify in response to flyers soliciting interest, posted in the workplaces of janitorial services companies. They may differ in unknowable ways from other workers who do not step forward. Participants will be screened in random sequence from among responders, and in that sense will be representative of the population of janitorial service workers in the Fresno area. There is no reason to think that janitorial service workers in Fresno are not representative of janitorial service workers in any other area of the United States.

"The most-recent US Census indicates that 40% of the population in Fresno, CA metropolitan area is Hispanic. The proportion of Hispanics in service industries, e.g., janitorial services, may be even higher than the general population." (V3:56).

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

No discussion was provided on the generalizability of the results.

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. They are listed on V3:58-59 and below:

"Inclusion Criteria:

- Males or females, 18 to 65 years of age
- In good health
- Willingness to sign the Informed Consent Form and Subject Self Reporting Demographic Form
- Speak and read English or Spanish
- Reside within Fresno County, California
- Have experience working in janitorial services

Exclusion Criteria

- Skin conditions on the surface of the hands or face/neck (e.g., psoriasis, eczema, cuts or abrasions)
- Pregnancy, as shown by a urine pregnancy test
- Lactation
- Allergies to household chemical-based products, soaps or isopropyl alcohol

- Declines to sign the Informed Consent Form or the Subject Self Reporting Demographic Form
- Does not read and understand English or Spanish
- Is less than 18 or more than 65 years old
- Is not in good health
- Severe respiratory disorders (e.g., moderate or severe asthma, emphysema)
- Cardiovascular disease (e.g., history of myocardial infarcts, stroke, congestive heart failure or uncontrolled high blood pressure)
- Is an employee of Golden Pacific Laboratories or Grayson Research, or is related by blood or marriage to personnel in either company."

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

Employees and relatives of employees of the investigators are excluded from participation as subjects. (V3:59)

(c) If any potential subjects are from a vulnerable population, what is the justification for including them?

No potential subjects are from a vulnerable population.

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

The recruiting process is described in V3:56-59

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

"Janitorial services located in Fresno County and providing professional cleaning services for commercial buildings in the Fresno County, CA area will be contacted and asked to post flyers soliciting study subjects independently from the janitorial service. . . . Those janitorial service managers expressing a willingness to post the flyers will be invited to a meeting. . . . At this meeting, the managers will be provided with the flyer and the informed consent form. One purpose of these meetings will be to . . . impress upon the managers the need to remain neutral (un-coercive) in their interactions with employees regarding study participation. Also, the meeting may provide an opportunity to hear from organized labor, if any of the shops represented are unionized. . . . To avoid the potential for coercion, subjects will not be recruited directly through contract janitorial service companies. Flyers will direct interested workers to contact the study Field Coordinator or Spanish-speaking coordinator directly." (V3:56-57)

3.3 Remuneration of Subjects

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

"Individuals that are not tested including anyone signing the informed consent form but not subsequently being monitored will be compensated for their time and inconvenience at the rate of $50 per day. . . . Subjects participating in a monitoring event (ME) will be compensated at $100 for the single day that they are monitored. The values for compensation are based roughly on a day's wage of $100 and represents potential lost time from secondary sources of employment, travel time and incidental expenses incurred in study participation. Compensation will be in the form of cash (U.S. currency) at the completion of participation." (V3:60)

(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 in the form of cash (U.S. currency) at the completion of participation." (V3:60)

4. Risks to Subjects

4.1 Risk characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?

The proposed test material is EPA-registered, with an essentially complete supporting database. The test material is of low toxicity to mammals.

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

Risks are of a reaction to the test material or the solvents used to obtain residues from hands and face/neck; of discomfort and possibly heat-related illness associated with wearing two layers of clothing; of a cardiovascular adverse event attributable to physical exertion; of discomfort or inconvenience from wearing the air sampling device; of embarrassment from disrobing in the presence of a research technician; of an unexpected result of pregnancy testing. (V3:43-45)

Risks discussed in the consent form include risk of a reaction to the test material, risk of over-exertion and stroke or heart attack, risk of discomfort, risk of stinging from alcohol wash and wipes, a small possibility of heat stress, risk of embarrassment, possible surprise at the results of a pregnancy test, unknown risks to the unborn, and unknown or unforeseeable risks including risks of allergic reaction or interaction with a medication. (V3:177-186)

(c) What is the probability of each risk associated with the research? How was this probability estimated?

All identified risks are characterized as of low probability. No quantitative estimates are reported.

4.2 Risk minimization

(a) What specific steps are proposed to minimize risks to subjects?

Use of test materials shown to be of low toxicity to mammals; use in strict accord with approved labeling; exclusion of candidates known to be sensitive to quaternary ammonium compounds; exclusion of candidates in poor health or with broken skin on hands, face, or neck; testing in a controlled-temperature environment; alerting subjects to signs and symptoms of heat stress; monitoring heat index with associated stopping rules; limited time of exposure with rest periods at 30-min intervals, or more frequently if requested; close observation of subjects; training of experienced technicians to minimize embarrassment; incorporation of procedures to keep results of pregnancy testing private and to permit discrete withdrawal; provision of appropriate work clothing and PPE. (V3: 43-45, 48-49, 60-62)

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

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 0.04% ai (1/64 product dilution x 2.54% ai in product = 0.04% ai) will not trigger a risk of concern. The inhalation toxicological endpoint identified for DDAC for all exposure durations is based on two oral toxicity studies (prenatal developmental toxicity in rats, MRID 41886701, and a chronic toxicity study in dogs, MRID 41970401). The selected NOAEL from both studies is 10 mg/kg/day. The inhalation exposure from the spray portion of the wipe study has the potential for inhalation exposure to aerosols.

There are two studies in PHED for inhalation exposure monitored while spraying an aerosol product. The PHED data are based on an application of an insecticide around baseboards in a kitchen.[3] The PHED inhalation unit exposure is 2.4 mg/lb ai sprayed. The proposed product dilution directions are to use 2 oz product/gallon of water x 2.54% ai in product x 8.34 lb per gallon density of water x (1 gallon/128 fluid oz) = 0.0033 lb ai/gallon. Therefore, assuming 1 gallon of treatment solution sprayed x 0.0033 lb ai/gallon x 2.4 mg/lb ai unit exposure x (1/60 kg BW) = 0.00013 mg/kg/day. The margin of exposure (MOE) = 10 mg/kg/day / 0.00013 mg/kg/day inhalation dose = 77,000.

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

Heat stress index above 95 (V3:62)

Other medical reasons (V3:61)

"If two or more subjects withdraw or are withdrawn from the study for the same medical reasons, the study will be suspended until the cause of the withdrawal is fully investigated and determined." (V3:61)

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

SOP 11.B for Management of Heat Stress (V6:78-92)

SOP 11.C for Emergency Procedures (V6:93-95)

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

"If a subject reports an adverse skin reaction during the work period, they will be asked to immediately stop working. Research staff will then assist the subject in gently washing exposed skin with clean water and mild soap. After drying the area with a clean towel, the Principal Investigator will be contacted for further instructions.

"The extra layer of clothing worn by subjects may increase the risk of heat-related illness. To minimize the possibility of heat stress, the study will be conducted indoors in an environment where the heat index (HI) is expected to be less than 85. Research personnel shall monitor the heat index, and stop subjects' work if the heat index exceeds 95. The SOP AEATF 11.B describes the procedure for identification and control of heat stress. The poster "Controlling Heat Stress Made Simple" will be posted at the field site.

[3] This PHED insecticide use scenario will be replaced by the data generated from this protocol for antimicrobial uses.

"In brief, researchers will observe subjects for possible signs of early heat illness such as fatigue, dizziness, irritability, or decreased concentration, especially if the worker has been working for a while. If these symptoms are observed, the subjects will be asked whether they would like to rest for a moment. If they answer affirmatively, they will stop working, be given their choice of water or a sports drink, and the Principal Investigator 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 asked to stop working immediately, and given their choice of water or a sports drink. The Principal Investigator will immediately be contacted for further medical management instructions. If the worker's condition appears to be serious, a member of the study team will call 911 and allow emergency medical personnel to respond and treat the subject." (V3:61-62)

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

"Subjects will be instructed to inform the Principal Investigator or research staff immediately if they feel ill, suffer a skin reaction or experience any other unanticipated adverse effects they feel may be related to the study during or following conduct of the study." (V3:61)

"If two or more subject develop an adverse skin reaction after they leave the study site, all subjects will be contacted by the Principal Investigator to determine whether further medical management is appropriate." (V3:62)

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

"If you are injured as a result of being in this study, medical treatment will be available from a near-by health care facility that knows about this study. The people who are paying for this study will pay any costs of your medical treatment that are not covered by your own insurance or by a third party. If necessary, Golden Pacific Laboratories will transport you to receive medical attention and pay costs associated with reasonable and appropriate treatment of any injuries you get as a result of participating in this study." (V3:183)

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

"While there are no direct benefits to the subjects participating in this research study, there are indirect benefits to both the volunteers and society. . . . If individual workers request their results, they may find that their work practice produces more or less exposure than average, and this could be a useful learning tool." (V3:45)

(b) What benefits to society are anticipated from the information likely to be gained through the research?

"Products containing antimicrobial chemicals are used extensively in hospitals, schools, homes, etc. to control pathogenic bacteria and viruses known to produce increased morbidity and mortality in humans, domestic animals and pets. Measuring exposure of workers in this research study will produce reliable data about the dermal and inhalation exposure of workers and the general population performing these tasks. The resulting data will improve the completeness and accuracy of the database used by the EPA to assess exposure to these chemicals. The ability to accurately predict risk may allow other chemical classes of antimicrobials to also be registered based on exposure estimates generated from the data to be produced by this study." (V3:45)

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

Not addressed.

(d) What is the likelihood that each identified societal benefits would be realized?

The research is very likely to produce more accurate and reliable information concerning exposure in the mop scenario, with resulting societal benefits in the form of more accurate and confident assessments of applicator 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 benefit of maintaining and potentially adding new antimicrobials that protect both the subjects involved in this research as well as society (including subjects' families) in general from microbial diseases far outweighs any incremental risks to subjects. Mortality and morbidity from microbial pathogens is well-documented. The very slight risks from participation in this study are far lower than the risk of not being able to use effective antimicrobials for lack of information on the exposure to users." (V3:45-46)

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Independent Investigational Review Board, Inc., Plantation FL (IIRB)

(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?

Not reported. IIRB is not listed as an accredited organization on the AAHRPP website (www.aahrpp.org). AAHRPP does not identify organizations for which accreditation is pending.

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

Not reported. IIRB is not listed as holding an FWA on the OHRP website.

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

The transmittal of the protocol and related materials to the IIRB (V4:5, 146, 171-196), the IIRB's approval letter (V3:1173-174 and V4:337-338), minutes of the IIRB meeting at which the proposed research was discussed and approved (V4:341-343), and an appropriate membership list (V4:344-346) are provided. Acceptable documentation of IIRB procedures has previously been provided directly to EPA under a claim of confidentiality.

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

"The primary ethical standards applicable to this proposal are 40CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply, and since the study will be conducted in California, the provisions of the California Code of Regulations, Title 3, §6710 would apply." (V3:39)

8. Informed Consent

(a) Will 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?

Literacy in English or Spanish is a criterion for inclusion (V3:59)

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

"Janitorial services located in Fresno County and providing professional cleaning services for commercial buildings in the Fresno County, CA area will be contacted and asked to post flyers soliciting study subjects independently from the janitorial service. . . . The initial contact with service providers will determine language preference (English and/or Spanish) for the flyers." (V3:56)

"Those janitorial service managers expressing a willingness to post the flyers will be invited to a meeting . . . . At this meeting, the managers will be provided with the flyer and the informed consent form. One purpose of these meetings will be to determine if the Spanish translations seems intelligible to the particular dialects that may be represented in the County." (V3:56)

"Flyers will direct interested workers to contact the study Field Coordinator or Spanish-speaking coordinator directly." (V3:57)

"A Spanish translator will be available at recruitment meetings to ensure communication with anyone preferring Spanish over English." (V3:57)

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

"A Spanish translator will be available at recruitment meetings to ensure communication with anyone preferring Spanish over English. The Principal Investigator will share information on the study design with interested participants, and provide them with copies of the IRB approved Informed Consent Form (Appendix B) and answer their questions. The Principal Investigator will describe the study to the individual in great detail and encourage each potential subject to ask questions and request clarification at

any time during this process as well as in all activities that follow. The Principal Investigator will provide each potential subject with a copy of the product label (Appendix A) and MSDS (Appendix E) and answer any questions regarding the product to be tested. The Principal Investigator will go over the Inclusion and Exclusion Criteria (see 9.1.3 below) for the study and answer any questions that the potential subjects have. They will be provided with copies of the Informed Consent Form (Appendix B), the Subject Self-Reporting Demographic Form (Appendix D) and the State of California Department of Pesticide Regulation "Experimental Subject's Bill of Rights" (Appendix C) and encouraged to take them home with them to discuss with family and friends. The Principal Investigator will explain to potential subjects wishing to remain in consideration that they may withdraw from the research study at any time without penalty to their compensation. The Principal Investigator will then read the "Experimental Subject's Bill of Rights" to the potential subjects. The amount and form of compensation, the potential risks and discomforts and treatment and compensation for injury will be more fully explained and potential subjects encouraged to ask questions. If the potential subjects do not have any questions and are interested in participating in this research study, they will then be asked to sign the Informed Consent Form and then fill out the Subject Self-Reporting Demographic Form." (V3:57-58)

Since the label and MSDS are available only in English, and since the Principal Investigator is not fluent in Spanish, these procedures may not be adequate to ensure subject comprehension of risks and discomforts.

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

See procedure quoted in 8(f) above.

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

"Janitorial services located in Fresno County and providing professional cleaning services for commercial buildings in the Fresno County, CA area will be contacted and asked to post flyers soliciting study subjects independently from the janitorial service. The initial contact with service providers will determine language preference (English and/or Spanish) for the flyers. . . . Those janitorial service managers expressing a willingness to post the flyers will be invited to a meeting. . . . One purpose of these meetings . . . will be to impress upon the managers the need to remain neutral (un-coercive) in their interactions with employees regarding study participation.

"To avoid the potential for coercion, subjects will not be recruited directly through contract janitorial service companies. Flyers will direct interested workers to contact the study Field Coordinator or Spanish-speaking coordinator directly." (V3:57)

9. Respect for Subjects

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

"Each volunteer will be assigned an identification number, and all research data will be recorded under that number. All analysis and reporting will be done using data identified only by the identification number. Your name will appear only in the field raw data, and there only once. The document linking your name to the identification number will be stored separately, in a locked cabinet, away from all other study data. You will not be identified by name or any other personal identifier in any reports of this study." (V3:184)

"On the day of the test all female volunteers under 50 will be given a pregnancy test kit like ones you can buy at the drug store. A female researcher will be able to explain how to use it and answer questions. After you give yourself the test, we'll ask you if you want to continue in the study or withdraw; if you decide to withdraw, you won't be asked why. . . . If you want to continue in the study, a female researcher trained to understand the results of this pregnancy test will check the results with you privately. No-one but you and she will see the results, and they will not be recorded." (V3:183)

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

See passage quoted in 8(f) above, and these passages from the consent document:

"If you decide to participate 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. Your alternative is not to participate." (V3:184)

"You are free to withdraw from this study at any time, for any reason. Simply tell Dr. Selim or another member of the research team if you wish to withdraw. Your decision not to participate in this study or to withdraw from this study will not affect your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled." (V3:185)

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

Those who decline to participate will simply go their way. The consent form states that subjects who withdraw will suffer "no loss of benefits to which you are otherwise entitled", but is unclear whether and how much they would be paid. Subjects who are withdrawn by the investigators—and all participating subjects in the case that the entire study is stopped—are promised payment in full. (V3:184-185)

§ 26.1111 Criteria for IRB approval of research
AEATF-II Wipe Scenario/Protocol AEA02/070264:Jan 16, 2008)

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 Wipe Scenario/Protocol AEA02/070264:Jan 16, 2008

Criterion		Y/N	Comment/Page Reference
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		OK	
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		OK	
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		N	More attention is needed to ensure bilingual competence among investigators who conduct recruitment and consent interviews
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		OK	
(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	OK	
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	OK	
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	OK	
	(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	OK	
	(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	OK	Although research doesn't involve more than minimal risk, compensation and treatment of injuries are provided for
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	OK	Must ensure Spanish capability, and express all time references in California time
	(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	OK	
(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	OK	
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	OK	
	(3) Any additional costs to the subject that may result from participation in the research	OK	
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	OK	
	(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	OK	
(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.		OK	

§26.1117 Documentation of informed consent
AEATF-II Wipe Scenario/Protocol AEA02/070264:Jan 16, 2008

Criterion	Y/N	Comment/Page Reference
(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.	OK	
(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	OK	
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	n/a	

40 CFR 26.1125 Prior submission of proposed human research for EPA review
AEATF-II Wipe Scenario/Protocol AEA02/070264:Jan 16, 2008

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/Page Refs
All information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	V3:8-171; V4:7-170; 197-335 V3:175-198
	(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	V4:341-342
	(3) Records of continuing review activities.		n/a	
	(4) Copies of all correspondence between the IRB and the investigators.		Y	V4:5, 146, 171-194
	(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 Y	V4:344-346 V4:344
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		Y	Separately submitted to EPA under confidentiality claim
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	
The following Information, to the extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	V3:43-45
		(2) The measures proposed to minimize risks to the human subjects;	Y	V3:45
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	Nature V3:45. No discussion of magnitude of benefits
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	V3:42
		(5) The balance of risks and benefits of the proposed research.	Y	V3:45-46
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Orig V4::64-74; 254-264 Approved V3:177-198
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	V3:56-58; 107-112
	§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	V3:57-58
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	V4:
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.		Y	V3:173-174