# Antimicrobial Exposure Assessment Task Force II (AEATF II)

# Aerosol Application Study

# VOLUME 1

## Transmittal Letter

## 40 CFR 26.1125 Checklist

## and

## Primary Documentation: Aerosol Application Scenario: Rationale for Study Design

**August 4, 2009**

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August 4, 2009

John Carley
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Dear Mr. Carley:

The American Chemistry Council Biocides Panel Antimicrobial Exposure Assessment Task Force II (AEATF) is pleased to provide the following documents for EPA's review and submission to the Human Studies Review Board for discussion at the October 20-21, 2009 meeting:

Volume 1 Transmittal Letter
40 CFR 26.1125 Checklist
Primary Documentation: Aerosol Application Scenario: Rationale for Study Design

Volume 2 Primary Documentation: Study Protocol and IIRB Approval and Documentation

Volume 3 Secondary Documentation: IIRB Communications

Volume 4 Standard Operating Procedures for a Multi-Year Antimicrobial Chemical Exposure Monitoring Program

Since the AEATF will be conducting the aerosol study in Fresno County, California, a revised protocol that incorporates both EPA's and HSRB's comments will be submitted to the Independent Investigational Review Board (IIRB) and the California EPA (Department of Pesticide Regulation and Office of Environmental Health Hazard Assessment) for their review and approval. I will send you the California EPA comments soon after I receive them.

John Carley
August 4, 2009
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Please feel free to call me at 703-741-5637, if you need any clarification or additional information.

Sincerely,

Hasmukh Shah

Hasmukh Shah
Manager, AEATF

cc: Kelly Sherman, OPP, EPA
William Jordan, OPP, EPA
Timothy Leighton, OPP, EPA
Cassi Walls, OPP, EPA

## 40 CFR 26.1125 Prior submission of proposed human research for EPA review

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

| | Requirement | | Y/N | Comments/Page Refs |
|---|---|---|---|---|
| All information relevant to the proposed research specified by § 26.1115(a) | (1) Copies of<br>• all research proposals reviewed by the IRB,<br>• scientific evaluations, if any, that accompanied the proposals reviewed by the IRB,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | **Y**<br>**n/a**<br><br>**Y**<br>**n/a** | **V1: 6-56; V2: 3-156**<br>**V3: 20-221**<br><br>**V2: 157-203** |
| | (2) Minutes of IRB meetings . . . in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• 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)<br>• 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;<br>• 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**<br><br><br><br>**Y** | **V3: 316-317**<br><br><br><br>**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: 17**<br>**No discussion of magnitude of benefits.** |
| | | (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**<br>**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** |

# Antimicrobial Exposure Assessment Task Force II (AEATF II)

# AEROSOL APPLICATION SCENARIO: RATIONALE FOR STUDY DESIGN

**July 13, 2009**

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# AEROSOL APPLICATION SCENARIO: RATIONALE FOR STUDY DESIGN

## 1. Introduction

This document summarizes the rationale for critical elements of the design of the AEATF II aerosol application exposure monitoring study. Aerosol application represents an exposure scenario being addressed as part of the overall AEATF II antimicrobial exposure assessment program. This study is being conducted to determine potential dermal and inhalation antimicrobial chemical exposures associated with the use of hand-held, pressurized aerosol cans. The resulting data will likely improve the completeness and accuracy of the database used by the U.S. Environmental Protection Agency (EPA) to assess potential exposures to antimicrobial chemicals used in aerosol products. The results of the study will provide EPA with data on exposure that has been made a condition of re-registration for a number of antimicrobials. Results from the study may reduce uncertainty about the range of exposure experienced by consumers and workers handling antimicrobials. The ability to accurately predict exposure may allow other chemical classes of antimicrobials to also be considered for registration based on exposure estimates generated from the data to be produced by this study.

## 2. Scenario Definition

An antimicrobial handling scenario is a set of related tasks, pesticide formulations, equipment, engineering controls, and worker and/or consumer practices. For the purposes of the AEATF II antimicrobial exposure assessment Program, 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. 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). The ready-to-use (i.e., no mixing or loading procedures are involved) pressurized aerosol represents a common application method in residential (consumer) settings, and is also used in institutional settings, as an alternative to "dilutable" products, such as an end-use solution filled into a trigger sprayer. The aerosol application scenario is being used to address potential exposures to hand-held spray products in general, including surface disinfecting sprays, air sanitizers, and foaming aerosols. The 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 (e.g., aerosol foam active ingredient application rates range from 0.002 to 0.007 mg/cm$^2$, and disinfecting aerosol spray application rates range from 0.0007 to 0.003 mg/cm$^2$) (Aklam, et al., 2006). Appendix A provides additional documentation supporting the selection of the disinfecting aerosol spray. This documentation includes the results of a non-human subject application parameter study which was needed to facilitate appropriate selection of a surrogate, representative product to be used in the aerosol scenario exposure monitoring study. 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. Appendix A describes how the product chosen for this study ranks with respect to commonly available antimicrobial-containing aerosols sold by the major manufacturers of these products. Specific characteristics examined were nozzle size, particle size generated, ejection rate, and a high percentage of non-volatile active ingredient for which there was an existing analytical method. In addition to the predilection for this product to produce measurable exposure under normal use conditions, the particular choice of location and intensity of use will likely produce high end measurements of exposure (see Section 5.4).

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). The distribution of daily exposures for the aerosol application scenario will directly characterize the handler's daily exposure to the antimicrobial expected from "leave-on" spray applications. Characterization of exposures resulting from the combination of aerosol and wipe applications would require exposure information from the wiping scenario as well. The actual approach used to combine exposures from two or more scenarios would naturally depend on the particular needs of each regulatory (or other) user of the antimicrobial database. For example, if only the arithmetic mean exposure of a combined aerosol and wipe application is needed for a risk assessment, then the sum of the two separate arithmetic means (i.e., one for the aerosol scenario and one for the ready to use wipe scenario) can always be used. Any other statistics will depend on what assumptions users wish to make about the correlation in exposure between two tasks performed by the same applicator. If perfect (i.e., 100%) correlation is assumed, percentiles can be summed to get a combined percentile. If the tasks are assumed to be independent, then pseudo MEs for an aerosol-plus-wipe combination can always be generated by combining every possible aerosol application ME with every possible wipe scenario ME. More sophisticated users will likely employ Monte Carlo simulation methods to accommodate other between-task correlations. Because there are multiple reasonable approaches and because regulatory objectives and required degrees of conservatism vary considerably among potential database users, AEATF II does not recommend any one particular method.

The AEATF II study restricts the aerosol application scenario to professional applicators only. This focus on professional applicators is a practical necessity, given that consumer handlers are typically involved in much shorter task durations where very low exposures are anticipated (see section 5.3). Such low exposures would likely be at or below the limits of quantification/detection of the analytical method. As a result, because of the higher range of daily amount of product used (i.e., pounds of active ingredient handled) and longer application task durations, professional aerosol applicator exposure is expected to be greater, on the average, than that of consumers. This amount of product handled per task, and per day is an important consideration, given that dermal exposure levels normalized to amount handled from other ready-to-use products (e.g., hand-held pressurized aerosols) have typically been observed to be higher than other products whose application may result in more direct interaction, including mixing and loading tasks, with the pesticide formulation (e.g., mixing, loading and application of manual, low pressure sprayers) (EPA 1998). Exceptions to this generalization would be ready-to-use products that may involve direct contact with end-use formulation, e.g., direct handling of ready-to-use wipe products that are impregnated with end-use formulation.

Thus, the AEATF II exposure data for pressurized aerosol spray application of antimicrobial pesticides would be 'conservative' (i.e., would over-predict) if used to describe consumer application exposure. However, it would be reasonable for regulatory agencies using the data to assume that exposure levels for consumer applicators, when normalized for the amount of active ingredient handled, are not greater than those for professional applicators.

# 3. Existing Aerosol Application Exposure Data

## 3.1 PHED Studies

Since 1992 the EPA has conducted professional and consumer mixer/loader and applicator exposure and risk assessments relying primarily on the exposure data in Pesticide Handlers Exposure Database (PHED). PHED version 1.01 was initially released in February 1992, followed by PHED version 1.1 in February 1995. PHED version 1.1 was described by the Agency as an incremental improvement over the 1.01 version (Pesticide Handlers Exposure Database, User's Guide Version 1.1, Health Canada, U.S. Environmental Protection Agency, American Crop Protection Association, February 1995). PHED does include two studies conducted using aerosol application methods. Relevant characteristics of these studies are summarized in Table 1.

Table 1: Summary of Aerosol Application Studies in PHED

| Study | Study 456 | Study 521 |
|---|---|---|
| Active Ingredient: | Insecticide | Insecticide |
| Type of Use: | Residential Crack/Crevice | Residential Crack/Crevice |
| Aerosol Spray: | 15 oz cans (4.33 g ai/can) | 16 oz cans (5.54 g ai/can) |
| Monitoring Events (ME): | 15 | 15 |
| Product Applied: | 1 can/ME | 1 can/ME |
| Different Houses Used: | 15 (1/ME) | 15 (1/ME) |
| Different Subjects Used: | 3 (5 houses/subject) | 5 (3 houses/subject) |
| Location: | Kansas City, MO | Vero Beach, FL |
| Type of Glove Used: | Chemical Resistant | None |
| Analytical Grade(s) | A (hands), C (dermal, inhalation) | A (hands, dermal, inhalation) |

Unfortunately, these studies have limitations that reduce their value for an antimicrobial-oriented generic database. Both of these studies involved aerosol application for indoor residential insecticide (crack and crevice) treatment. The exposures typical for this product use may not be applicable to antimicrobials. Although both studies monitored application in different houses, the same subjects were used for multiple MEs. Lastly, 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.

Study 456 has additional problems: All subjects in this study 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 study 456 have only an analytical quality grade of C. To support the registration of a pesticide, the data should have an analytical grade of A or B. As a result, study 456 is rarely considered in regulatory exposure assessments.

PHED study 521 meets some of the AEATF II acceptance criteria for evaluating existing data. Although acknowledging that these data are of limited value, the EPA does use this study for antimicrobial exposure assessments. However, because the aerosol product was not an antimicrobial product and there was a lack of diversity with respect to amount of AI handled (and an associated range of duration of product spraying), additional data are needed. It is also noteworthy that descriptions of study 521 or 456 provided in PHED do not include particle size distribution documentation.

## 3.2 CMA Study

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). In total, the CMA study obtained both dermal and inhalation exposure measurements for 88 separate monitoring events (MEs) using nine different application methods (pour liquid, pump, pour solid, place solid, aerosol spray, high pressure spray, low pressure spray, mop and wipe). For aerosol (pressurized canisters), trigger-sprayed aerosol, and wiping applications, exposures to the active ingredients ortho phenyl phenol (OPP) and ortho benzyl p-chlorophenol (OBPCP) were measured.

In the CMA study aerosol application (for the purpose of disinfecting) resulted in only five MEs with measurable exposures. Only hand exposures were detectable for these MEs. MEs were conducted in different rooms distributed over a dental office, private residences, and public buildings. The applicators were dental office employees, professional housekeeping staff, or members of the general population. All applications were made using products contained in aerosol spray cans. The application duration, only a fraction of which involved actual aerosol spraying, ranged from 9 to 260 minutes.

Based on EPA's review (Mostaghimi 1995), CMA's study data met some regulatory agency requirements, but were lacking in other areas. In particular, the following areas of the CMA study were found to be lacking:

1) Good laboratory practice, especially in the area of providing quality assurance, was not always followed closely.

2) A majority of extraction efficiencies were below the minimum level suggested in EPA guidelines. Perhaps more importantly, the percent field recoveries (which represent the amount recovered under actual conditions encountered in the study) of many of the chemicals were lower than the minimum needed to assess exposure.

3) Flow volume of the air sampling equipment resulted in most of the inhalation exposure data being less than detection; and

4) None of the application method/end use settings had the minimum number of replicates (i.e., 15) recommended in EPA's guidelines. ('Replicate' is an historical term for monitoring event, or ME.)

The EPA concluded that the limited number of replicates combined with poor recovery data severely limits the conclusions that can be made from CMA's study. In many Re-registration Eligibility Decisions (REDs) issued during 2005 and 2006, EPA has stated that "the risk assessment noted deficiencies in the surrogate dermal and inhalation exposure data available from the Chemical Manufacturers Association (CMA) database. 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's study data were also echoed

by regulatory agencies in California (Powell et al., 1995) and Canada (Worgan and Rozario, 1993). 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.

## 4. The AEATF II Aerosol Application Monitoring Study

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 (AaiH) is $H_1$, then the predicted exposure when AaiH 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.

## 4.1 General Method: Random Sampling and Diversity Selection

Potential monitoring events could be identified by obtaining a random sample of applicator-days from within some well-defined population of professional applicators and from among the days on which they plan aerosol application of antimicrobial chemicals. Each selected applicator (that agrees to participate) would then be monitored for exposure in the workplace location (or locations) on the day selected. In this case, each ME corresponds to an actually-occurring applicator-day and the application conditions would not be under any experimental control. This pure random sampling approach would be an observational study since no subject is intentionally exposed to chemicals.

For the aerosol application scenario this pure random sampling approach is neither practical nor desirable. Because aerosol-spray products are more expensive than those with a trigger sprayer, the routine use of these aerosol products by professionals tends to be limited. Consequently, identifying a population of aerosol application days from which to select a random sample would be quite difficult. Even if identified, a random sample from this population would not be expected to include applicator days with larger amounts of product use unless the sample sizes are very large. Because the cost of monitoring events is very high, large sample sizes are not feasible. Thus, capturing the possible range of amount used is unlikely and the predominance of the lower application amounts would be associated with a high degree of non-detects on dosimetry garments (this was observed with the CMA study and PHED data discussed in section 3 above). Finally, many antimicrobial products that janitors use contain ADBAC, so it would not be possible for a purely observational study to separate aerosol application exposure from the other types of ADBAC application (e.g. mop, wipe, trigger spray, etc.) exposure.

A sample of N professional applicators will still be randomly selected. However, the selected workers will not be observed during one of their scheduled antimicrobial aerosol application days. Rather, the N randomly selected workers will be randomly assigned to a set of N synthetic aerosol application-day conditions. As described in Section 5, the MEs using these synthetic applicator-day conditions will be conducted in rooms within vacant commercial lodging facility buildings (e.g., hotels, motels with kitchenette or full kitchen) or, if motels with full kitchens are not available, in unoccupied apartments that are within non-vacant commercial lodging facility buildings. Obviously, many ME conditions will be associated with the particular subject assigned (e.g., aerosol application behaviors). Those conditions not associated with the subject, however, will be constructed or selected to exhibit diversity in factors expected to influence exposure. In particular, some MEs will be conducted in different buildings and use differing amounts of antimicrobial product.

It is important to emphasize that although a random sample of observational MEs are not being obtained from a population of all possible (i.e., current or future) aerosol applicator-days, the data will in most instances be treated by users of the database as if it were such a random sample. That is, simple descriptive statistics such as means and percentiles will be used to characterize the diversity of exposure in this set of MEs. Users will not usually view these MEs as a set of N experimental units assigned to N fixed 'design points'. As is always the case, extrapolation from this set of MEs to a set of future aerosol applicator-days for regulatory purposes depends on the objective and requires subject matter expertise.

## 4.2 Restriction of Study to Fresno County, California

All MEs for the aerosol application monitoring study will be conducted in rooms inside vacant buildings (or inside non-occupied rooms within non-vacant buildings) in Fresno County, CA. This particular geographic area was selected given its proximity to the analytical laboratory. Fresno County also contains a moderately large metropolitan area and offers a population of over 500,000 persons. Consequently, there is a substantial janitorial population whose members are potentially acceptable for monitoring activities.

The use of a single geographic area is based on the premise that the type and variety of indoor janitorial aerosol application tasks being performed throughout one geographical area will not differ substantially from a similar array of tasks being performed at sites in another geographical area. That is, the variation in exposure associated with aerosol application inside of buildings throughout Fresno County, CA would not be expected to differ substantially if another metropolitan area was used or multiple cities over the country were spanned. This premise is supported by the Popendorf et al. (1992) antimicrobial exposure monitoring study which concluded that variability in dermal and inhalation exposures across workers was primarily influenced by the application method and by implication, each individual worker's implementation of that application method (i.e., their work practices and behavior), rather than the location or setting in which the application method is performed. This implies that monitoring multiple subjects and capturing diversity in indoor aerosol application conditions that might influence behavior is more important than geographic diversity.

Geographic differences in exposure that have been observed in some agricultural cohorts are not expected for aerosol applications. For example, in harvesters, climatic conditions that influence the degree of dustiness, the rate of dissipation of foliar pesticide residues, or the amount of perspiration may influence exposure. Those differences cannot really be considered regional, but rather environmental. In the case of janitorial services conducted indoors, the environmental conditions are constrained by heating, ventilating and air conditioning systems that control dustiness, temperature, humidity and airflow. Therefore, these conditions are expected to be similar throughout the country.

Limited standardization of janitorial practices is another factor that is expected to lessen the importance of geographic area. The janitorial business is supported by organizations (e.g., International Sanitary Supply Association; www.issa.com) and companies (e.g., JohnsonDiversey; www.johnsondiversey.com; JohnsonDiversey offers a "Power Tools" training series) that supply

training and guidance on issues such as duration of a particular job function, the types of supplies that are required and how to use equipment and supplies most efficiently. This helps to insure that janitorial work tasks are conducted somewhat uniformly across the country. By examining the documentation supporting training and use of janitorial supplies, the AEATF II found no evidence of regional work differences.

Lastly, there is increased efficiency, convenience, and cost savings associated with the use of a single location near the analytical laboratory. The use of buildings located over multiple cities would be especially costly. The cost of selecting both buildings and subjects would increase at least in proportion to the number of geographic locations due to field team logistics and resources required. For the reasons outlined above, there would appear to be little benefit from such an increase in cost.

## 5. Construction of Monitoring Events

As noted above a combination of random sampling and diversity selection is being used by the AEATF II to obtain N monitoring events (MEs) for the aerosol application study. In the AEATF II approach, instances of possible handler-day conditions under the scenario are synthetically constructed and handler-day exposures measured. Although application conditions are synthetic, actual applicators will have been randomly sampled from among professional applicator volunteers recruited from janitorial services located in Fresno County California. Each of N professional applicators will be randomly assigned to one of the N synthetic applicator-days. Each combination of applicator and set of synthetic application-day conditions comprises a single monitoring event (ME).

The synthetic application-day conditions are either purposively or randomly chosen in such a manner that the MEs capture diversity likely in the aerosol application scenario. The approach used by the AEATF II achieves diversity by:

1. Using multiple sites (i.e., facilities/dates) within the study area (Fresno Co., CA) rather than conducting all monitoring at a single site;
2. Varying the levels of potential AI contact among MEs within each site.
3. Using a different subject for every ME.

Diversifying these three ‘meta-characteristics’ (site, AI contact level, and subject) indirectly varies many known and unknown application-conditions. Additional diversification by varying minor ME application-conditions (e.g., different configurations of aerosol surfaces) may also be added but is not a formal part of the design.

The resulting set N MEs provides a diverse set of applicator-days that mimic the diversity likely within the actual aerosol application scenario. The AEATF II has determined, in consultation with the U.S. EPA, Health Canada, and California EPA, that this combination of random sampling and diversity selection is appropriate considering the regulatory purpose of the data and feasibility. As described below, a diversity selection approach is one that can be purposive or can be coupled with random choice elements when feasible to reduce intentional selection bias.

The AEATF II Governing Document (2008) describes diversity selection more generally in the context of the AEATF II antimicrobial exposure assessment program.

## 5.1 Random Sample of Professional Applicators

The most important single meta-characteristic that is formally varied when constructing MEs is the applicator. These are professional workers with experience in performing aerosol applications, who are available and consent to perform these tasks under the synthetic application-day conditions of the study. Although these applicators will be a random sample from an existing population of workers, they can be equally viewed as just another component of the synthetic ME being constructed to predict a single instance of a future day's exposure to an arbitrary antimicrobial pesticide. Each selected worker provides his/her unique set of behaviors to the aerosol application task. A random sample of applicator-days could, in theory, contain two or more days with the same worker. However, the random sampling method used for this study permits only one monitoring event per worker in order to capture a larger diversity of application behaviors.

The applicators will all be professional janitorial workers in the Fresno County, CA metropolitan area. Flyers and/or advertisements soliciting subjects will be posted at all cooperating janitorial service providers in the area and in selected local print media (all materials will have been reviewed and approved for use by the IRB). Callers responding to flyers and/or media advertisements who are interested in participating in the study may be scheduled for Informed Consent meetings at the volunteer's convenience. It is not necessary to wait until the recruiting period is closed before enrollments begin. These individuals will then be contacted and screened, individuals who meet the study requirements will be recruited until the required number of applicators is obtained. As a precaution, more applicators are selected than are expected to be needed. Individuals who are enrolled to participate in the study will then be randomly ordered and assigned a subject identification sequence number (SISN). This random sample of workers is then allocated to MEs by SISN.

The recruitment process will terminate when sufficient subjects have been recruited for the study, i.e., have agreed to participate and signed the ICFs. If fewer than the required number of subjects has been recruited during the open recruitment period, the enrollment period will be extended in 7 days increments, until at least the minimum number of subjects and alternates have been enrolled into the study.

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.

## 5.2 Selection of Monitoring Sites

Monitoring will always be conducted within vacant lodging facility buildings or vacant areas and rooms within otherwise occupied buildings. The purpose in conducting these studies in vacant or unoccupied areas in buildings/areas is to be free from personal interferences with non-subjects and the potential contamination from other sources of a commonly-used active ingredient (i.e., ADBAC). It also makes it easier to design monitoring events that focus on aerosol application only as opposed to the broad range of janitorial activities a subject might engage in that could also involve the active ingredient. Using vacant or unoccupied areas in buildings also offers greater control of the scheduling of monitoring events.

Each combination of facility (building or building complex) and monitoring period (i.e., dates) is termed a 'site'. Diversity is induced by requiring that the N monitoring events occur at $N_C$ different sites over the Fresno County metropolitan area. As noted above, environmental conditions (e.g., temperature, humidity, air exchange rates) may be similar between facilities and at different times. On the other hand, buildings and dates might still be surrogates for other confounding factors that could cause systematic differences in exposure. Conceivable confounding factors might be architectural differences in room size, construction materials and configuration, and dirtiness or organic loading levels on surfaces to be cleaned. Temporal separation of sites tends to average out subtle 'study effect' correlations that can result when the same research personnel, equipment, and area-wide environmental conditions are involved.

Obviously, between-site diversity is maximized if every ME for a scenario occurs at a different site (i.e., $N_C$=N). However, there are practical efficiencies to be gained by conducting multiple MEs (i.e., $N_M$) per site. Consequently the aerosol study achieves a balance by using multiple sites with multiple MEs per site. Any correlation resulting from having multiple MEs/site can be overcome, at least partially, by also increasing within-site diversity. Thus, facilities are preferred if they provide diverse indoor room and area configurations, e.g., individual offices, bathrooms, kitchen areas, dining areas.

For the AEATF II Monitoring Program, the term cluster is defined as the set of MEs for a scenario associated with the same building (or building complex) and span of days during which exposure monitoring occurs. In contrast, the term site refers to the physical facility and temporal monitoring period considered together as a unit (the temporal aspect of a site is not always emphasized but is important nevertheless). A total of $N_C$ sites are required for the aerosol scenario. Each site will be used for a single cluster of $N_M$ aerosol application MEs. The set of different sites should posses the following general design characteristics:

1. Each site must be located in a different facility (i.e., building or building complex).
2. The configuration of rooms actually used for MEs at the different sites should differ in ways that might influence exposure.

For purposes of the aerosol application study, the available space in each facility must also be large enough and have bathrooms and/or food preparation areas (e.g., kitchens or 'kitchenettes')

that provide relevant and adequate surface areas for aerosol treatment. Commercial lodging facilities (e.g., hotels, motels with kitchenettes or full kitchen, and/or if needed, small apartments) are buildings that are most likely to provide an adequate amount of relevant aerosol application surface area for the monitoring events, e.g., bathroom sinks and fixtures, toilets and fixtures, bathtubs and fixtures, shower stalls and fixtures, bathroom counter tops, kitchen sinks and fixtures, kitchen countertops, and trash cans. While other building types, such as offices (e.g., medical suites) and meeting locations (e.g., universities) 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.

A random sampling approach will be used to select $N_C$ acceptable facilities. First, a list of all properties that meet the following criteria will be compiled:

- The property is commercially advertised on YellowPages.com or similar listings under "hotel, or motel " in "Fresno County, California," and;
- The property is at least partially within the boundaries of Fresno County, California; and

This list of commercial lodging facilities will then be randomized. Next, these properties will be investigated in (random) order until $N_C$ qualifying facilities have been found. To qualify, the properties must meet the following general criteria:

- The facility management is willing to cooperate in the study and provide the necessary number of units with bathrooms and/or food preparation areas (FPAs).
- The configuration of available and ME-suitable rooms provides acceptable diversity of application surfaces (e.g., horizontal and vertical surfaces, kitchens, bathrooms, sinks, countertops, toilets).
- There is a functional HVAC system
- Electric service is on or available for a short period (i.e., less than 32 days).
- The property does not require specialized cleaning or maintenance prior to use.

In addition to these criteria, an acceptable facility must also fall into one of $N_C$ different building/room categories (see Section 6.5). To insure diversity among the selected sites, only a single facility will be selected from each category. Properties will be investigated (in random order) until the first $N_C$ acceptable facilities are found.

This procedure results in a (stratified) random sample of $N_C$ acceptable and diverse facilities from the population of all such qualified facilities in Fresno County, California. Monitoring activities are then scheduled purposively for each facility.

## 5.3Varying Amount of Product Applied

Another key diversity meta-parameter used to construct synthetic application-day conditions is the amount of active ingredient handled (AaiH). All MEs in the study will apply the same active

ingredient at the same concentration using a different number of 19-oz (538 g) aerosol cans. Consequently, AaiH will be directly proportional to of the total amount of product (i.e., number of cans) sprayed during the monitoring period. To properly diversify the amount of product sprayed, some reasonable estimate for the expected range of this meta-parameter among professional applicators is needed. Data on the total amount of product applied are unavailable. Consequently, the expected range must be inferred indirectly from existing data on components of total workday product use.

Table 2 summarizes information on the average amount of formulated aerosol or trigger spray product applied to various surfaces in bathrooms and kitchens during observed cleaning events. These data were obtained from an observational study of actual product use by consumers (Aklam et al., 2006).

Table 2: The amount of product formulation (aerosol and trigger sprays) applied (g) for bathroom and kitchen surfaces.

| Location | Type of Surface | N | Mean Amount Sprayed, g |
|---|---|---|---|
| Bathroom | Counter | 12 | 10.16 |
| | Sink | 6 | 9.04 |
| | Toilet | 15 | 11.91 |
| | Tub/Shower/Shower Door | 15 | 93.31 |
| | Wastebasket | 3 | 3.67 |
| Kitchen | Counter | 13 | 41.50 |
| | Sink | 9 | 22.14 |
| | Wastebasket | 4 | 34.95 |

Each row in Table 2 only characterizes cleaning events for individual surface types, not the entire room. The mean amount of product applied if an entire room were treated can be approximated by assuming that a bathroom or a kitchen contains one surface of each surface type listed in Table 2. The resulting two room totals are shown in Table 3 along with the amount averaged over both room types. This overall average of 113 grams/room represents the mean total amount of product used in a ‘generic’ or ‘typical’ room treated on a given workday.

Table 3: The estimated average total amount of product formulation applied (g) when treating either the entire bathroom or the entire kitchen.

| Room Type | Mean Amount of Product Used (g/room) |
|---|---|
| Bathroom | 128.1 |
| Kitchen | 99.59 |
| Generic Room[1] | 113.3 |

[1] A 'typical' average amount of product used per room per day based on bathrooms and kitchens.

Obviously, 113 grams represents only the mean amount of product applied per room by a residential consumer. The actual amount will vary from room to room, from day to day, and from person to person. However, this amount is not expected to vary independently. There will certainly be some degree of correlation for all rooms cleaned by the same individual. More importantly a negative correlation is expected to exist between the total number of rooms per workday and the amount of product used per room. That is, when a larger number of rooms are treated, there could be a tendency to spend less time, and apply less product, per room.

Logically, on days when antimicrobials are used, at least one room will be treated. In this case 113 grams of product would be used on average. This translates to 21% of the 19 oz (538 g) canister that will be used for this study. Given the negative correlation between number of rooms/day and amount/room, this lower bound should probably be larger than the generic room average. (i.e., more than the 'average' amount of product might be sprayed on surfaces when only a single room is cleaned). In addition, for the AEATF II aerosol study, the analytical method LOQ sets a practical lower limit on the amount of product that should be used for an ME. Obviously it is desirable to obtain actual measurements, rather than non-detects, beneath normal work clothing. For this scenario, it is felt that a practical lower bound of one canister (i.e., 538 grams) per ME will achieve detectable levels of active ingredients on dosimetry matrices.

Information about the upper limit on number of rooms/day is based completely on inferences about the professional housekeeping population. Aerosol products used by professionals are in smaller, specialty business venues, such as medical offices and specialty hotels. Thus, while consumers may treat only a single kitchen and one or two bathrooms on a single day, this number in institutional settings such as hospitals is expected to be much larger. According to JohnsonDiversey Inc. (personal communication with AEATF II, September 19, 2008), information from multiple sources[1] indicate that a single individual at a hospital would typically

[1] JohnsonDiversey's expert opinion 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 (JCAHO Environment of Care Standards 1.3,2.3,4.0, November 2005).

clean from 15 to 20 hospital patient rooms per day. However, aerosol use is more likely at medical and dental offices and specialty lodging facilities than in hospitals. In these settings JohnsonDiversey Inc. feels that the typical range would extend below 15 rooms per day. Consequently, 20 rooms/day would appear to be a reasonable upper bound for professional aerosol applicators.

As noted above, when such a large number of rooms are cleaned per day, it is very likely that the mean amount of product applied per room will be less than the 'overall average' of 113 grams. However, using 20 rooms/day and 113 grams of product per room should still provide a conservative upper bound for total product applied per day by professional cleaners. This approximation gives a maximum of 2,260 grams of product (113 g/room x 20 rooms/day), or about 4.2 19-oz canisters (2,260 g / 538 g per canister), per day.

Thus, these results suggest that reasonable diversity in AaiH among MEs could be obtained by varying the number of 19-oz canisters applied between 1 and 4. This will be accomplished by dividing this range into $N_M$ intervals, or strata, of amount of product (i.e., number of canisters) sprayed (see Section 6.5). Each of the $N_M$ MEs at a site will be assigned to one of these product use intervals.

## 5.4 Potential Sources of ME Bias

As noted above, a practical study goal is that the set of aerosol application MEs represents a diversity of potential applicator-day conditions that might impact exposure. To the extent this is achieved, the set of MEs will tend to exhibit greater variation in log-exposure than would an actual population of all possible applicator-days. Because applicator-day exposures are expected to be distributed lognormally, greater variation of log-exposure implies greater positive skewness of non-transformed exposure. Consequently, statistics that are sensitive to positive skewness (e.g., arithmetic mean and upper percentiles) might be biased upwards.

It is also important to recognize that some degree of potential overestimation bias is inherent in any study if the exposures measured on the inner dosimeters from MEs are less than limit of quantitation (LOQ). This is more likely to occur when the amount of product applied is smaller, although AEATF is making every effort to obtain measurable exposures for all MEs.

Another potential source of inherent potential overestimation bias in the study design described in this document and the associated protocol is reusing the same rooms for multiple applicators. The residue remaining from a prior day's use might represent a significant source of dermal contamination for subsequent users.

Other potential sources of potential overestimation bias result from characterizing all aerosol exposure from situations having higher-than-average exposure potential such as:

- 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.

For most regulatory users of these data, however, potential overestimation of exposure will likely be of little concern because it would still be inherently protective of workers. The AEATF does not foresee significant sources of underestimation bias for exposure estimates derived from data resulting from the proposed study.

# 6. Sample Size Determination

For the most part, sample sizes can only be determined using statistical theory alone when either

1. There is assumed random sampling from a population and the goal is to estimate some characteristic of that population; or

2. There is assumed randomization of experimental units to treatments and the goal is only to compare or contrast treatments in some manner; or

3. It is assumed that all non-random influences can be mathematically 'removed' in some fashion through modeling and any remaining deviations from the model are 'naturally' random (although such natural residual randomness may take a complicated form).

Only in these general situations can statistical theory predict how increasing sample size decreases estimation error. In other data-collecting situations, sample size must be determined using one of the three 'random' situations above as a reference model. The random reference model is constructed so that it reflects important aspects of the actual situation. The sample size that is appropriate for the reference model is then used for the actual study design. The use of a random reference model is not, however, a claim that the pure situation described by the reference model actually occurs.

This 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 above, 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 (1) above. As a result, a reference model for random sampling will be used for the determination of sample size.

## 6.1 Reference Sampling Model

In a general sense, the aerosol application study involves selecting $N_C$ buildings and then conducting $N_M$ MEs within each building. This results in a total of $N=N_C \times N_M$ monitoring events. The simplest reference model would be one that treats the N MEs as a simple random

sample of N independent applicator-days from a population of future applicator-days. However, if there is a correlation between MEs conducted in the same building, the sample sizes calculated from this reference model will be too small. A better reference model would accommodate this simple type of ME correlation. More complicated reference models that incorporate specific aspects of the sampling and random assignments could also be proposed. However, such models would be of little practical value since they would require estimates for many parameters for which no information is available.

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 $N_C$ clusters (i.e., sites) and $N_M$ MEs per cluster. The total number of MEs is, therefore, $N=N_C \times N_M$.

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.

## 6.2 Benchmark Objective

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 ($N_C$) and the number of MEs per cluster ($N_M$).

For the aerosol application study, the benchmark objective is that (when the reference model is true) sample estimates of the arithmetic mean and 95$^{th}$ 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.

## 6.3 Expected Variation in Normalized Exposure

Some idea of the variability of normalized exposure is necessary in order to determine the sample size that meets the benchmark objective. In terms of the reference nested-random sampling model, the variation structure is determined by the geometric standard deviation (GSD) and the intra-cluster correlation (ICC). GSD measures the total relative variation between future applicator-days of normalized exposure. The ICC describes how similar within-site exposures are with respect to the total variation in (normalized exposure). An ICC of zero means that MEs within the same cluster are no more similar than are MEs in different clusters. At the other extreme, ICC=1 means that all MEs in the same cluster have identical exposure.

As noted previously, the CMA study (Popendorf et al. 1992) provides the only directly relevant existing data for the aerosol application of antimicrobial pesticides. This study, however, provides just five aerosol applicator monitoring events spread over three different facilities. Although only hand exposures were detectable, these data can provide a crude estimate of total relative variation (GSD). However, the numbers of facilities and MEs per facility are too small to provide a useful estimate of ICC.

Although obtained for crack and crevice insecticide applications, PHED study 521 can provide normalized dermal exposure data for 15 hand-held aerosol monitoring events collected from 15 different residential houses. For this measure, there were no significant differences among the five subjects ($p=0.1833$). Thus, it is reasonable to treat these as 15 independent MEs for the purpose of estimating total relative variation. As was the case for the CMA study, these data can provide no estimate of ICC since each ME was conducted in a different house.

In addition to the two aerosol studies discussed above, exposure data from additional, non-aerosol application sources are also available (Table 4): The CMA study provided data for mopping applications (6 MEs) and for wiping applications (6 MEs). As is the case for aerosol, both mopping and wiping application are repetitive-motion tasks. Although the magnitude of the normalized exposures for mopping, wiping, and aerosol application are not expected to be the same, the relative variation for repetitive-motion activities might be expected to be driven primarily by variation in subject behavior. If so, then these four sets of data might have a common geometric standard deviation and a more robust estimate of GSD can be obtained by using all of this information.

The feasibility of using the normalized dermal exposure results from the two aerosol data sets or from all four 'repetitive task' data sets together to estimate relative total variation for the aerosol study was first evaluated. Only dermal exposure was considered given that it was associated with higher exposures, i.e., was found to be the primary route of exposure in these studies. Levene's test for equal variability among groups (Glazer, 1983) was applied to the $\log_e$-transformed, normalized dermal exposure values. These results are summarized in Table 5. Although the log-scale standard deviations (SD) ranged from 0.62 to 1.61 there was no significant difference ($p > 0.05$) in relative variability among the four data sets. A common-variance ANOVA model gave a pooled log-scale SD of 0.74 for the two aerosol studies and 1.05 for all four repetitive-motion studies. The corresponding estimates of geometric standard deviation (GSD = exp SD) would then be 2.1 and 2.9, respectively. These two GSD values are considered in the determination of sample size in the next section.

None of these studies can provide an indication of the expected magnitude of the within-cluster correlation (ICC) in normalized exposure resulting from aerosol application. Much of the variation resulting from such a repetitive task is expected to track the variation in worker behaviors and within-facility diversity. In contrast, small variation in indoor environmental conditions (surface types and configurations, temperature, humidity, air exchange rate) is expected across indoor locations (e.g., building types) in which the monitoring events take place. This would suggest an intra-cluster correlation (ICC) near zero. A central tendency ICC value across many outdoor agricultural exposure scenarios, where moderate levels of within-site

correlation are expected, is 0.3 (AHETF, 2007, Appendix C). This represents a likely upper-bound for most indoor antimicrobial exposure scenarios.

Table 4: Source (Study)-Specific Normalized Dermal Exposure Values for each Monitoring Event

| Source (Study) | Monitoring Event ID | Normalized Dermal Exposure (µg / lbs ai handled) |
|---|---|---|
| CMA (Aerosol, Hands)[1] | 47 | 126,263 |
| | 79 | 48,913 |
| | 80 | 666,667 |
| | 87 | 413,043 |
| | 90 | 340,909 |
| PHED (Aerosol, Study 521)[2] | 521-A-1 | 2,180,000 |
| | 521-A-2 | 657,000 |
| | 521-A-3 | 365,000 |
| | 521-B-4 | 488,000 |
| | 521-B-5 | 459,000 |
| | 521-B-6 | 199,000 |
| | 521-C-7 | 815,000 |
| | 521-C-8 | 1,140,000 |
| | 521-C-9 | 1,720,000 |
| | 521-D-10 | 1,020,000 |
| | 521-D-11 | 521,000 |
| | 521-D-12 | 384,000 |
| | 521-E-13 | 683,000 |
| | 521-E-14 | 617,000 |
| | 521-E-15 | 410,000 |
| CMA (Mop)[3] | 1 | 20,855 |
| | 5 | 22,186 |
| | 7 | 503,250 |
| | 9 | 16,656 |
| | 10 | 34,394 |
| | 11 | 37,088 |
| CMA (Wipe)[4] | 2 | 4,313,916 |
| | 6 | 1,747,115 |
| | 8 | 1,058,688 |
| | 61 | 49,252 |
| | 62 | 471,758 |
| | 73 | 2,570,922 |

[1] Monitoring events corresponded to separate individuals each treating a different room. Rooms were spread over multiple buildings. Dermal residues were only detectable on hands. Three monitoring events that yielded non-detectable residues for all body parts were excluded.
[2] Monitoring events corresponded to three separate evaluations of 5 different individuals. Each of the 15 monitoring events occurred in a different house.
[3] Monitoring events corresponded to separate individuals treating a different room (over a variety of locations).

[4] Monitoring events corresponded to individuals treating a different room. Rooms were spread over multiple buildings. Two monitoring events that yielded non-detectable residues for all body parts were excluded.

Table 5: Estimates of the Variation in Total Normalized Dermal Exposure from Existing Studies.

| Study | N | Standard Deviation of $Log_e$ Normalized Exposure |
|---|---|---|
| PHED (Aerosol, Study 521) | 15 | 0.62 |
| CMA (Aerosol-Hands) | 5 | 1.05 |
| CMA (Wipe) | 6 | 1.61 |
| CMA (Mop) | 6 | 1.26 |

**Common Relative Variation Models:**[1]

***PHED and CMA Aerosol Studies only:***

| | |
|---|---|
| Common SD of $Log_e$ Exposure | 0.74 |
| Common GSD of Exposure[2] | 2.1 |

***All 4 Repetitive Task Studies:***

| | |
|---|---|
| Common SD of $Log_e$ Exposure | 1.05 |
| Common GSD of Exposure[2] | 2.9 |

[1]Assuming a separate mean for each study, but a common standard deviation on the log scale.
[2]Geometric standard deviation = exp(SD).

## 6.4Determination of Sample Size

A Monte Carlo simulation approach was used to examine the impact of number of clusters ($N_C$) and number of MEs per cluster ($N_M$) on accuracy of the arithmetic mean and 95$^{th}$ percentile for the reference model. For each examination 10,000 random data sets were generated using the reference nested-random sampling model and assumed values of the total GSD and the intracluster correlation (ICC). From each simulated set, estimates of the arithmetic mean and 95$^{th}$ percentile were calculated.

The fold relative accuracies (*fRA*) for the mean and 95$^{th}$ percentile were also computed. If $\theta$ is the parameter of interest and T is the corresponding calculated statistic, then fold relative accuracy is defined as:

(1) $$fRA = \text{Maximum of } T/\theta \text{ and } \theta/T$$

Fold relative accuracy simply expresses how far T is from θ in a relative sense. The result is 10,000 random values of *fRA*. The empirical 95$^{th}$ percentile of these 10,000 *fRA* values, $fRA_{95}$, is the quantity of interest. By definition, T is within $(fRA_{95})$-fold of θ, 95% of the time. Thus, if 3-fold accuracy is desired, $fRA_{95}$ should be approximately equal to 3. (Note that for historical reasons, the EPA and others sometimes refer to $fRA_{95}$ as the 'K-factor'.) The simulation procedures and the definition of fold relative accuracy are the same as those used for the AHETF monitoring program (AHETF, 2007, Appendix C). This simulation method and its theoretical basis are described in greater detail in the AHETF documentation.

For a configuration of $N_C$=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.

Table 6: Relative accuracy profile when there are $N_C$=3 clusters (sites) and the number of monitoring events per cluster ($N_M$) is chosen to give 3-fold accuracy or better at ICC=0.3.

| ICC | 95% Bound on Relative Accuracy ($fRA_{95}$) or "K-factor" | | | |
|---|---|---|---|---|
| | Aerosol Studies GSD of 2.1 $N_M$=2 MEs per cluster | | Repetitive Task Studies GSD of 2.9 $N_M$=6 MEs per cluster | |
| | Arithmetic Mean | 95th Percentile | Arithmetic Mean | 95th Percentile |
| 0 | 2.0 | 2.6 | 1.9 | 2.2 |
| 0.1 | 2.0 | 2.7 | 2.1 | 2.4 |
| 0.2 | 2.1 | 2.8 | 2.3 | 2.7 |
| 0.3 | 2.1 | 3.0 | 2.5 | 3.0 |

It is also possible to obtain equivalent accuracies with different configurations of $N_C$ and $N_M$. For example, when GSD=2.9 the three configurations listed in Table 7 are essentially equivalent. Although they may be statistically equivalent, the configuration with fewer clusters and more MEs per cluster (and more total MEs) is actually more cost effective and also permits a greater diversity in amount of product applied within each cluster. Thus, a design of 3 sites and 6 MEs per site appears reasonable if the reference model is assumed. By analogy, this configuration

will be used for the aerosol application study as well.

Table 7: Practically equivalent configurations of clusters and MEs per cluster when ICC=0.3.

| Number of Clusters, $N_C$ | MEs per Cluster, $N_M$ | Total MEs, N | $fRA_{95}$ for 95th Percentile | |
|---|---|---|---|---|
| | | | ICC=0 | ICC=0.3 |
| 3 | 6 | 18 | 2.2 | 3.0 |
| 4 | 4 | 16 | 2.2 | 2.8 |
| 6 | 2 | 12 | 2.6 | 2.8 |

## 6.5Building/Room Categories and Product Use Intervals

The scenario design in Section 6.4 indicated that NC=3 clusters are required. As discussed in Section 5.2 each of these three clusters of MEs should be conducted at a monitoring site that can be generally described as a qualifying commercial lodging facility (i.e., hotel, motel with kitchenette or full kitchen). MEs will be conducted in available bathrooms and, if present, food preparation areas within the facility. A food preparation area (or FPA) is defined as a room containing a stove/oven, refrigerator, and food preparation sink.

A simple random sample of qualifying facilities could be selected. However, this might result in two or more monitoring sites with similar configurations of ME-appropriate rooms. Although valid, 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 FPA (i.e., kitchen or 'kitchenette') configurations which might be expected to impact exposure potential differently. Although other, equally acceptable, classifications could be proposed, this one is considered both intuitive and logistically practical.

As described in Section 5.2 above, one facility will be randomly selected from each category. It is important to emphasize that this study is not concerned with testing whether average exposure differences exist between the three different configuration categories. Nor would it be especially relevant if true exposure differences actually do not exist, on the average, between these categories. Rather, the purpose of the patterned randomization is simply to reduce the likelihood that the three selected monitoring sites will be too similar by chance.

The scenario design also requires $N_M$=6 MEs within each cluster. As noted in Section 5.3, each of these MEs will require an amount of product in the range of 1 to 4 19oz cans. Thus, a reasonable approach is to require that the six MEs have applicators apply product amounts somewhere within the following six ranges:

A. 1 to 1.5 cans B. 1.5 to 2 cans C. 2 to 2.5 cans

D. 2.5 to 3 cans E. 3 to 3.5 cans F. 3.5 to 4 cans

Ranges for the different product application volumes are used since partial can amounts are difficult to control exactly without impacting the behavior of an applicator. Actual product levels are not randomly assigned within each interval. Rather, each applicator will be asked to stop applying when the ME observer estimates that the amount applied is somewhere in the target interval assigned to the ME.

The N=18 randomly sampled professional applicators will be randomly assigned to the N=18 combinations of building/room configuration category and application volume illustrated in Table 8. This provides a diverse set of MEs with respect to three meta-parameters: (1) applicator, (2) types of rooms, and (3) product volume applied.

Table 8: The structure of the N=18 MEs proposed for the aerosol application study

| Number of 19 oz cans applied per ME | Building/room configuration category | | |
|---|---|---|---|
| | Motel with bathrooms and Full Kitchen FPAs | Hotel/motel units with bathrooms and Kitchenette FPAs | Hotel/motel units with bathrooms only |
| 1 to 1.5 | ● | ● | ● |
| 1.5 to 2 | ● | ● | ● |
| 2 to 2.5 | ● | ● | ● |
| 2.5 to 3 | ● | ● | ● |
| 3 to 3.5 | ● | ● | ● |
| 3.5 to 4 | ● | ● | ● |

It is reasonable to ask if it would be simpler to abandon the attempt to structure diversity in building/room configuration and application volume. One might simply select three facilities at random from among the qualifying facilities in Fresno County. In addition, six application volumes anywhere between 1 and 4 cans could also be randomly selected. Table 9 illustrates possible consequences of such an unstructured approach. Because facility selection was completely at random, one category was missed and two monitoring sites in another category (motel with full kitchen) were selected by chance. This still provides some diversity, but not as much as provided by the stronger diversity selection approach in Table 8. The randomly selected application volumes cover all but the 1 to 1.5 can amounts. But there is no balance within each facility and some of the intervals are more heavily represented than others.

Table 9: A structure of the N=18 MEs generated by randomly selecting building and product amount

| Number of 19 oz cans applied per ME | Building/room configuration category | | | |
|---|---|---|---|---|
| | Motel with bathrooms and full kitchen | | Hotel/motel units with bathrooms and kitchenette FPAs | Hotel/motel units with bathrooms only |
| 1 to 1.5 | | | | |
| 1.5 to 2 | ●●● | ● | | |
| 2 to 2.5 | | ●●● | | ●●●● |
| 2.5 to 3 | | | | ●● |
| 3 to 3.5 | ● | ●● | | |
| 3.5 to 4 | ●● | | | |

Table 9 illustrates only one example of the possible random configurations that could be generated. However, the lack of diversity shown by this configuration is rather typical of other randomly generated configurations. In general, when sample sizes are relatively small, random selection is less likely to produce a diverse set of MEs. Although neither of the approaches shown in Tables 8 and 9 can yield a true random sample of future applicator days, it is felt that the diversity selection approach (Table 8) will be better able to characterize the future applicator-day diversity in exposure. On balance, therefore, the AEATF II considers that constructing MEs with the greater diversity shown in Table 8 is well worth the additional effort.

It should be noted that the ME design illustrated in Table 8 has the superficial appearance of a fixed-effect treatment structure with two fixed factors: building/room configuration category and application volume. In such an experimental framework this could be thought of as 18 experimental units (applicators) assigned to 18 design points (combinations of category and amount). However, regulatory agencies and most other users of these data will prefer to view these MEs not as a fixed-factor 'comparative' experiment, but merely as a set of N=18 synthetic applicator-days that characterize the diversity of exposures possible for the aerosol application scenario. This 'diversity characterization' objective was envisioned by AEATF II when determining sample size. A statistical comparison of exposure between building types or between application volumes was not envisioned as an objective for the purpose of sample size determination. However, statistically sophisticated users of these data are always free to analyze such aspects of the exposure data if they so desire.

## 7. References

AEATF II (Antimicrobial Exposure Assessment Task Force II). 2008. Governing Document for a Multi-Year Antimicrobial Chemical Exposure Monitoring Program. Interim Draft Document. American Chemistry Council, Arlington, VA.

# APPENDIX A

Study Rationale
Product Selection Justification

# RATIONALE FOR STUDY

## 1. Introduction

This document is designed to provide relevant information and rationale for the conduct of the subject study. Prior to initiation of protocol development, an effort was made to check for existing data that could be utilized / substituted to estimate exposure from use of antimicrobial aerosol products both in household and commercial/institutional settings. Additionally, the information collected would also provide a valuable tool in selection of the product/s and study design for estimating exposure from use of pressurized aerosol cans.

## 2. Literature Review

A literature search revealed that very little data existed on exposure to pressurized aerosol products. The most relevant articles were selected and a summary of those reports/publications is provided as part of the justification for the conduct of the subject study and its application in the proposed study design and product selection.

### 2.1. Berger-Preiss et al. (2005):

This study was conducted in response to the EU Directive 98/8/EC, to estimate inhalation and dermal exposure during spray applications of biocides. The study involved an extensive survey of published and unpublished literature regarding use of biocides and categorized the information according to the uses e.g., greenhouses, indoor pest control, stables, wood preservatives and antifouling agents. Measurements were performed at selected workplaces during disinfection operations in food and feed areas; pest control operations for private, public and veterinary hygiene; wood preservative and anti-fouling agents. In order to compare literature results regarding influence of parameters relevant to exposure (e.g., spraying equipment, nozzle size, direction of application), model experiments were conducted in 60 $m^3$ rooms. The sprayers used in the model experiment were Frowein "Spray Boss" with various nozzle sizes (low pressure); Wagner (airless sprayer); and a cold fogging apparatus which represented the range of equipment used in the work place. In the extensive literature survey conducted by the authors, only one reference regarding use of aerosol cans for indoor and/or green house pest control was available.

The research literature survey of work place measurements were mostly related to agrochemicals, wood protection, and paint with high or low pressure aerosol generation. The inhalation exposure monitoring data was mostly from green houses, including re-entry type of studies for worker safety using stationary sampling or personal pumps. The results from work place measurements and model experiments revealed the following:

- Particle size distribution was the most important parameter and was dependent on the nozzle size of the sprayer
- Fine particles stayed suspended longer and gave higher inhalation exposure
- Inhalation exposure was lowest when spraying direction was downward
- Inhalation exposures was higher during overhead spraying
- Highest inhaled dose rates were measured during fogging
- Sprayers' distance from the sprayed object was of minor importance

- Higher pressure spraying led to higher exposure
- Spraying of higher application volumes (amount of active material) per time led to an increased inhalation exposure
- Air concentrations were higher without ventilation
- Dermal exposures were very much dependent on the spraying direction and apparatus
- Spraying the upper part of the wall, the head, upper arms and thighs had most exposure (with Spray Boss) and exposure was lower during fogging and horizontal spraying and also lower during spraying of the lower part of the wall
- Dermal exposures varied by a factor of 10 and were dependent on the behavior of the user
- Model experiments were predictive of the field measurements
- Aqueous solutions gave higher concentrations compared to higher vapor pressure solvent based solutions
- No major differences between stationary sampling or personal pumps, with slightly higher trend with the personal pump

The study does not provide exposure data which is directly applicable to the cleaning and disinfecting aerosol products in cans represented by the Task Force membership. However, the study provides useful information in selecting the product/s and in study design. Based on this information one can conclude that a product which will have a higher number of particles in the inhalable range (fine spray), used in multi-directional orientation, in confined spaces and with relatively low vapor pressure will provide the greatest exposure.

### 2.2. Marquart et al. (2003)

This publication is a review of available literature on the subject and discusses various determinants influencing exposure and use of the information in developing models for risk assessment. Inhalation and dermal exposures are complex processes and determinants of exposure depend on exposure scenario. In the aerosol spraying process the most important exposure determinants are:

- Spray volume i.e., amount of liquid sprayed
- Area treated
- Orientation of worker in relation to application or orientation of the spray applicator
- Proximity of the worker to the source i.e., distance from the application surface
- Spray pressure is related to particle size distribution; and deposition velocity is important for both inhalation and dermal exposure from use of aerosols
- Type of surface
- Worker habits

The publication does not provide data that can be directly substituted for estimating inhalation and dermal exposure from use of aerosol products. However, the information available supports the arguments, made subsequently, for product selection in the proposed study and provides guidance in study design. In the proposed study the most influential determinants for inhalation and dermal exposure will be considered both in the selection of the product and study design.

## 2.3. Nazaroff et al. (2006)

This was an extensive study undertaken for the California Air Resources Board (ARB) to determine the exposure from air contaminants produced by indoor use of consumer products for cleaning and as air fresheners. The study focused on the volatile organic components that contributed to production of photochemical smog including indoor reactive chemistry. The main emphasis was on the terpene-ozone reaction.

The indoor household products were identified by a shelf survey of five retail outlets in Northern California and by literature review on air pollutants. The product list included disinfectants, general-purpose degreasers, general-purpose cleaners, wood cleaners, furniture maintenance products, spot removers, multi-purpose solvents and air fresheners. From the list, six products (one from each group) were selected to study emissions and concentrations of the primary constituents in simulated-use experiments in room-sized research chambers. Experiments were also conducted in a bench-scale chamber under controlled conditions to study the reactivity of volatiles with ozone. The test atmosphere was analyzed for various components and particle size distribution was measured only up to four micrometers for the aerosol products. The data was analyzed for its relevance to humans.

The study concluded that inhalation exposure to air pollutants can be expected to occur under some circumstances during the use of common household cleaning products.
In this elaborate study on exposure to household products no effort was made to determine the concentration of the active ingredients in air and the focus was on the volatile liquids and gases. Therefore, the data is not directly applicable to estimate exposure to the aerosol products represented by the Task Force membership.

## 2.4. PHED and CMA Studies

These studies have been discussed in detail previously in the Scenario Design Document and will not be considered further.

## 2.5. Conclusions from the Existing Data

From the review of the relevant literature, it can be concluded:

- The existing information does provide useful general information on the behavior of the aerosol products and identifies variables which are most influential in defining inhalation and dermal exposure by use of aerosols.
- The data are very limited and do not fully represent the use patterns and exposure scenarios of the products represented by the Task Force and therefore, are not suitable for estimating the inhalation and /or dermal exposures by use of aerosol cans.
- The available knowledge could be helpful in the proposed study design and selection of the product.

The proposed study can be designed to provide exposure data most suitable for use in the risk assessment of the aerosol biocide products in cans.

## 2.6. Relevance of Existing Data to the Study Goals

As discussed above in the conclusions the data cannot be directly used to assess the inhalation or dermal exposure associated with use of pressurized aerosol cans, but has relevance in defining the parameters that contribute to and influence the degree of exposure. 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 aerosol cans.

### 2.6.1. Most Influential Variables Effecting Exposure

The most influential variables described in the existing data and relevant for the current study design and selection of the representative product (test material) are:

- 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

These influential variables are considered and discussed in more detail in the following section - rationale for selection of the test substance for the study.

## 3.0 RATIONALE FOR SELECTION OF TEST SUBSTANCE

Test substance selection was based on the hypothesis that a representative product /products could be selected and data generated with the following characteristics:

- Serve as a surrogate for most pressurized aerosol use categories
- Use pattern represents high end exposure – a conservative scenario
- Use scenario covers most influential variables of exposure
- Has a stable active ingredient with a low Limit of Quantification
- Results can be extrapolated to most antimicrobial aerosol products

In order to meet the above **criteria for product selection**, the following information was considered:

1. Survey of the products represented by the AEATF II
    a. Product profile including aerosol characteristics, release rate, nozzle size and use scenarios
    b. Consideration of influential variables
2. Identify product categories based on use scenarios
3. Conduct of a pilot/ method development study using a representative product from each category
4. Identify product to serve as surrogate to meet criteria for the study design and product selection

## 3.1 Antimicrobial Products Represented by AEATF II

**3.1 .1 Survey of products** For selection of the surrogate product/s, an informal survey of the Task Force Membership, representing the number and type of aerosol products was conducted, and the following 18 products marketed by 9 major companies were identified. Table 1 presents details on the product use and other associated characteristics. It should be noted that the number of products represented by these companies are sold under various brand names in retail stores either by the companies or their customers and cover a vast range of antimicrobial aerosol products sold on the market. Therefore, the product representation covers the range of use categories both for household and commercial/institutional applications.

**Table 1– Products Represented by the Task Force Membership**

| Product name | Company Name | Use Scenario | Spray Type |
|---|---|---|---|
| Lysol Brand Disinfectant Spray; Lysol Brand IC Disinfectant Spray; Professional Lysol Brand Disinfectant Spray; (EPA Reg--Biosol) | Reckitt Benckiser | Hard surface disinfectant & sanitizer; Soft surface sanitizer | Fine spray |
| EPA Reg. name: Lysol Brand foaming Disinfectant Basin Tub & Tile Cleaner II; Sold under several other names | Reckitt Benckiser | Hard surface cleaner & disinfectant | Foaming Spray |
| Lysol Brand Disinfectant Spray (Lysol Neutra Air) | Reckitt Benckiser | Disinfectant air treatment | Fine Spray |
| Clorox Disinfecting Spray | Clorox Services Company | Spot treatment; surface disinfectant (hard nonporous surfaces); other | Fine Spray |
| Raid Ant & Roach Killer Germ Fighter | S.C. Johnson & Son, Inc. | Other--Insecticide with antimicrobial agent (0.1%) | Fine Spray |
| Oust Air Sanitizer | S.C. Johnson & Son, Inc. | Disinfectant/sanitizer (Air) | Fine Spray |
| Oust Surface Disinfectant & Air Sanitizer | S.C. Johnson & Son, Inc. | Disinfectant/sanitizer | Fine Spray |
| Antibacterial Scrubbing Bubbles Bathroom Cleaner | S.C. Johnson & Son, Inc. | Foaming aerosol products | Foaming spray |
| Envy Multipurpose Cleaner | JohnsonDiversey Inc. | Disinfectant/sanitizer; Cleaning--industrial, institutional | Foaming Spray |
| Endbac II | JohnsonDiversey Inc. | Disinfectant/sanitizer; Cleaning--industrial, institutional | Foaming Spray |
| Aerosol Surface Disinfectant | Stepan Company | Surface disinfectant | Fine Spray |
| Aerosol Detergent/ Disinfectant | Stepan Company | Surface cleaner/disinfectant | Fine Spray |
| Aerosol SDAS | Stepan Company | Surface sanitizer/ disinfectant; air freshener, air sanitizer | Fine Spray |
| Staphene Spray | Steris Corporation | Surface disinfectant air sanitizer | Fine Spray |
| Asepti-Steryl | Ecolab, Inc. | Hard surface hospital disinfectant | Fine Spray |
| Asepticare | Ecolab, Inc. | Hard surface hospital disinfectant | Fine Spray |

| | | | |
|---|---|---|---|
| Febreze Air Effects/Swiffer Furniture Polish | Proctor and Gamble | Air freshener and furniture polish | Fine Spray |
| Withheld | International Paint | Anti-fouling agent | Fine–coarse Spray |

The concentration of the AI(s) is available on request. The main active ingredients found in these products are shown in Table 2:

**Table 2 – Active Ingredients in Products Shown in Table 1**

| Active Ingredient (AI) | No. Products |
|---|---|
| • Octyl decyl dimethyl ammonium chloride (ODAC) | 2 |
| • Dioctyl dimethyl ammonium chloride (DODAC) | 2 |
| • Didecyl dimethyl ammonium chloride (DDAC) | 2 |
| • Alkyl dimethyl benzyl ammonium saccharinate (ADBAS) | 1 |
| • Dimethyl benzyl ammonium chlorides (DBAs) | 1 |
| • Alkyl dimethyl benzyl ammonium chloride (ADBAC) | 10 |
| • Alkyl dimethyl ethylbenzyl ammonium chloride (ADEBAC) | 5 |
| • BTC 2125M | 3 |
| • Ethanol (EtOH) | 5 |
| • 2-phenylphenol | 1 |
| • o-benzyl-p-chlorophenol (OBPC) | 1 |
| • p-tertiary amylphenol (TAP) | 1 |

### 3.1.2 Consideration of Most Influential Criteria/Variables in Product Selection

**Particle size distribution, Release rate and Nozzle technology**

It is well known, as summarized previously, that particle size and amount of product released/unit time are some of the influential variables impacting dermal and inhalation exposure from use of aerosol products. The particle size and the release rate are related to and controlled by the nozzle characteristics (size or orifice diameter and technology) along with various other parameters. Therefore, nozzle characteristics were also considered in justifying the product selection for the aerosol exposure study.

In the aerosol spray applications, it is desirable to deliver a spray of small particles (>10-200 μm) with somewhat uniform diameter and most of the products have particle sizes less than 200 μm (Table 3). The actuator or nozzle design (orifice size or diameter and taper) is one of the parameters that influence the particle size, release rate and hence exposure to the user. The release rate and particle size are also limited by the container pressure and container characteristics (e.g., size or surface to volume ratio, container material including plastic, steel or aluminum) and fluid properties including surface tension and viscosity (Shieh et al. 2008). There are numerous variations on the combination of nozzle size and design, container pressure and size which are used in controlling the average droplet size and release rate for an aerosol product (Lionstar Corporation; Giles et al. 2005). The aerosol cans are generally made of metal and

plastic and the propellant pressure ranges from 40 to 60 PSI based on the material. The can sizes range from 2.5 to 19 ounces.

**Release rates/Nozzle technology**
Table 3 provides Release rates and nozzle sizes for the aerosol products. 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″. (It should be noted that the information provided in Table 3 on the aerosol generation technology used by the companies is propriety in nature and the products are coded for public release of this information. However, the EPA will be provided with complete information). As mentioned previously, 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 pressure is limited by the material used that allows safe use of the cans. One can conclude that release rate and particle size distribution are controlled by combination of nozzle technology and can pressure. Therefore, the release rates and particle size have a limited range. The exposure to the biocide is not only related to the release rate, it is also associated with the concentration of the biocide in the product. Data in Table 4 show that at similar release rates (1.36 g/s vs.1.3 g/s for the *Clorox Disinfectant Spray vs. Lysol Brand Disinfectant Spray)*, the concentration of the active ADBAC was 17.2 mg vs. 6.7 mg for *Clorox Disinfectant Spray vs. Lysol Brand Disinfectant Spray* respectively. Therefore, in selecting the product for the study, concentration of active ingredient in the product is an important consideration. *Clorox Disinfectant* Spray had the highest % of actives among the products listed in Table 1.

(Note: When release rates were not available from the companies, the data was experimentally generated in the laboratory according to the method described in the pilot study).

**Particle size distribution:**
Particle size information was collected during the survey on the products listed in Table 1 and when this information was not supplied by the company, it was generated in the laboratory according to the method described in the pilot study report (see section 4.3). The particle size distribution data on each of the 18 products is provided in Table 3. The data show that particle size distribution 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 with *Clorox Disinfectant Spray* having the lowest particle size distribution. 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. The lower particle sizes of 24-34 μm is for the products where data was generated in the laboratory. This is attributed to the difference in methodology by which data was generated and the phenomenon where larger particles impacted on the target surface and were not captured and only small particles were collected.

**Surface and Orientation**:
A hard target surface with a vertical and over head 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.

used in the definitive study. The main objectives of the preliminary/method development phase were:

1. Cover a range of aerosol products, nozzle sizes and release rates.
2. Determine the volume/amount sprayed per unit time to establish the detection limits and determine the anticipated air concentration of the product near the breathing zone of the user.
3. Characterize the aerosol spray (particle size distribution) produced by the selected products.
4. Develop the method for subsequent sampling in the exposure monitoring study.
5. Compare the results of the products and select product/products for the exposure monitoring study.

**4.2 Products Selected for the Pilot Study**

The following products with active ingredients were selected:

*1.* Hard surface disinfectant fine spray (Nozzle 0.02″; Release rate 1.36 g/s)

*Clorox Disinfecting Spray* (DDAC, ADBAC, ODAC, DODAC, Ethanol)

2. Foaming aerosol product (Nozzle 0.016″; Release rate 1.8-2.4 g/s)

*Antibacterial Scrubbing Bubbles Bathroom Cleaner* (ADBAC)

3. Soft surface disinfectant (Nozzle 0.02″; Release rate 1.1-1.6 g/s)

*Lysol Brand Disinfectant Spray (*ADBAS, Ethanol)

4. Air freshener (Nozzle 0.03″; Release rate 1.3 g/s)

*Stepan Aerosol SDAS* (ADBAC)

**4.3 Study Design Overview**

**Release rate:**

Four or five cans of each product were discharged for 10 seconds each after shaking. The cans were weighed before and after discharge to determine the mass emitted in 10 seconds. Similarly, for the products in Table 1 when such data was not volunteered, 10 second samples (4-6) were taken and the average of the samples was used in estimating the release rate.

**Design considerations:**

The preliminary investigation was conducted in an environmental chamber (8x16x16 feet and having temperature and airflow controls) at the Golden Pacific Laboratories, in Fresno, California. It is well known and as discussed in Section 1.2, the exposure to aerosol products can be influenced by environmental conditions and orientation/behavior of the user. Therefore, the

most important variables influencing the air concentrations and exposure were considered in comparing the products and the following parameters were selected for the preliminary investigations:

**Orientation of the aerosol can and surface –** A hard target surface with a vertical orientation of the spray can was considered the most conservative scenario and expected to give the most bounce back from the spray and increase the air concentration in the breathing zone and hence increased potential inhalation and dermal exposure.
**Distance from the surface –** The distance between the surface and spray can was six inches representing the lower bound of ranges indicated on labels of each surface applied product.
**Room temperature –** Room temperature of 72° F was selected as the ambient temperature of a household or institutional setting where most of the aerosol products are used.
**Airflow –** Airflow rates vary from a mean of 0.6 ACH (Air Change per Hour) for household environments to 10-16 for institutional environments (EPA, 2001). For the preliminary exploratory study, an air flow of 0.6 ACH was selected to represent the more conservative scenario.

All products except the air freshener were sprayed against a hard surface for 10 seconds from a distance of 6 inches and height of about 5 feet at three different location in the in the room (three replicates). The air freshener was applied in the air at about 6 feet height. For each replicate (Spray location) samples for air concentration were taken concurrently using both OVS and IOM tubes (for comparison and subsequent selection). The IOM and OVS tubes are commonly used for collecting both volatiles and particulate matter in the breathing zone. Particle size distribution was determined using a RespiCon 3-stage Impactor with particle size cuts at 2.5, 10.0 and 100 μm (RespiCon™ Particle Sampler - Model 8522, TSI Inc.). Samples were collected by placing sampling tubes/samplers on a laboratory stand at about five feet height representing the breathing zone and position of the user. The sampling tubes/samplers were placed facing the wall where test material was applied, again simulating the exposure position of the user. For the air freshener the sampling stand was placed under the area where test substance was applied. The amount sprayed per unit time (10 seconds) was determined from four to five replicates per product by weight difference of the aerosol cans before and after application. All samples were collected using personal air pumps drawing 2 L/min and 3.2 L/min, for IOM/OVS and Respicon, respectively. All samples were analyzed for C14 ADBAC, the active ingredient (AI) common in the selected products using HPLC MS/MS. The environmental chamber was vented prior to each product use.

## 4.4 Results

- **Amount Dispensed Per Unit Time**

The average amount of each product (average of 4 to 5 samples) dispensed in 10 seconds is provided in Table 4. All products except for *Antibacterial Scrubbing Bubbles (hard surface)* were similar with regard to mean emission rate of total product. The emission rate for the *Stepan Aerosol SDAS (air Freshener*) was rather erratic. The results clearly indicate that the *Clorox Disinfecting Spray* (hard surface fine Spray) consistently emits the highest amount of AI per unit

time and represents the greatest potential for aerosol exposures on either a time or can-used basis. This is attributable to *Clorox Disinfecting Spray* having the highest percentage of the active ingredient compared to other products.

**Table 4: Amount of Product Dispensed per Unit Time**

| Product(Labeled Application Site) | Product Dispensed per 10 sec (g) | | | | | Mean (g) | Fraction C14 ADBAC | C14 ADBAC Dispensed (mg) |
|---|---|---|---|---|---|---|---|---|
| Clorox Disinfecting Spray (hard surface) | 13.6 | 13.3 | 13.8 | 13.8 | | 13.6 | 0.00126 | 17.2 |
| Antibacterial Scrubbing Bubbles (hard surface) | 18.8 | 18.9 | 18.7 | 18.8 | | 18.8 | 0.00066 | 12.4 |
| Lysol Brand Disinfecting Spray (soft surface) | 12.6 | 12.5 | 13.0 | 12.4 | | 12.6 | 0.00053 | 6.7 |
| Stepan Aerosol SDAS (air freshener) | 13.0 | 22.5 | 15.6 | 4.9 | 9.1 | 13.0 | 0.0006 | 7.8 |

- **Air Concentration (Amount of ADBAC)**

The 10 second spray duration was sufficient for detecting the test substance in the air samples. Results for the air concentration measurements are summarized in Table 5 and Figure 1. The results indicate that *Clorox Disinfecting Spray* (hard surface fine Spray) and *Stepan Aerosol SDAS* (Air Freshener) produced comparable air concentrations of the AI (14C ADBAC) and were higher than *Antibacterial Scrubbing Bubbles Bathroom Cleaner or* Lysol *Brand Disinfectant Spray* (soft surface spray). Of these four product types, the *Clorox Disinfecting Spray* and/or *Stepan Aerosol SDAS* represent the use pattern scenarios with potentially highest exposure and could be selected as surrogate for representing the exposure to use of aerosol products if one assumed that they are used for comparable durations.

- **Selection of Sampling Tube**

There was no apparent difference in air concentrations when the samples were taken by either the IOM or OVS tubes, suggesting that either of these commonly used air sampling tubes could be used in subsequent exposure monitoring. For the main study the OVS tubes were selected for collection of air samples to measure potentially inspirable air concentrations.

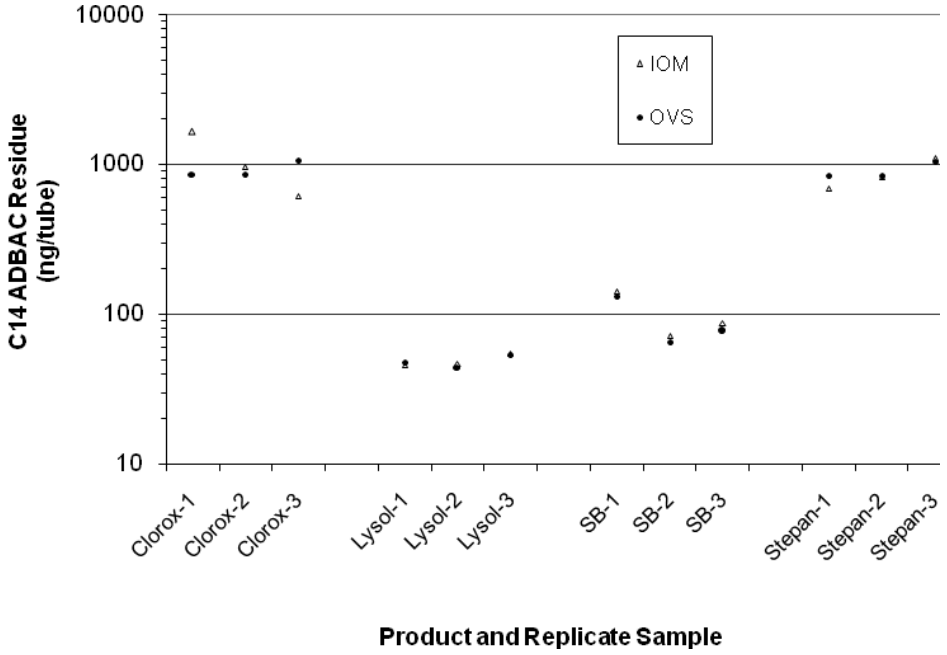
**Table 5: Comparison of C14 ADBAC Air Concentration Measurement Methods**

| Product | Sampling Tube | C14 ADBAC Residue (ng/tube) | | | | |
|---|---|---|---|---|---|---|
| | | Replicate Spray 1 | Replicate Spray 2 | Replicate Spray 3 | Arithmetic Mean | Geometric Mean |
| Clorox Disinfecting Spray (hard surface) | OVS | 865 | 862 | 1063 | 930 | 925 |
| | IOM | 1652 | 967 | 615 | 1078 | 994 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Antibacterial Scrubbing Bubbles (hard surface) | OVS | 132 | 65 | 77 | 91 | 87 |
| | IOM | 143 | 72 | 88 | 101 | 97 |
| Lysol Brand Disinfecting Spray (soft surface) | OVS | 48 | 44 | 54 | 49 | 48 |
| | IOM | 46 | 47 | 55 | 49 | 49 |
| Stepan Aerosol SDAS (air freshener) | OVS | 840 | 847 | 1043 | 910 | 905 |
| | IOM | 692 | 826 | 1113 | 877 | 860 |

The data from Table 5 have been summarized graphically in Figure 1.

**Figure 1: Relative Mass Trapped by Co-Located IOM and OVS Samplers**




- **Particle Size Distribution**

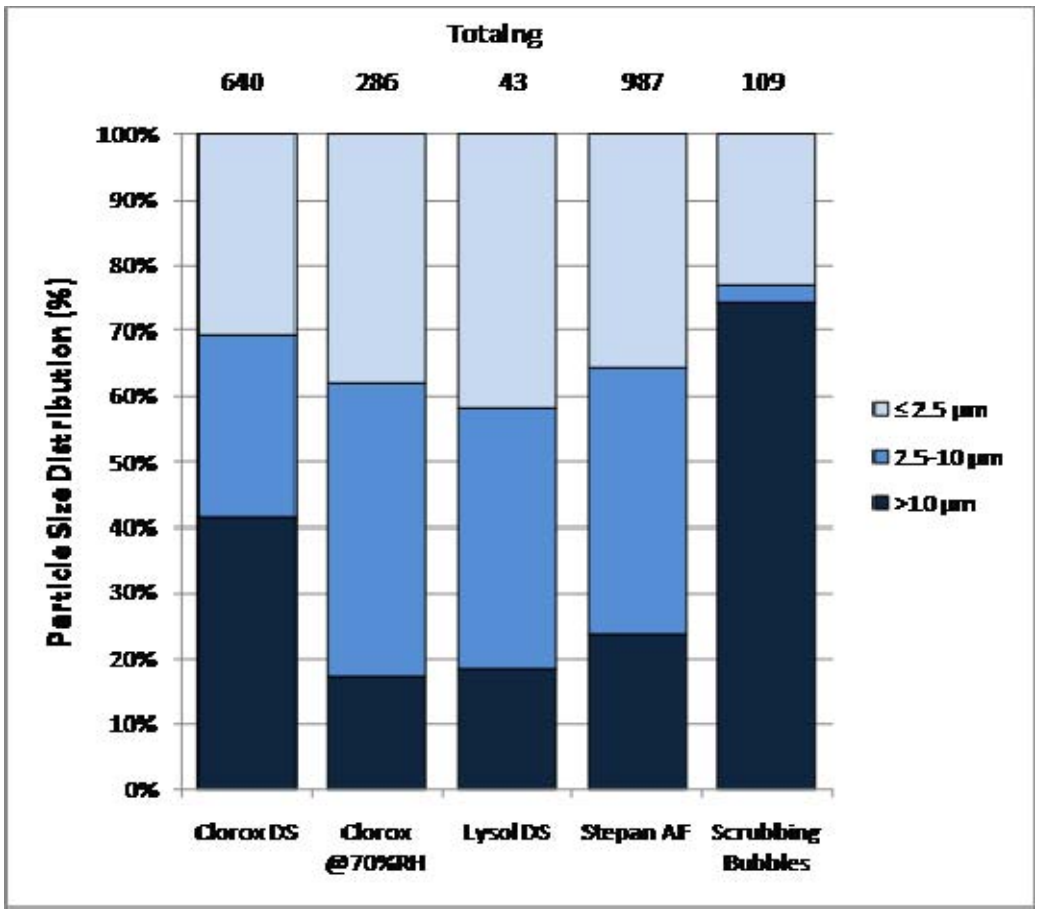
The particle size distribution results (Table 6 and Figure 2) show clear differences in the four product categories. The *Clorox Disinfectant Spray* (hard surface) had about 31% of the suspended particle mass ≤ 2.5 µm (respirable range) with total inhalable mass of 640 ng. The *Antibacterial Scrubbing Bubbles Bathroom Cleaner* (hard surface) had ~23 % of the mass with particle sizes ≤ 2.5 µm and total inhalable mass of 109 ng, indicating that large particles were impacted on the surface and converted into foam/bubbles and only a very small fraction was suspended in air. The *Lysol Brand Disinfectant Spray* (soft surface spray) produced the highest percentage of particles ≤2.5 µm (42%), but the total mass collected (43 ng) was the lowest representing the least potential for dermal and overall exposure. The inhalation exposure would be further reduced when the product is used on soft surfaces due to minimum bounce from the soft surface, typical of aerosol behavior (Pauluhn, 2003). The air freshener, *Stepan Aerosol SDAS* had the highest suspended inspirable particulate mass (987ng) and intermediate percentage (36%) of particle mass ≤ 2.5 µm. As discussed previously, the amount used is substantially lower and the overall exposure will be lower than the other products; the *Clorox Disinfectant Spray* represents the most conservative scenario. The 2.5 µm particle size is of particular interest, because this is the size targeted for delivery to laboratory animals during inhalation toxicity testing.

**Table 6: Respicon C14 ADBAC Residue in ng/stage (% on the stage)**

| Product | Respicon 2.5 µm Respirable | Respicon 10 µm Thoracic | Respicon 100 µm Inhalable | Total Inspirable (ng) |
|---|---|---|---|---|
| Clorox Disinfecting Spray (hard surface) | 196 (30.6) | 179 (28.0) | 265 (41.4) | 640 |
| Antibacterial Scrubbing Bubbles (hard surface) | 25 (23.0) | 3 (2.7) | 81 (74.3) | 109 |
| Lysol Brand Disinfecting Spray (soft surface) | 18 (41.9) | 17 (39.5) | 8 (18.6) | 43 |
| Stepan Aerosol SDAS (air freshener) | 351 (35.6) | 399 (40.4) | 237 (24.0) | 987 |

The IOM, OVS and Respicon samplers each captures approximately the same total mass of suspended particles in air. However, as a fraction of the total mass emitted from the spray can, they collect from ~0.001 to 0.01%. This collection selectivity reflects the nature of particles that remain suspended in air for more than a few seconds, and in this case specifically those particles that remain suspended after collision with a hard surface. It also reflects the fact that air collectors designed to sample inspirable particles don't pick up the vast majority of mass that is transiently in the air following emission from the nozzle. This also has very significant implications when comparing MMAD in Table 3, because different methodologies were employed for measuring particle size. Laser spectrometry allows characterization of the entire spectrum of particle sizes emitted into the air, while the Respicon sampler picks up a maximum particle size of 100 µm.

**Figure 2. Particle Size Distribution Captured by Respicon**



# 5 Conclusions

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.
The selected product would also meet objectives of the study and test material selection criteria, i.e.:

- Serve as surrogate for most aerosol use categories
- Use pattern represents high end exposure – a conservative scenario
- Use scenario covers most influential variables of exposure
    - Highest % of AI
    - Nozzle size of majority of the aerosol products
    - Particle size distribution representative of fine spray
    - Used for hard surface and confined spaces
- Having stable active ingredient
- Results can be extrapolated to most products on the market

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