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

OFFICE OF
PREVENTION, PESTICIDES AND TOXIC
SUBSTANCES

September 21, 2009

MEMORANDUM

SUBJECT: Science and Ethics Review of AEATF II Aerosol Scenario Design and Protocol for Exposure Monitoring

FROM: Timothy Leighton
Cassi Walls, Ph.D.
Antimicrobials Division

Kelly Sherman
Human Research Ethics Reviewer

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

REF: Selim, S. (2009) Transmittal Letter, 40 CFR 26.1125 Checklist, and Primary Documentation: Aerosol Application Scenario: Rationale for Study Design. 56 pp. (**Volume 1**)

Selim, S. (2009) A Study For Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using a Pressurized Aerosol Can for Indoor Surface Disinfecting. Unpublished protocol dated August 4, 2009, prepared by Golden Pacific Laboratories for the Antimicrobial Exposure Assessment Task Force II under Sponsor ID AEA04 and GPL Study No. 070270. 203 pp. (**Volume 2**)

Selim, S. (2009) AEATF II Aerosol Study. Secondary Documentation: IIRB Communications. August 4, 2009 (**Volume 3**)

Selim, S. (2009) AEATF II Aerosol Study. Standard Operating Procedures for a Multi-Year Antimicrobial Chemical Exposure Monitoring Program. August 4, 2009 (**Volume 4**)

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.

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

- Transmittal Letter (pp. 3-4)¹
- 40 CFR 26.1125 Checklist (p. 5)
- Aerosol Application Scenario: Rationale for Study Design (pp. 6-56)

Volume 2 of the submitted package includes the following documents—all considered in this review:

- IIRB-approved protocol (pp. 3-57)²
- Product Label for test material, in English (p. 59-60) and Spanish (pp. 61-63)
- IRB-approved Informed consent form, in English (pp. 65-74) and Spanish (pp. 75-85)
- IRB-approved Experimental Subject's Bill of Rights, in English (p. 87) and Spanish (p. 88)
- Subject Self-Reporting Demographic Form, in English (p. 90) and Spanish (p. 91)
- MSDS for test material, in English (p. 93) and Spanish (pp. 94-95)
- IRB-approved Flyer soliciting research subjects, in English (p. 97) and Spanish (p. 98)
- IRB-approved Newspaper advertisement soliciting research subjects, in English (p. 99) and Spanish (p. 100)
- Employer contact script and subject invitation to participate script, in English (pp. 103-104) and Spanish (pp. 105-106)
- Executive Summaries from ADBAC and DDAC Reregistration Eligibility Decision Documents (pp. 111-156)

¹ Most page images in the submitted volumes bear more than one page number. All page references in this review are to page "N of 56" in Volume 1; page "N of 203" in Volume 2; page "N of 317" in Volume 3; and page "N of 128" in Volume 4.

² The protocol submitted to EPA on August 4, 2009 (pages 3-57 of Volume 2) bearing a cover page dated August 4, 2009, is identical to the version of the protocol submitted to IIRB on July 14, 2009, and approved by IIRB on July 27, 2009. This is documented in a September 15, 2009, letter from Hasmukh Shah (Manager, AEATF II) to Kelly Sherman (EPA, Office of Pesticide Programs). A copy of the letter is included in the supplemental materials.

- IIRB approval letter of July 27, 2009 (pp. 157-159)
- Recruitment and Consent documents submitted to IIRB, showing IIRB-requested changes (pp. 160-203)

Volume 3 of the submitted package includes documentation of communications with IIRB, Inc. concerning the aerosol protocol, including:

- Protocol version transmitted to IIRB (bearing cover page dated July 14, 2009; subsequent pages dated July 13, 2009) (pp. 20-168)³

Volume 4 of the submitted package includes all of the AEATF II's Standard Operating Procedures (SOPs) supporting the aerosol study protocol.

In future protocol submissions, it is imperative that the AEATF assign a version date to protocols and consent materials. The version date must be made a permanent attribute of the file. The AEATF's re-dating of the IIRB-submitted and approved protocol jeopardizes the integrity of the record. Please refer to the September 15, 2009, letter from Hasmukh Shah (Manager, AEATF II) to Kelly Sherman (EPA, Office of Pesticide Programs) for details.

A. 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 from an aerosol spray can. Aerosol spraying can be accomplished with different types of nozzles, volumes, and techniques. AEATF II defines "...the aerosol application scenario is defined as the hand-held pressurized aerosol-based application of a label-specified end-use formulation containing an antimicrobial chemical." (V1:8)⁴ The actual task of spraying will be to spray a smooth, sweeping, overlapping pattern until the treated surface is wet. The scope of the choices of aerosol can characteristics that are reasonably expected to influence exposure includes nozzle size, particle size generated, ejection rate, and generation of non-volatile active ingredient. From this array of choices, the industry and regulatory consensus was to monitor the selected product – Clorox Commercial Solutions Clorox Disinfecting Spray (EPA Reg. No. 67619-03). A more detailed description of the process used to select the product is

³ The protocol submitted to EPA on August 4, 2009 (pages 3-57 of Volume 2) bearing a cover page dated August 4, 2009, is identical to the version of the protocol submitted to IIRB on July 14, 2009, and approved by IIRB on July 27, 2009. This is documented in a September 15, 2009, letter from Hasmukh Shah (Manager, AEATF II) to Kelly Sherman (EPA, Office of Pesticide Programs). A copy of the letter is included in the supplemental materials.

⁴ This pagination convention is used throughout this review. "V1" refers Volume 1 of the AEATF submission; "V2" refers to Volume 2; "V3" refers to Volume 3; "V4" refers to Volume 4. Entries after the colon are page references; many page images bear more than one page number. In Volume 1, the cited page number is always from the expression "p. N of 56". Volume 2 page references are always from the expression "p. N of 203." Volume 3 page references are always from the expression "p. N of 317". Volume 4 page references are always from the expression "p. N of 128."

provided below in Attachment 1 and Appendix A Study Rationale Product Selection Justification. (V1:34)

EPA intends to use the data developed by the AEATF II for the aerosol spraying scenario to describe a typical occupational handler's daily exposure to the antimicrobial spray. The data must be generic enough to be useful for estimating exposures using various types of aerosol spray products (i.e., disinfecting sprays onto surfaces, air sanitizers, and foaming aerosols for bath tub/toilets), different types of surfaces, 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 aerosol study generically to estimate dermal and inhalation exposures and risks for other antimicrobial ingredients where the product is packaged in a pressurized aerosol spray can.

Antimicrobial products have been grouped by EPA into the 12 Use Categories listed below as presented in the proposed 158W data requirements. Although aerosol spraying of surfaces or air sanitizers may occur in many Use Categories, most aerosol spray 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

EPA believes that the AEATF II aerosol scenario is 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 aerosol scenario as defined in this proposal will adequately describe a typical occupational handler's daily exposure to the antimicrobial application. This exposure can then be extrapolated to the likely exposure of a home user of aerosol antimicrobial products.

- 2. Sampling Design:** The AEATF II has described in detail their sampling design for the aerosol scenario and has incorporated random elements where feasible. The AEATF II proposes to monitor dermal and inhalation exposures using passive dosimetry techniques to measure exposure of human subjects spraying indoor surfaces with an aerosol can. The proposed sample size is 3 clusters (sites) with 6 subjects at each. This is believed adequate to provide data to meet EPA's needs.

The aerosol scenario will consist of professional applicators using 19-ounce pressurized cans to spray aerosols on surfaces such as laminate, tile, porcelain, glass, and/or metal. The physical aspects of spraying include holding the spray can, depressing the nozzle with a finger, and spraying in a smooth, sweeping, overlapping pattern. The surfaces will be sprayed from a distance of 6 to 10 inches until the surface becomes visibly wet. The aerosol spray cans are ready-to-use (i.e., no mixing/loading is involved.). Additionally, the spray solution will be left on the surface, so no wiping will occur.

The amount of product applied during each monitoring event will be varied from 1 to 4 cans. MEs will be based on ½ -can increments (i.e., 1 to 1.5 cans, 1.5 to 2 cans, up to 3.5 to 4 cans). The spraying duration will consist of the time it takes to spray a given number of cans. The focus on professional applicators is a practical necessity, given that residential consumer spraying efforts are of shorter duration (i.e., less product sprayed) and would have a greater chance that samples would be at or below the limit of detection of the analytical methods used. Because of longer task duration and consequent exposure to greater quantities of antimicrobial, professional spray applicator exposure is expected to be greater than that of consumers.

The AEATF II aerosol spray study is further limited to application using a surface disinfecting spray. Other registered aerosol spray uses include air sanitizers and foaming aerosols (e.g., bath tub and toilet cleaners). The surface disinfecting spray was selected to represent the high end of potential exposure, based on a pilot study reported in the protocol submission (V1:34). The AEATF II, in consultation with EPA/CDPR/PMRA, considered the various configurations of aerosol spraying and the results of the pilot studies' nozzle size, particle size generated, and amount of material dispensed per unit time, air concentration, and ejection rate, and agreed that the hard-surface disinfection spray application representing the reasonable high end of exposure. Other key factors considered in the selection of an aerosol application included its common use among consumers; its use in tight spaces such as shower stalls; and the high exposure potential for applicators walking into sprayed mist while spraying a surface disinfectant in small rooms.

The scenario does not include wiping the sprayed product from surfaces that have been sprayed, for two reasons. First, some antimicrobial sprayed products are leave-on, not requiring the user to wipe the surface. Secondly, the AEATF II is developing other data under the "wipe" scenario which can be considered along with the results of this study when the situation warrants. This will allow the regulatory agencies to assess either leave-on products or those products that are subsequently wiped from surfaces.

The amount of product to be handled by each subject will be randomly selected. The subjects will be randomly ordered as they are enrolled. At each site the subject's tasks are defined by a specific amount of product to be applied ranging from 1 to 4 cans. Set durations will not be established. Subjects will apply the amount of

product assigned to them as they normally would work. The first subject randomly selected will be assigned to the task with the largest amount to be applied (i.e., 3.5 to 4 cans), although if the subject is unable to complete the assigned amount to be sprayed, the monitoring event may fit the specification for a lesser amount sprayed. As additional subjects are assigned to tasks, all defined spraying amounts will be reflected in one monitoring event. The actual duration of the spraying task will vary among the subjects; the AEATF II anticipates the monitoring events will range from 30 to 180 minutes.

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.

The aerosol scenario design calls for three clusters of MEs, each at a different site. A site is defined as the facility (i.e., building). The protocol specifies 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 building/room configurations, specifically hotels/motels with 20 or more units containing various full kitchens, kitchenettes, or bathroom-only configurations. The need for multiple rooms within a building differs from the previous AEATF II mop and wipe protocols. The multiple rooms are required in this study because it is believed that the smaller rooms with multiple surfaces to be sprayed such as shower fixtures, toilets, sinks found in typical bathrooms in hotels/motels will lead to the high end of potential exposures occurring from aerosol applications of antimicrobial chemicals.

Three sites will be selected using a stratified random sampling approach. A listing of potential sites will be developed using YellowPages.com. This list will be based on a search using the following criteria: *“hotel or motel with kitchenette or full kitchen” in “Fresno, California”*. A caveat is added to the protocol stipulating that if motels with kitchens are not available the search will be broadened to include empty apartments. The three sites will be randomly selected from this list. The three sites will need to meet the following selection criteria:

- Willing to cooperate in the study;
- Configured for a diversity of treatment surfaces (e.g., kitchens, bathrooms, sinks, countertops, toilets);
- Has a functional HVAC system;
- Has operating electrical service;
- Does not require specialized cleaning or maintenance before use.

The final selection of the three sites will be those facilities that fit into one of the following three categories (i.e., one site per each of the three categories):

- Hotel/motel with full kitchen and 20 or more units;
- Hotel/motel with kitchenette and 20 or more units;
- Hotel/motel without kitchen/kitchenette and 20 or more units.

The aerosol scenario calls for monitoring 6 subjects at each of three sites as they spray horizontal and vertical surfaces. Therefore, a total of 18 test subjects will be monitored. Two additional test subjects will be enrolled for each site, making a total of 24 subjects in all, in case some subjects withdraw or fail to meet all eligibility criteria. Subjects will be professional janitors, selected 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. In addition to the flyers, advertisements will be run simultaneously in three newspapers: (1) Fresno Bee, (2) California Advocate, and (3) Vida en el Valle. Enrolled subjects will be randomly assigned to spraying tasks of differing amounts of product at one of the three test sites.

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 ADBAC 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 the aerosol scenario a design of 3 clusters of 6 monitoring events (MEs) each, as discussed in the Governing Document. The AEATF II reviewed two data sets in determining the statistical design. The two data sets include aerosol-specific exposure data from PHED and the data set presented in the Governing Document for repetitive-motion tasks. The existing data set for aerosol exposure data in PHED indicates less variation than the larger data set of repetitive-motion tasks. The existing PHED aerosol-specific data indicate the need for a 3 clusters of 2 MEs to achieve the 3-fold accuracy goal. However, ... “[g]iven the sensitivity of the sample size to GSD [geometric standard deviation] and the belief that the repetitive-motion GSD is a better indicator of the expected true relative variation for this scenario, the AEATF II prefers to assume $GSD=2.9$ for the purposes of determining sample size.” (V1:28, 29) This assumption is consistent with the proposed design of 3 clusters of 6 MEs each.

- 2. Proposed pattern of human exposure:** The AEATF II proposes to select professional janitors as subjects for the aerosol scenario. The test subjects will use Clorox Commercial Solutions Clorox Disinfecting Spray (EPA Reg. No. 67619-03) in 19 ounce ready-to-use pressurized spray cans, and each subject will spray from 1 to 4 cans. The duration of spraying will be based on the amount of product sprayed, the room configuration, and the normal work habits of the test subject. The protocol anticipates the duration to range from 30 to 180 minutes. The actual spraying mechanics are to hold the spray can 6 to 10 inches from the surface, then to hold the nozzle down with a finger and spray overlapping swaths until surfaces are wet. The test subjects will not wipe the solution from the surface – the wiping task will be monitored in a separate AEATF II study.

Clorox Commercial Solutions Clorox Disinfecting Spray which contains the active ingredients didecyl dimethyl ammonium chloride (DDAC) at a concentration of 0.0945%, n-alkyl (40% C12, 50% C14, and 10% C16) dimethyl benzyl ammonium chloride (ADBAC) at a concentration of 0.252%, octyl decyl dimethyl ammonium chloride (ODAC) at a concentration of 0.0945%, and dioctyl dimethyl ammonium chloride (DODAC) at a concentration of 0.189%, and ethanol at a concentration of 65% (plus 34.37% inerts). The C14 portion of ADBAC is the active ingredient to be measured on the dosimeters. The aerosol product is ready-to-use so it will be sprayed at the concentrations listed above with no dilution. The concentration of the test material will be constant for all subjects. Variation in exposures will result from differing amounts handled by each subject.

The EPA believes that the AEATF II aerosol study will represent typical worker methods of applying the test substance to indoor surfaces. The selection of janitorial subjects, test material, and spraying activities as described in the protocol is justified.

- 3. Endpoints and Measures:** The AEATF II proposes to measure dermal and inhalation exposures resulting from spraying of indoor surfaces. Dermal and inhalation exposure will be measured using whole-body dosimeters (inner and outer), hand and face washes, and personal air monitors. The Agencies are most interested in the inner dosimeters to assess potential exposure. The outer dosimeters will add to the existing data base on the development of protection factors for single layer of clothing. The potential for foot exposure is minimal and the feet will not be monitored. The hand and face wash is an appropriate method to determine exposure to the hands and face. 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 XAD2 sorbent. Because the air sampling will not size particles, the Agencies will assume conservatively that all of the residues are inhalable and/or respirable, which will tend to overestimate inhalation exposure. The sampling pumps will be calibrated prior to use.

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 II QA/QC plan for the aerosol 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, and break-through analyses of the air samplers. Method validation results should be included in the final study report.

Primary components of the field recovery analyses include: two fortification levels per matrix at the LOQ, 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 and transported and stored in the same way as the actual study samples, and will be analyzed concurrently with the actual exposure samples. Correction for loss in field recoveries will correct for all phases of potential losses.

A storage stability study is ongoing. The storage stability samples are being stored for up to 6 months.

- 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 aerosol spray monitoring data will be imported into the AEATF II 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 air 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 II has addressed the technical aspects provided in the applicable exposure monitoring guidelines (i.e. Series 875 Group A and OECD Applicator Guidelines) as well as Good Laboratory Practices (GLPs).

The following element in the protocol requires revision before the research goes forward:

- The AEATF II needs to revise the protocol to indicate the course of action if the benchmark accuracy goals (i.e., $k=3$) are not achieved.
 - In a September 18, 2009, letter from Hasmukh Shah (Manager, AEATF II) to Timothy Leighton (Office of Pesticide Programs, Antimicrobial Division), the AEATF II committed to address deviations from the benchmark accuracy goal (i.e., $k=3$) as follows: “[I]f large deviations from the benchmark goals are observed in the aerosol study, 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.” (a copy of the letter is included in the supplemental materials provided for review by the HSRB).

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 monitoring study is to develop more accurate information on worker exposures to liquid antimicrobial products applied using pressurized aerosol cans for indoor surface disinfecting. Because many millions of Americans apply antimicrobial products using aerosol cans, the research question is important; it cannot be answered with confidence without new monitoring data meeting contemporary standards of quality and reliability.
2. **Subject Selection:** Twenty-four adult subjects will be recruited among professional janitorial workers of Fresno County. Participants will self-identify in response to flyers posted in the workplaces of janitorial services companies and advertisements in three Fresno newspapers targeting different demographic groups.

The use of newspaper advertisements is a new recruiting method adopted by the AEATF II because workplace flyers were ineffective during recruiting for the mop and wipe studies. Although more than 50 flyers soliciting subjects for the mop and wipe studies were distributed to janitorial firms in Fresno County, no one attended either janitorial firm manager meeting held to explain the study. Many janitorial firms that reviewed the flyer declined to post, and there were very few responses from employees of those employers who did agree to post a flyer. In June 2009, the

AEATF II amended the mop and wipe protocols to allow for the use of newspaper advertisements in addition to workplace flyers for recruiting. Since the amendment, subjects have been recruited for the mop and wipe studies through both methods. The AEATF II intends to employ both recruiting methods simultaneously for the aerosol study.

Callers responding to either the workplace flyers or the newspaper advertisements will be screened, scheduled for informed consent meetings, and enrolled at the volunteer's convenience. Although additional randomization could be obtained if candidates for informed consent meetings and enrollment were randomly selected from a pool of respondents, the AEATF II has concluded that it is necessary to enroll subjects as they are processed. The AEATF II learned in recruiting for the mop and wipe studies that delaying enrollment in order to compile and randomize a list of potential subjects is infeasible because it results in significant attrition among potential participants and delays in the recruiting process.

Participants will be screened from among respondents to either the workplace flyers or the newspaper advertisements, 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 typical of janitorial service workers in any other area of the United States.

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

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

- 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 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-minute 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 applying antimicrobials in pressurized aerosol cans, usable by EPA and other regulatory agencies to support exposure assessments for a wide variety of antimicrobial products and their uses.
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 antimicrobial products applied with pressurized aerosol cans.
6. **Independent Ethics Review:** The proposed research has been reviewed and approved by the Independent Investigational Review Board, Inc., (IIRB) of Plantation Florida. 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 in the language preferred by the subject. Literacy in English or Spanish is a requirement for inclusion.

All written recruitment, consent, and risk communication materials will be available in both English and Spanish. In order to ensure effective communication and thorough comprehension by anyone preferring Spanish over English, a Spanish-speaking member of the research team will be present at the meetings at which candidates are qualified and sign consent forms.

8. **Respect for Subjects:** Subject-identifying information will be recorded only once; all subsequent data records and reports will refer to individual subjects only by an arbitrary code. Provision is made for discrete handling of 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.

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 Attachments 2-5 to this review.

The following specific deficiency in the protocol should be addressed before the research is initiated:

- In the statement about compensation for research-related injuries (p. 7 of 10 of the consent form), please make the following clarifying revision:
 - Current language: “We will pay for needed medical treatment that is not paid for by your own insurance or by someone else.”
 - Change to: “We will pay for needed medical treatment that is not paid for by your own insurance or by the insurance of a third party under which you are covered.”

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.

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

Attachments:

1. Summary Review of Aerosol Scenario Design dated August 4, 2009
2. Summary Review of AEATF-II Protocol AEA04 dated August 4, 2009
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 Aerosol Application Scenario/Protocol

Title: **AEROSOL APPLICATION SCENARIO: RATIONALE FOR STUDY DESIGN** (AEATF-II Volumes I and II)

Date: August 4, 2009

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

1. Scope of Scenario Design**(a) Is the scenario adequately defined?**

Preliminary versions of the aerosol field study protocol have been reviewed by EPA, PMRA, and CDPR to determine the appropriate aerosol scenario to assess exposure as accurately as possible, while ensuring that any error does not underestimate exposure. Many varied antimicrobial products can be applied by hand-held pressurized aerosol cans for air and surface odor elimination, and for sanitizing and disinfecting hard or soft surfaces. Aerosol applications are common in residential (consumer) settings as well as in commercial settings such as hotels, hospitals, schools, or restaurants.

Aerosol choices include hard and soft surface disinfecting sprays, air sanitizers, and foaming aerosols. From this array of choices, the consensus among the Task Force and the three regulatory agencies was to select the pressurized disinfecting aerosol spray for hard surfaces. The hard surface “pressurized disinfecting aerosol spray was selected to represent this group of spray products because it is a commonly used product type, the application process (spray nozzle actuation) is similar across all aerosol product types, and the surface application rates, normalized to mass of formulation per surface area are comparable across product types.” (V1:8)

The AEATF II aerosol protocol appropriately proposes to use *Clorox Commercial Solutions® Clorox® Disinfecting Spray* (EPA Reg. No. 67619-03), based on the nozzle size, amount of material dispensed per unit time, air concentrations, and aerosol characteristics, across products in the four major aerosol categories (hard surface disinfecting sprays, hard surface foaming aerosols, soft surface sprays, air fresheners).

“The aerosol application scenario involves application according to typical practices, e.g., spraying surfaces from a distance of approximately 6-10 inches in a manner to apply enough formulation to provide an adequate amount for cleaning. Hard surface

applications are typically sprayed until visibly “thoroughly” wet per label direction.” “Surface applications are typically made in smooth, sweeping, overlapping patterns. Examples of ‘representative’ spray application techniques that this scenario is expected to capture include horizontal spraying moving upward and downward from the starting point to hard surfaces such as laminate, tile, porcelain, glass, and metal.” (V1:8)

Aerosol applications may or may not involve wiping the sprayed surface. Some aerosol products are labeled as “leave-on” sprays that do not require post-spray wiping. Only the actual aerosol spray application is covered by this scenario; the exposure from post-application wiping, such as a potable water rinse and wipe following aerosol application to a food preparation surface, will not be evaluated in this scenario. Wiping exposure will be monitored in a separate AEATF II study. This separation of tasks will allow regulatory agencies to assess the exposure associated with either professional “leave-on” products or other products requiring post-spray wiping.

The AEATF II study proposes to recruit only professional janitors. Janitors have been selected to provide longer task durations than are typical for consumers, to reduce the likelihood of undetectable residues on sampling materials. Thus, the scenario design will generate conservative data when used to estimate consumer application exposures.

The amount of product applied during each monitoring event will be varied from 1 to 4 cans. MEs will be based on ½ -can increments (i.e., 1 to 1.5 cans, 1.5 to 2 cans, up to 3.5 to 4 cans). The spraying duration is not predetermined. The duration will consist of the time it takes to spray a given number of cans and is anticipated to range from 30 to 180 minutes.

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

PHED contains two studies conducted using aerosol application methods. These studies have limitations that reduce their value for an antimicrobial-oriented generic database. Both of these studies involved aerosol application for indoor residential crack and crevice insecticide treatment which may not be representative of antimicrobial use patterns. Although both studies monitored application in different houses, the same subjects were used for multiple MEs. Every ME within a study applied an identical amount of product. Thus, there is no variation in amount of a.i. handled within a study and very little difference between the two studies (V1:11). Lastly, these studies do not report particle size distribution.

Furthermore, all subjects in study 456 wore chemical resistant gloves, a practice that is not typical for aerosol application of antimicrobials. In addition, both the dermal and inhalation exposure data from this study have low quality analytical data; as a result, study 456 has rarely been considered in regulatory exposure assessments (V1:11).

Data from the CMA study for aerosol application include only 5 monitoring events with measurable exposures, and only hand exposures were detectable for these MEs. The application duration, only a fraction of which involved actual aerosol spraying, ranged

from 9 to 260 minutes. Finally, the regulatory agencies agreed that the limited number of replicates combined with poor recovery data severely limits the conclusions that can be made from the CMA study (V1:12).

Based on the PHED and CMA data limitations, the Antimicrobial Division is requiring dermal and inhalation exposure data in many of its assessments to fill this data gap for aerosol products.

2. Rationale for Scenario Sampling Design

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

The design choices in the pressurized aerosol 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 AEATF II evaluated several different types of products and equipment (i.e., spray/can) parameters in order to select the most representative and appropriate aerosol spray product for use in the study. This discussion summarizes the AEATF II's aerosol product/can selection process; Appendix A of Volume 1 presents the process in complete detail (V1:34).

The selected aerosol product needs to meet the following criteria (V1:38):

- Serve as surrogate for most aerosol use categories where results can be extrapolated to most products on the market
- Use pattern represents high end exposure
- Use scenario covers most influential variables of exposure
- Have stable active ingredient

Based on a review of the existing literature and exposure data for pressurized aerosol products, the following variables were identified as having the most impact on potential exposure (V1:38):

- Amount of material used
- Release rate
- Particle size distribution
- Nozzle technology
- Pressure in the can
- Temperature / humidity
- Surface on which product is used
- Orientation of the can during use

AEATF II aerosol product/can selection process was conducted in three phases. The first phase consisted of conducting an internal membership survey that identified all of the members' aerosol products and characterized them by some of the influential

exposure variables. The next phase categorized each of the products into one of four major use scenarios. The final phase consisted of a method development study where one representative product from each of the four categories was selected for further analysis on the influencing variables. Based on the results of the method development study, one of the four products was selected as the representative aerosol product for use in the overall exposure study.

Results of the phase 1 AEATF II survey identified 18 products marketed by 9 major companies used in both household and commercial/institutional settings. Many products contain more than one active ingredient; 10 of the 18 products, however, contain ADBAC. Nozzle size, release rates, and particle size parameters were compiled for each of the 18 products. If the release rates or particle sizes were not available from the company, the data were experimentally obtained. “The data show that the release rates range from 0.66 g/second – 2.8 g/second and the nozzle sizes range from 0.013 – 0.03 inches, and most of the nozzles sizes were ~0.02”. The release rate and particle size is dependent on the combination of nozzle technology and can characteristics. Aerosol can sizes range from 2.5 -19 oz and are pressurized at 40-60 PSI with the propellant of choice. . . . The particle size distribution data ranged from 16 -164 μm depending on the product type and method of particle size determination. The hard surface fine spray products had particle size distribution 40-157 μm . The surface disinfectants which are also used as air fresheners/sanitizers and air treatment products had particle size range of 16-87 μm , and most of them had the smallest nozzle size. The foaming spray products had particle size distribution of 24-164 μm ” (V1:43).

The targeted surface type (i.e., hard vs. soft surface) and the orientation of the can are variables that were also considered in the product selection process. “A hard target surface with a vertical and overhead orientation of the spray can was considered the most conservative scenario (highest exposure use) and is expected to give the most bounce-back from the spray that increases the air concentration in the breathing zone and dermal deposition.” (V1:43)

The second phase of the selection process placed all of the surveyed antimicrobial aerosol products into the following four major use categories:

- Hard – surface disinfectant fine sprays
- Foaming aerosol products – coarse sprays
- Soft surface disinfectants
- Air fresheners

In the final phase of the product selection process, one representative product from each of the four categories was selected for inclusion in the pilot study (i.e., further analysis on its influencing parameters (i.e., release rate and particle size distribution)) for selection as the overall representative aerosol product in the exposure study.

“The results of the pilot study clearly show that based on nozzle size, amount of material dispensed per unit time, air concentrations, and aerosol characteristics, the

hard surface disinfectant product, i.e., *Clorox Disinfecting Spray* (EPA Reg. No. 67619-03), represents the high-end exposure scenario and the product most likely to produce measurable exposure and would therefore serve as the surrogate for the study entitled, “Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using a Pressurized Aerosol Can for Indoor Uses”. Taking type of surface and the inspirable mass into consideration, the *Clorox Disinfecting Spray* (hard surface fine Spray) and *Stepan Aerosol SDAS* (Air Freshener) represent uses with the most inhalation and/or dermal exposure potential. The Air Freshener seemed to have comparable inspirable mass to the hard surface spray. However, as mentioned previously, the total mass of the active ingredient dispensed per unit time for the *Clorox Disinfecting Spray* is more than double the *Stepan Aerosol SDAS* (17.2/6.7 mg, Table 4) and dermal exposure will likely be higher for the *Clorox Disinfecting Spray*. Additionally, the hard surface spray product will be used to a much greater extent in a day, especially in commercial use, than the air freshener. Based on the available data, the *Clorox Disinfecting Spray* (hard surface fine spray) would represent a high end conservative choice for exposure monitoring studies” (V1: 55).

Sites. Three sites (i.e., vacant commercial lodging facilities or vacant areas and rooms within otherwise occupied buildings) in Fresno County, CA, will be selected for this study. “Commercial lodging facilities are buildings that are most likely to provide an adequate amount of relevant aerosol application surface area for the monitoring events. While other building types, such as offices and meeting locations represent locations where disinfecting aerosols may be applied, and provide diversity in architecture and floor plan, these categories are less likely to provide the number of separate rooms and surface areas needed for the range of amount of aerosol to be sprayed” (V1:19).

“...Greater diversity among monitoring sites can be obtained if each of the three clusters is conducted in a somewhat different room configuration. Consequently, for the aerosol application study the AEATF II will consider only the following three building/room configuration categories:

- A. Hotels/motels with 20 or more available units containing full kitchens
- B. Hotels/motels with 20 or more available units containing kitchenettes
- C. Hotels/motels with 20 or more bathroom-only units.

These three categories were chosen because they vary with respect to bathroom and food preparation areas (i.e., kitchen or ‘kitchenette’) configurations which might be expected to impact exposure potential differently” (V1:30).

The choice of one geographical location of Fresno County assumes indoor aerosol application tasks will not differ substantially from one geographic location to another. This assumption is supported by the previous CMA study. Moreover, the available training material for janitorial practices is supported by national organizations (e.g., International Sanitary Supply Association (ISSA)), and regional differences are not expected. 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 aerosol application only as opposed to the broad range of janitorial activities a subject

might engage in...” (V1:18). 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 number of cans applied. The AEATF II cites existing survey data the Antimicrobial Exposure Joint Venture (AEJV) and information provided by JohnsonDiversey which was based on was based in part on information from the following sources: 1) the American Hospital Association (http://www.aha.org/aha_app/index.jsp), the American Society for Health Care Environmental Services (http://www.ashes.org/ashes_app/index.jsp), and the U.S. EPA’s Environmental Best Practices for Health Care Facilities. The AEJV indicates that consumers spray an average of ~113 g product per room (kitchen or bathroom) (or ~20% of a 19 oz can). Information from JohnsonDiversey indicates that a single individual would clean 20 rooms/day, which is considered to be a reasonable upper bound value. Therefore, the maximum amount of total product applied daily by a professional janitor is 2,260 g (or 4.2 19-oz cans). The aerosol protocol will monitor subjects spraying from 1 to 4 19-oz aerosol cans. (V1:22) EPA/CDPR/PMRA concurs that the four aerosol cans is an appropriate maximum rate.

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 selected worker provides his/her unique set of behaviors to the aerosol application task...this study permits only one monitoring event per worker in order to capture a larger diversity of application behaviors” (V1:17). The use of professional applicators is believed to be a reasonable surrogate for the range of potential users that may apply aerosol antimicrobial products, including consumers, school janitors, hospital janitors, commercial lodging janitors, employees of janitorial services 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 this is not technically the same as a random sample from the existing population of professional janitorial workers. By definition, volunteers are self-selected and could, in theory, have different characteristics than non-volunteers. Such fine distinctions have little relevance in this case, however, because this is not an observational study of existing applicator-days. Because workers are randomly assigned to synthetic application-day conditions, the resulting MEs are still considered synthetic applicator-days. Thus, any type of random sampling of just one ME component (e.g., applicator in this case) provides no statistical advantage other than reduction of selection bias.” (V1:17)

A stratified random sampling approach will be used to locate acceptable facilities. (V1:19)

“This list of commercial lodging facilities will then be randomized. Next, these properties will be investigated in (random) order until Nc qualifying facilities have been found.” (V1:19)

“Individuals who are enrolled to participate in the study will then be randomly ordered and assigned a subject identification sequence number (SISN). ... This process results in a simple random sample of qualifying subjects from the volunteer pool.” (V1:17)

“...workers are randomly assigned to synthetic application-day conditions...” (V1:17)

“The N=18 randomly sampled professional applicators will be randomly assigned to the N=18 combinations of building/room configuration category and application volume. This provides a diverse set of MEs with respect to three meta-parameters: (1) applicator, (2) types of rooms, and (3) product volume applied. ” (V1:31)

(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 **aerosol application scenario** is defined as the hand-held pressurized aerosol-based application of a label-specified end-use formulation containing an antimicrobial chemical. This includes the task of actual aerosol spraying for purposes of air and surface odor elimination, sanitizing, or disinfecting. The aerosol application scenario involves application according to typical practices, e.g., spraying surfaces from a distance of approximately 6-10 inches in a manner to apply enough formulation to provide an adequate amount for cleaning. Hard surface applications are typically sprayed until visibly “thoroughly” wet per label direction. ... Surface applications are typically made in smooth, sweeping, overlapping patterns. Examples of “representative” spray application techniques that this scenario is expected to capture include horizontal spraying moving upward and downward from the starting point to hard surfaces such as laminate, tile, porcelain, glass, and metal).” (V1:8)

Application surfaces include horizontal and vertical surfaces, kitchens, bathrooms, sinks, countertops, toilets, (V1:19) and food preparation areas (or FPA) which is defined as a room containing a stove/oven, refrigerator, and food preparation sink (V1:30).

“The Clorox Disinfecting Spray will be applied by janitorial professionals according to typical practices, i.e., spraying surfaces from a distance of approximately 6-10 inches in a manner to apply enough formulation to provide an adequate amount for cleaning. Hard surface applications are typically sprayed until visibly ‘thoroughly’ wet per label direction. No wiping will be conducted as part of this application scenario. Surface applications are typically made in smooth, sweeping, overlapping patterns. Examples of ‘representative’ spray application methods that this study is expected to capture (i.e.,

“horizontal spraying moving upward and downward from the starting point to hard surfaces such as laminate, tile, porcelain, glass, and metal”) are specified in the informed consent form.” (V2:21)

Additional sources of aerosol application exposure include “spraying in an enclosed space (e.g., shower enclosure), spraying above and below the chest height, spraying near air exhaust vents, or walking into spray mist sprayed overhead.” (V1:22)

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

The study will monitor only professional janitors, so any differences in behavior that a consumer may exhibit while applying an aerosol product will not be monitored. However, given that spraying a pressurized can is not a specialized task, the exclusion of consumers from the sampling design is not considered to be a limiting factor.

The aerosol scenario excludes the task of post-application wiping. The exposures to wiping a liquid film will be monitored in a separate wiping study as outlined in the AEATF II Governing Document. “In practice, aerosol application may or may not involve follow-on tasks, such as wiping the sprayed surface. Some aerosol products are considered ‘leave-on’ sprays that do not require post-spray wiping. Only the actual aerosol spray application is covered by this scenario. Applicator exposure associated with wiping is being addressed in another AEATF II scenario. Therefore, in the case of the aerosol application scenario, the applicator’s exposure during a single workday would arise only from the task of application (spraying) of the product (i.e., not from post-application wiping, such as a potable water rinse and wipe, following aerosol application to a food preparation surface).” (V1:9)

3. Is the proposed test material an appropriate surrogate?

The test substance, Clorox Disinfecting Spray, 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 aerosol sprays, and its principal active ingredient ADBAC has been demonstrated to have a low analytical limit of detection.

“The test substance for these studies is the formulated product, Clorox Commercial Solutions® Clorox® Disinfecting Spray (referred to as Clorox Disinfecting Spray in this protocol), containing didecyl dimethyl ammonium chloride (DDAC), n-Alkyl (C12, C14, and C16) dimethyl benzyl ammonium chlorides (ADBAC), octyl decyl dimethyl ammonium chloride (ODAC), and dioctyl dimethyl ammonium chloride (DODAC). The quaternary ammonium antimicrobials are commonly known as “quats”. C14 ADBAC is the active ingredient selected for measurement, based on its stability, abundance in the formulation, and sensitivity of its analytical method.” (V2:18)

“Clorox Disinfecting Spray is an end use product registered with the EPA for use on smooth surfaces in indoor environments. Clorox Disinfecting Spray contains ADBAC, DDAC, ODAC and DODAC. ADBAC was selected as the analyte based primarily upon its abundance in aerosol products, on its stability, and the sensitivity of its analytical method. The quats ADBAC, ODAC, DODAC, 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 ADBAC was not apparent. The analytical method for ADBAC on the proposed monitoring matrices at very low concentrations has been validated (GPL, 2004). The freezer storage stability of ADBAC on the different matrices to be used in this study is ongoing (GPL, 2009; in progress).” (V2:19)

“The very sensitive and selective analytical method developed for the analysis of ADBAC 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, Clorox Disinfecting Spray has been deemed suitable by the Sponsor and EPA as a surrogate compound for generating exposure data for other antimicrobial pesticides.” (V2:20)

ADBAC and DDAC have been approved for use in many formulations, and are extensively used in many janitorial products. The EPA has recently re-registered both DDAC and ADBAC and issued REDs for both (EPA, 2006a,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.

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

AEATF II proposes for the aerosol scenario the design of 3 clusters of 6 monitoring events (MEs) each. This configuration is appropriate to the characteristics of this scenario.

“The primary challenge is that for the aerosol application scenario (as is true for all AEATF II scenarios) only a small number of expensive experimentally-obtained monitoring events are feasible.” (V1:14)

“For the aerosol application study, therefore, random nested sampling will be used as a reasonable reference model for the combination of random sampling, randomization, and diversity selection actually used.” (V1:24)

“For a configuration of NC=3 clusters (i.e., sites or buildings), Table 6 shows the sample size necessary to achieve 3-fold relative accuracy with GSD=2.1 or GSD=2.9 and an intra-cluster correlations (ICC) as high as 0.3. For the aerosol-only GSD of 2.1, only 2 MEs per cluster are needed giving a total of N=6 MEs for the aerosol scenario. However, when the more robust repetitive-motion task GSD of 2.9 is used, 6 MEs per cluster are

required giving N=18 MEs for the scenario. Given the sensitivity of the sample size to GSD and the belief that the repetitive-motion GSD is a better indicator of the expected true relative variation for this scenario, the AEATF II prefers to assume GSD=2.9 for the purposes of determining sample size. As also shown in Table 6, smaller, and perhaps more likely, ICCs will yield accuracies much better than 3-fold.” (V1:29) The reader is referred to Table 6 in Volume 1 (page 29) for a review of the results of the accuracy given n=2 versus n=6 MEs per cluster.

“Benchmark objectives specify accuracy goals that must be achieved within the framework of the reference sampling model when sample size is adequate. In this study, ‘sample size’ means both the number of clusters (NC) and the number of MEs per cluster (NM). For the aerosol application study, the benchmark objective is that (when the reference model is true) sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time.” (V1:24)

EPA Protocol Review: AEATF II Aerosol Application Scenario/Protocol

Title: A Study For Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using a Pressurized Aerosol Can for Indoor Surface Disinfecting.

Date: August 4, 2009

Principal Investigator:
Sami Selim, Ph.D.

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

Eurofin | Grayson
211 N Main Street
Creedmoor, NC 27522

Sponsor: American Chemistry Council
Antimicrobial Exposure Assessment Task Force II
c/o Hasmukh 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 aerosol application monitoring study is to develop more accurate information on worker exposures to antimicrobials . . . that broadly represent those expected for the future application of arbitrary antimicrobial pesticides.” (V1:13)

“The main goal of the study is to generate data using a product with high exposure potential and covering the most influential variables associated with inhalation and dermal exposure. The data generated can then be used in risk assessments for most exposure scenarios resulting from use of [antimicrobial products in] aerosol cans.” (V1:38)

**(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 antimicrobial chemical exposures associated with the use of hand-held, pressurized aerosol cans.” (V1:8)

“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. . . . PHED does include two studies conducted using aerosol application methods. . . . Unfortunately, these studies have limitations that reduce their value for an antimicrobial-oriented generic database.” (V1:10-11)

“In addition to PHED, another source of existing data being used by regulatory agencies in the case of antimicrobials is the *Chemical Manufacturers Association Antimicrobial Exposure Assessment Study* directed by Dr. William Popendorf at the University of Iowa (Popendorf et al. 1992). . . . The EPA concluded that the limited number of replicates combined with poor recovery data severely limits the conclusions that can be made from the CMA study. Therefore, the Agency is requiring confirmatory data to support the uses assessed with the CMA exposure data within this risk assessment. The limitations identified by EPA in the CMA study data were also echoed by regulatory agencies in California and Canada. All note that the exposure data cannot be used as generic data for all antimicrobials because recoveries were low, precision of the measurements were not established, and CMA did not establish the validity of generalizing the information among applications and end-use settings.” (V1:12-13)

(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 hand-held, pressurized aerosol cans to apply an antimicrobial pesticide to indoor 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.” (V2:13)

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 aerosol 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 that broadly represent those expected for the future application of arbitrary antimicrobial pesticides.

Although this study will only monitor a single active ingredient, AEATF II and regulatory agencies generally recognize two important principles that allow such exposure results to be generalized to a larger set of conditions:

1. Dermal and inhalation exposure to antimicrobial chemicals are considered generic (i.e., independent of the particular active ingredient used). This *generic principle* permits use of a single surrogate active ingredient to predict exposure for other active ingredients.
2. The *principle of proportionality* of exposure to appropriate measures of active ingredient contact potential. For example, if measured exposure is E1 when the amount of active ingredient handled (AaiH) is H1, then the predicted exposure when AaiH is H2 is just $E2 = H2(E1/H1)$.

Consequently, AEATF II anticipates the resulting database will contain sufficient data to support exposure assessments for aerosol application for a number of antimicrobial active ingredients over a range of AaiH levels.” (V1:13)

“Benchmark objectives specify accuracy goals that must be achieved within the framework of the reference sampling model when sample size is adequate. In this study, ‘sample size’ means both the number of clusters (NC) and the number of MEs per cluster (NM).

For the aerosol application study, the benchmark objective is that (when the reference model is true) sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time. The EPA, in discussion with AEATF II, determined that this benchmark is sufficient for regulatory purposes.” (V1:24)

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

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

The objective cited above can be achieved by the study as proposed.

2.1 Statistical Design

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

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. The “...random reference model approach is used to determine sample sizes for the aerosol application scenario. The aerosol application study will utilize a combination of random sampling, randomization, and diversity selection methods. While this methodology contains some elements of all three pure situations ...[statistical theory], none apply completely. The ultimate goal of this study is to construct synthetic MEs that can be used to characterize the diversity of future daily exposures to antimicrobials through aerosol application. Hence, the study objectives are more closely aligned with the random sampling situation.... As a result, a reference model for random sampling will be used for the determination of sample size.” (V1:23)

“For the aerosol application study, therefore, random nested sampling will be used as a reasonable reference model for the combination of random sampling, randomization, and diversity selection actually used. This reference model assumes that:

1. Exposure, normalized by the amount of active ingredient handled, is lognormally distributed with a known geometric standard deviation (GSD). Equivalently, the logarithm of normalized exposure is normally distributed with known standard deviation Log GSD.
2. There are NC clusters (i.e., sites) and NM MEs per cluster. The total number of MEs is, therefore, $N=NC \times NM$.
3. There is a possible within-cluster (i.e., within-site) correlation of log normalized exposure. This is referred to as the intra-cluster correlation, or just the ICC. “ (V1:24)

“...the benchmark objective is that (when the reference model is true) sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold 95% of the time.” (V1:24).

“A Monte Carlo simulation approach was used to examine the impact of number of clusters (NC) and number of MEs per cluster (NM) on accuracy of the arithmetic mean and 95th percentile for the reference model.” (V1:28).

“For the aerosol-only GSD of 2.1, only 2 MEs per cluster are needed giving a total of $N=6$ MEs for the aerosol scenario. However, when the more robust repetitive-motion task GSD of 2.9 is used, 6 MEs per cluster are required giving $N=18$ MEs for the scenario. Given the sensitivity of the sample size to GSD and the belief that the repetitive-motion GSD is a better indicator of the expected true relative variation for

this scenario, the AEATF II prefers to assume GSD=2.9 for the purposes of determining sample size.” (V1:29)

(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 from among respondents to recruiting flyers and/or newspaper advertisements will be assigned randomly to one or another ME, pre-defined in terms of its amount handled and location. (V2:26)

MEs with more aerosol cans to be sprayed will be executed first; a subject who is unable to continue spraying for the given amount will be reassigned to a lesser amount ME, and the next subject in random order will be assigned to the uncompleted ME. (V2:26)

“As long as each subject achieves the target spraying amount, the process is continued down to the smallest spray amount stratum (A, 1 to 1.5 canisters) and six MEs have been obtained, one for each of the six strata. If this process proceeds as expected, the last two subjects allocated to each site are never used for MEs and will remain alternates.” (V2:26)

(e) Can the data be statistically analyzed?

The results of the analysis from the sampling will be provided in the final report. (V2:51, 52).

(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 II, 2008).

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.” (V2: 47, 48)

(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 spraying pressurized aerosol cans for extended durations can inform assessments of the likely exposure of others spraying aerosol products for shorter durations with other types of aerosol products/cans. EPA is confident that this design will provide data on aerosol spray 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 *Clorox Commercial Solutions® Clorox® Disinfecting Spray* (EPA Reg. No. 67619-03), which contains active ingredients 0.0945% didecyl dimethyl ammonium chloride (DDAC), 0.252% n-Alkyl (40% C12, 50% C14, and 10% C16) dimethyl benzyl ammonium chlorides (ADBAC), 0.189% octyl decyl dimethyl ammonium chloride (ODAC), and 0.0945% dioctyl dimethyl ammonium chloride (DODAC). (V1:9; V2:19).

Test subjects will be exposed during aerosol spraying activities using *Clorox Commercial Solutions® Clorox® Disinfecting Spray* (EPA Reg. No. 67619-03). The aerosol application scenario involves application according to typical practices, e.g., spraying surfaces from a distance of approximately 6-10 inches in a manner to apply enough formulation to provide an adequate amount for cleaning. Hard surface applications are typically sprayed until visibly “thoroughly” wet per label direction. No wiping will be conducted as part of this application scenario. Surface applications are typically made in smooth, sweeping, overlapping patterns. Examples of “representative” spray application techniques that this scenario is expected to capture include horizontal spraying moving

upward and downward from the starting point to hard surfaces such as laminate, tile, porcelain, glass, and metal. (V1:8)

“Each ME will apply the test substance to bathrooms and/or food preparation areas which include horizontal and vertical surfaces (e.g. shower stall/tub, toilet, countertops, sinks, cabinets and appliances). Each bathroom is expected to include some combination of shower stall/tub enclosure, toilet, and/or sink/countertops. Each kitchen or food preparation area is expected to include counter tops and some appliance surfaces. All interior surfaces of the shower/tub, the horizontal surface of the countertop/sink, and exterior surface only of toilets will be sprayed with the test substance. One complete can of aerosol product will cover the shower, sink and toilet in approximately two bathrooms if every surface were sprayed; however, that is not typical practice and each participant will be encouraged to apply the spray as they would in normal practice.” (V2:21)

“The procedures described represent typical consumer and professional worker methods of applying the test substance to indoor surfaces. The test substance chosen is utilized in the described scenario that employs aerosol application of antimicrobials.” (V2:22)

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

“Based on the nozzle size, amount of material dispensed per unit time, air concentrations, and aerosol characteristics, across products in the four major aerosol categories (hard surface disinfecting sprays, hard surface foaming aerosols, soft surface sprays, air fresheners), *Clorox Commercial Solutions® Clorox® Disinfecting Spray* (EPA Reg. No. 67619-03), was selected as a representative, albeit conservative surrogate and a product most likely to produce measurable exposures for purposes of the aerosol application study.” (V1: 9)

“C14 ADBAC is the active ingredient selected for measurement, based on its stability, abundance in the formulation, and sensitivity of its analytical method” (V2:18)

“Clorox Disinfecting Spray is an end use product registered with the EPA for use on smooth surfaces in indoor environments. Clorox Disinfecting Spray contains ADBAC, DDAC, ODAC and DODAC. ADBAC was selected as the analyte based primarily upon its abundance in aerosol products, on its stability, and the sensitivity of its analytical method. The quats ADBAC, ODAC, DODAC, 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 ADBAC was not apparent.” (V2:19)

“The analytical method for ADBAC on the proposed monitoring matrices at very low concentrations has been validated (GPL, 2004). The freezer storage stability of ADBAC on the different matrices to be used in this study is ongoing (GPL, 2009; in progress).” (V2:19)

“The very sensitive and selective analytical method developed for the analysis of ADBAC 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, Clorox Disinfecting Spray has been deemed suitable by the Sponsor and EPA as a surrogate compound for generating exposure data for other antimicrobial pesticides.” (V2:20)

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

In this study all MEs will apply the same substance, i.e., Clorox Disinfecting Spray in 19 oz (538 g) canisters. This substance contains several active ingredients. However, only one of these, C14 ADBAC, will be quantified. Because the concentration of ADBAC in the aerosol canisters is the same for all MEs, the amount of active ingredient ‘handled’ is varied simply by having MEs that apply different amounts of the formulated product. The total amount of product sprayed, will range between 1 and 4 canisters (i.e., 538 to 2152 grams of formulated product). (V2:25)

ADBAC was selected because of its relatively high concentration, its stability, and the sensitivity of the analytical method.

The same concentration will be used by all MEs. The total amount of ai handled will vary with the number of aerosol cans sprayed.

(c) What duration of exposure is proposed?

Each predefined ME will apply different amounts of the formulated product. Therefore, the amount of product applied is proposed, not specific time durations. The AEATF II does anticipate that the duration to apply the specified amounts will range from 30 to 180 minutes. The total amount of product sprayed, will range between 1 and 4 canisters (i.e., 538 to 2152 grams of formulated product). This interval is partitioned into six amounts handled for aerosol spray strata as follows:

- A. 1 to 1.5 canisters
- B. 1.5 to 2 canisters
- C. 2 to 2.5 canisters
- D. 2.5 to 3 canisters
- E. 3 to 3.5 canisters
- F. 3.5 to 4 canisters

Within each monitoring site, a single ME is targeted for each of the above six strata. As long as the subject is within the correct AaiH interval, it is unnecessary to control the exact amount of product precisely. However, the actual amount of product sprayed by each subject will be recorded. (V2:25)

Any test subjects not able to spray the given number of canisters are allowed to stop and as long as at least one canister is applied the dosimeters will be analyzed. If the subjects fail to spray a single canister, the ME will not be used and the monitoring media will not be analyzed. (V2:26)

The AEATF II cites existing survey data the Antimicrobial Exposure Joint Venture (AEJV) and information provided by JohnsonDiversey which was based on was based in part on information from the following sources: 1) the American Hospital Association (http://www.aha.org/aha_app/index.jsp), the American Society for Health Care Environmental Services (http://www.ashes.org/ashes_app/index.jsp), and the U.S. EPA's Environmental Best Practices for Health Care Facilities. The AEJV indicates that consumer's sprays an average of ~113 g product per room (kitchen or bathroom) (or ~20% of a 19 oz can). Information from JohnsonDiversey indicates that a single individual would clean 20 rooms/day, which is considered to be a reasonable upper bound value. Therefore, the maximum amount of total product applied daily by a professional janitor is 2,260 g (or 4.2 19-oz cans). The aerosol protocol will monitor subjects spraying from 1 to 4 19-oz aerosol cans. (V1:22)

2.3 Endpoints and Measures

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

“Potential dermal exposure to the test substance will be measured externally using whole body inner and outer dosimeters, hand washes, and face/neck wipes. All monitored subjects will wear the outer dosimeter (representative outer clothing consisting of cotton long pants and cotton long sleeve shirts) directly over the inner dosimeter (consisting of 100% cotton long underwear). Inner and outer dosimeters will be provided by AEATF. Subjects will wear their own socks and shoes. Hand exposure will be measured by rinsing the hands with a solution of 50% isopropyl alcohol/ 50% distilled water. Face and neck exposure will be measured by wiping the face and neck with gauze pads moistened with 50% isopropyl alcohol / 50% distilled water.” (V2:11)

“The potential total inhalation exposure for each subject will be measured with an OSHA Versatile Sampler (OVS) tube attached to a personal air sampling pump set at a typical sampling rate (2 L/minute). Potential exposure to respirable, thoracic and inhalable particles (100, 10 and 2.5 μm , respectively) will be characterized with a three stage RespiCon™ Particle Sampler (Model 8522, TSI Inc.) attached to a personal air sampling pump operating at ~3.1 L/min.” (V2:12) In addition, pre-sampling for ambient air will be performed to determine if there are background ADBAC air concentrations. (V2:34)

“Airflow of pumps attached to the OVS tube and RespiCon™ sampler will be calibrated to a nominal flow rate of approximately 2 and 3.1 L/min respectively using

SOPs of field study procedures. The beginning flow rate of each pump will be checked and documented just before being fitted to the subject.” (V2:35, 36)

“The inner and outer dosimeters, OVS tubes, filters from the RespiCont™ Particle Sampler, hand wash solutions, and face/neck wipes will be analyzed for residues of C14 ADBAC using validated analytical methods.” (V2:12)

“The amount of test substance applied during each ME will be determined by the total change in weight of all canisters used in the ME. Each canister will be uniquely identified prior to experimental start. Prior to each ME a sufficient number of unused canisters will be individually weighed, and the beginning weights of each canister recorded in the raw data. Following completion of the ME, each canister used in the ME will be individually weighed, and the end weight and amount of change for each canister recorded in the raw data. The total amount of test substance applied will be determined by the amount of change (i.e., test substance discharged) from all canisters used in the ME. All information necessary to reconstruct the amount of test substance applied by each ME will be documented.” (V2:22)

“Air temperature and relative humidity of the work area for the duration of exposure monitoring will be documented with automated instrumentation logging and recording at intervals appropriate for the duration of the work period per SOP AEATF II-10C. Environmental monitoring equipment will be calibrated or standardized according to SOPs. HVAC and room volume will be described in detail and documented in study field notes, and it will be noted for each room sprayed whether the HVAC and/or vent fans were on at the time of application.” (V2:40)

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

The AEATF II SOPs provide specific procedures to ensure accurate measurements such as calibration of inhalation monitoring devices (SOP 10G.1 (V4:107)).

“GLP purity analysis (content of active ingredient in the test substance) will be performed by the Sponsor, and a Certificate of Analysis will be kept in the raw data file.” (V2:19)

“Full details regarding field recovery evaluation procedures for all sampling media are given in the most recent version of the SOPs of the AEATF II-8E[.1].” (V2:41)

(c) What QA methods are proposed?

Volume 2, Section 12, Analytical Procedures, discusses QA methods for reference substances, fortification solutions, internal standards, analytical method, etc. (V2:44-48)

Volume 2, Section 10.A, *Air Sampling for Ambient Pre-existing ADBAC*, discusses sampling for background air concentrations of ADBAC (V2:34)

“This study will be conducted according to FIFRA GLP Standards (40 CFR 160).” (V2:51)

(d) How will uncertainty be addressed?

In a September 18, 2009, letter from Hasmukh Shah (Manager, AEATF II) to Timothy Leighton (Office of Pesticide Programs, Antimicrobial Division), the AEATF II committed to address deviations from the benchmark accuracy goal (i.e., $k=3$) as follows: “[I]f large deviations from the benchmark goals are observed in the aerosol study, 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.” (a copy of the letter is included in the supplemental materials).

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 aerosol scenario.

“The community of individuals that use an aerosol to clean/disinfect surfaces is enormous and includes millions of workers and at least 100 million residents in the U.S. alone” (V2:17-18)

(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 capture the ethnic diversity in the Fresno area, recruitment materials and all communications with potential subjects will be available in English and Spanish, as preferred by the subject.” (V2:27)

“IRB approved recruiting advertisements... will be simultaneously (within the same week) placed in the Fresno Bee, the California Advocate and the Fresno edition of Vida en el Valle. The Fresno Bee is a large, general circulation daily paper in Fresno County. The California Advocate is the dominant African American community

weekly paper in Fresno County, and Vida en el Valle is a weekly targeting the San Joaquin Valley, with separate editions for Fresno and other central valley municipalities.” (V2:28)

(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, or in response to advertisements placed in three Fresno-area newspapers. Volunteers may differ in unknowable ways from other workers who do not step forward. There is no reason to think that janitorial service workers in Fresno are atypical of janitorial service workers in any other area of the United States.

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

“The AEATF II program, as described in the Governing Document (2008), intends to develop a database of exposure monitoring data that can be used to support practical regulatory decisions about future exposures for different (including currently nonexistent) active ingredients and their associated products. The database needs to address a variety of exposure scenarios for which no or limited data currently exist. The aerosol application scenario is an important component of the AEATF II program and the focus of this study. As noted in the previous section, existing monitoring data for this scenario are considered inadequate.

“The primary purpose of the aerosol 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 that broadly represent those expected for the future application of arbitrary antimicrobial pesticides.

“Although this study will use only a single active ingredient, AEATF II and regulatory agencies generally recognize two important principles that allow such exposure results to be generalized to a larger set of conditions:

1. Dermal and inhalation exposure to antimicrobial chemicals are considered generic (i.e., independent of the particular active ingredient used). This *generic principle* permits use of a single surrogate active ingredient to predict exposure for other active ingredients.
2. The *principle of proportionality* of exposure to appropriate measures of active ingredient contact potential. For example, if measured exposure is E_1 when the amount of active ingredient handled ($A_{ai}H$) is H_1 , then the predicted exposure when $A_{ai}H$ is H_2 is just $E_2 = H_2(E_1/H_1)$.

“Consequently, AEATF II anticipates the resulting database will contain sufficient data to support exposure assessments for aerosol application for a number of antimicrobial active ingredients over a range of AaiH levels.

“An applicator-day is defined as a single professional applicator and a single day on which he/she performs the scenario-specific task as described in Section 2 above. Each possible applicator-day is implicitly associated with a set of application conditions that includes, but is not limited to, applicator behavior, formulation type, location, and environmental conditions. Therefore, the aerosol application scenario can be viewed as the collection (or ‘population’) of all possible applicator-days that conform to the scenario definition. The basic experimental unit for this scenario is a monitoring event (or ME). During a monitoring event, AEATF II researchers will collect dermal and inhalation exposure information from a worker while he/she performs aerosol application. Each ME is designed to represent a single applicator-day and its corresponding exposure potential. Therefore, the set of N MEs obtained for the aerosol application scenario are designed to characterize future aerosol application scenario applicator-days. The primary challenge is that for the aerosol application scenario (as is true for all AEATF II scenarios) only a small number of expensive experimentally-obtained monitoring events are feasible.” (V1:13-14)

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 V2:30-31 and below:

“Inclusion Criteria:

- Males or females, at least 18 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
- Resident of Fresno County
- Experience in providing janitorial services

Exclusion Criteria:

- Skin conditions on the surface of the hands (e.g., psoriasis, eczema, cuts or abrasions)
- Pregnancy, as shown by a urine pregnancy test
- Lactation
- Allergies 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 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, or is related by blood or marriage to an employee of Golden Pacific Laboratories, Grayson | Eurofins, or a cleaning product manufacturer.”

(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. (V2:31)

(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 V2:27-30.

(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 providing professional cleaning services for commercial buildings in Fresno County, CA will be contacted by qualified research personnel and asked whether they would be willing to post a flyer soliciting volunteers for a study to be conducted independent of the janitorial service...If the firm wishes to post the flyer, research personnel will provide a general description of the study, explain the need and importance of remaining neutral (un-coercive) in their interactions with employees regarding study participation, and determine whether the flyer seems intelligible for the firm’s employees. Assuming the owner/manager still wishes to post the flyer, research personnel will provide approval to do so....To avoid the potential for coercion, subjects will not be recruited directly through contract janitorial service companies. Flyers will direct interested workers to contact research personnel directly.” (V2:27-28)

3.3 Remuneration of Subjects

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

“All individuals that show up for the informed consent interview will be compensated \$20 in cash at completion of the interview for their time and inconvenience. All individuals who are qualified, sign the informed consent form, and report to their

assigned study site, will receive \$100 in cash for their time and inconvenience when they leave the study site, whether they are monitored or not. If a subject signs the consent form and fills out the demographic form, information that may disqualify them from participation may become evident. If this occurs, the disqualified subject will be paid \$100 as if a participant and dismissed. The value for compensation is based roughly on a day's wage of \$100 and represents potential lost time from secondary sources of employment, travel time and incidental expenses incurred in study participation. Compensation will be provided to individuals who complete their assigned participation or who need to withdraw for whatever reason." (V2:32)

(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). "All individuals that show up for the informed consent interview will be compensated \$20 in cash at completion of the interview...All individuals who are qualified, sign the informed consent form, and report to their assigned study site, will receive \$100 in cash...when they leave the study site, whether they are monitored or not." (V2:32)

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 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. (V2:14-17)

Risks discussed in the consent form include risk of a reaction to the test material, 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. (V2:70-71)

(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. (V2: 14-17, 20, 32-34)

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

The formulated product for the aerosol study contains more than one active ingredient. Clorox Commercial Solutions Clorox Disinfecting Spray (EPA Reg. No. 67619-03) contains the test substance, ADBAC, and another active ingredient (i.e., DDAC). Therefore, the established NOAELs for both ADBAC and DDAC are provided below.

The ADBAC risk assessment developed to support the Reregistration Eligibility Decision (RED) document provides for the selection of the toxicological endpoints for risk assessment purposes. The dermal toxicological endpoints indicate no systemic toxicity. However, dermal irritation has been observed in 21- and 90-day dermal toxicity studies in guinea pigs and rats, respectively (MRIDs 41105801 and 41499601, respectively). The short-term dermal endpoint selected from the 21-day study is 333 ug/cm² and 80 ug/cm² in the 90-day study. The proposed use of ADBAC in this protocol by subjects exposed to 0.252% ADBAC in a formulated product will not trigger a risk of concern. The inhalation toxicological endpoint identified for ADBAC for all exposure durations is based on a developmental toxicity

study in rabbits (MRID 42392801) with a NOAEL of 3 mg/kg/day. The inhalation risk assessment for aerosol inhalation exposure in the RED document indicates that at this low concentration of ADBAC no inhalation risks are anticipated.

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 concentration of 0.378% active ingredient (i.e., aggregate of octyl dimethyl ammonium chloride, dioctyl dimethyl ammonium chloride, and didecyl dimethyl ammonium chloride) 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 risk assessment for aerosol inhalation exposure in the RED document indicates that at this low concentration of DDAC, no inhalation risks are anticipated.

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

Heat stress index above 95 (V2:33)

Other medical reasons (V2:32-33)

“If two or more subjects withdraw or are withdrawn from the study for the same medical reasons, the study will be suspended until the cause of the withdrawal is fully investigated and determined.” (V2:33-34)

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

SOP 11.B.1 for Management of Heat Stress (V4:112-123)

SOP 11.C.1 for Emergency Procedures (V4:124-126)

(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 in the subject dressing area, and the information contained on the poster available to subjects and research personnel at the field site.

"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." (V2:33)

(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." (V2:32)

"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." (V2:33)

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

The informed consent form states: "If you are hurt while you are in this study, a nearby medical facility that knows about this study will provide care. If necessary, we will take you there. We will pay for needed medical treatment that is not paid for by your own insurance or by someone else. To find out more, or if you think you

may have been hurt during the study, call Dr. Selim at Golden Pacific Laboratories (559-275-9091) from 9 am to 5 pm Monday through Friday.” (V2:71)

To clarify the meaning of the phrase “by someone else” in the statement about compensation for research-related injuries, the AEATF II should make the following revision:

- Current language: “We will pay for needed medical treatment that is not paid for by your own insurance or by someone else.”
- Change to: “We will pay for needed medical treatment that is not paid for by your own insurance or by the insurance of a third party under which you are covered.”

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.” (V2:17)

(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. . . . 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.” (V2:17)

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

“Results from the study may benefit EPA. . . . by reducing uncertainty about the range of exposure experienced by consumers and workers handling antimicrobials. Registrants of antimicrobials will benefit because they will provide EPA with data on exposure that has been made a condition of re-registration for a number of antimicrobials, and they may be aided in registering new antimicrobials using the data generated from this study.” (V2:17)

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

7. Independent Ethics Review**(a) What IRB reviewed the proposed research?**

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?

No.

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

No.

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

Yes.

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

“This is a protocol for third-party research involving what EPA has interpreted to be intentional exposure of human subjects to a pesticide. The study is being conducted with the intention of submitting the resulting data to EPA under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA). Thus, the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply, and since the study will be conducted in California, the provisions of the California Code of Regulations, Title 3, §6710 would apply. The protocol will be reviewed by an Institutional Review Board (IRB).” (V2:7)

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. (V2:30)

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

Two field research associates (Victoria Standart and Noé Galván) are fluent in both English and Spanish. (V2:9)

All written materials provided to subjects will be available in both English and Spanish. (V2:14,20) A copy of the poster entitled “Controlling Heat Stress Made Simple” in English and Spanish will be posted in the dressing area at each site. (V2:20)

“Therefore to adequately capture the ethnic diversity in the Fresno area, recruitment materials and all communications with potential subjects will be available in English and Spanish, as preferred by the subject.” (V2:27)

“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.” (V2:27)

“If the firm wishes to post the flyer, research personnel will provide a general description of the study . . . and determine whether the flyer seems intelligible for the firm’s employees.” (V2:27)

“The recruiting flyers will include telephone numbers for both English and Spanish speakers, and voicemail in the appropriate language will be available for messages when direct human contact is not possible.” (V2:28)

“The recruiting advertisements [placed in area newspapers] will include a brief description of the study and include telephone numbers for English and Spanish speakers to call for more information.” (V2:28)

“A Spanish-speaking member of the research team will be present during monitoring events involving subjects whose preferred language is Spanish.” (V2:32)

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

All written recruitment, consent, and risk communication materials will be available in both English and Spanish (including label, MSDS, recruiting materials, flyers, and poster entitled “Controlling Heat Stress Made Simple”). (V2:14, 20)

“During the scheduled informed consent, the Principal Investigator or designee 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 or designee 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 or designee will provide each potential subject a copy of the product label (Appendix A), make available the MSDS (Appendix E) and answer any questions regarding the product to be tested. The Principal Investigator or designee will go over the Inclusion and Exclusion Criteria (see 9.A.iii. below) for the study and answer

any questions that the potential subjects have. Potential subjects will be provided with copies of 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 asked if they would like to take any of the materials home to discuss with family and friends before deciding whether to enroll in the study. If the potential subject wishes to continue with the enrollment process at that time, the Principal Investigator or designee will explain to potential subjects they may withdraw from the research study at any time without penalty to their compensation. The Principal Investigator or designee will then read the “Experimental Subject’s Bill of Rights” to the potential subject. 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 will be 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.” (V2: 28-29)

“A Spanish-speaking member of the research team will be available at recruitment meetings to assist and ensure communication with anyone preferring Spanish over English.” (V2:30)

- (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 providing professional cleaning services for commercial buildings in Fresno County, CA will be contacted by qualified research personnel and asked whether they would be willing to post a flyer soliciting volunteers for a study to be conducted independent of the janitorial service...If the firm wishes to post the flyer, research personnel will provide a general description of the study, explain the need and importance of remaining neutral (un-coercive) in their interactions with employees regarding study participation, and determine whether the flyer seems intelligible for the firm’s employees. Assuming the owner/manager still wishes to post the flyer, research personnel will provide approval to do so....To avoid the potential for coercion, subjects will not be recruited directly through contract janitorial service companies. Flyers will direct interested workers to contact research personnel directly.” (V2:27-28)

9. Respect for Subjects

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

“Individual data, excluding the subject’s name and address, will be entered in Golden Pacific Laboratories’ computer data base by SISN. All subjects’ names and personal identifiers provided will be kept confidential to ensure their privacy.” (V2:31)

“If a subject is female, she will be taken to a private area and asked to take a urine pregnancy test using an over-the-counter pregnancy test kit...Results of the pregnancy test will be kept in confidence, they will not be recorded, and they will be discussed only with the subject that provided the urine sample.” (V2:34-35)

(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.” (V2:72)

“You are free to withdraw from this study at any time, for any reason. Simply tell any member of the research team. If you decide not to participate in this study or to withdraw from it, you will not be penalized in any way or lose any benefits.” (V2:73)

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

“All individuals that show up for the informed consent interview will be compensated \$20 in cash at completion of the interview for their time and inconvenience. All individuals who are qualified, sign the informed consent form, and report to their assigned study site, will receive \$100 in cash for their time and inconvenience when they leave the study site, whether they are monitored or not...Compensation will be provided to individuals who complete their assigned participation or who need to withdraw for whatever reason.” (V2:32)

Subjects who are withdrawn by the investigators—and all participating subjects in the case that the entire study is stopped—are promised payment in full. (V2:73)

**§ 26.1111 Criteria for IRB approval of research
AEATF II Aerosol Scenario/Protocol AEA04/070270: August 4, 2009**

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 Aerosol Scenario/Protocol AEA04/070270: August 4, 2009**

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

§26.1117 Documentation of informed consent
AEATF II Aerosol Scenario/Protocol AEA04/070270: August 4, 2009

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

40 CFR 26.1125 Prior submission of proposed human research for EPA review
 AEATF II Aerosol Scenario/Protocol AEA04/070270: August 4, 2009

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

Requirement		Y/N	Comments	
All information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of <ul style="list-style-type: none"> all research proposals reviewed by the IRB, scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects. 	Y n/a Y n/a	V1: 6-56; V2:3-156 V3:20-221 V2:157-203	
	(2) Minutes of IRB meetings . . . in sufficient detail to show <ul style="list-style-type: none"> attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; a written summary of the discussion of controverted issues and their resolution. 	Y	V2:157-159; V3:310-317	
	(3) Records of continuing review activities.	n/a		
	(4) Copies of all correspondence between the IRB and the investigators.	Y	V3:4-317	
	(5) <ul style="list-style-type: none"> A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant. 	Y Y	V3:316-317 V3:316-317	
	(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	V2:14-17
		(2) The measures proposed to minimize risks to the human subjects;	Y	V2:14-17
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	Nature -V2:14-17 No discussion of magnitude
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	V2:13
		(5) The balance of risks and benefits of the proposed research.	Y	V2:17
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Original V3:80-90 Approved V2:64-85; 182-203	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	V2:27-32; 96-100; 101-107	
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.	Y	V2:27-32	
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	V3:4-317	
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.	Y	V2:157-159	

US EPA ARCHIVE DOCUMENT