

US EPA ARCHIVE DOCUMENT



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Dear Tim:

This Document summarizes changes to the aerosol study protocol following the October 20-21, 2009 HSRB meeting and December 16, 2009 HSRB final report. A revised protocol with track changes is attached. The changes made to the protocol fall into four categories: 1) changes in the study personnel; 2) changes to the study design; 3) changes in ethics sections; and 4) justification for separating monitoring activities between clusters from seven days to two days.

1. **Changes in Personnel**

Grayson/Eurofin personnel were replaced with the Golden Pacific Laboratories (GPL) personnel throughout the protocol.

2. **Changes in Study Design Sections**

In each of the following sections a) through d), HSRB comments are italicized followed by an explanation of how the AEATF has addressed them in a revised protocol.

a) *Sample Size and Analysis: Raw and descriptive data will be provided, but no statistical analyses have been planned. Sample size adequacy cannot be judged without a statistical analysis plan. Placing 18 subjects into three clusters of six each requires consideration of cluster effects, and may complicate analysis of the results. Assumed constants related to exposure to the active ingredient may also prove to be incorrect, and additional subjects may need to be enrolled.*

If the benchmark accuracy goal (i.e., $k=3$) is not met once the data are collected and analyzed, the AEATF II will, in consultation with regulatory agencies, determine the best course of action to take. This may mean the development of guidance for the use of these data that takes the increased imprecision of the estimates into account. It is possible that collection of additional clusters might be considered. See Data Analysis Section 12 E page 53.

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- b) *Application of Spray: The target number of cans sprayed in each location by each worker on each day could be specified better within the protocol. For example, does a worker need to continue spraying a room if the target application is met before completion of the room? Additional protocol clarifications needed include: addressing the issue of the interval between sampling at different sites (currently, it appears that no two monitoring events can occur within the same building within one week); clarifying the issue of using empty apartments rather than motel rooms; and clarifying the effect of exhaust vent effects on exposure, which could be different than indicated in the protocol.*

No more than 2 MEs per day could be monitored at a given site on a given day, and will depend upon the number of rooms available as well as on the number of canisters assigned. Rooms at a given site will only be used once per day. Subjects in the A, C, and F groups will be provided with half full canisters to easily fulfill the assigned amount without going over it. See Study Design Section 8B, page 26.

- c) *Setting the minimal spike to two to four times that of the limit of quantitation (LOQ; cf. AEATF II 2009b: 42, 46).*

This is covered in two sections. A table summarizing the LOQ (see below) was added Under Test Substance Section 7B, page 21.

Matrix	LOQ
Air Sampling Tubes	25 ng/tube
Hand Washes	1.0 ng/mL
Face/Neck Wipes	100 ng/sample
Inner Dosimeter Section	3.0 µg/sample
Outer Dosimeter Section	3.0 µg/sample
Respicon Fiberglass Filters	25 ng/filter

A second table (shown below) showing the 4X fortification levels was added under Field Recovery Evaluation Section 10H page 47.

Matrix	Fortification Level
Air Sampling Tubes	100 ng/sample and 2.0 µg/sample
Hand Washes	4.0 and 400 ng/mL
Face/Neck Wipes	400 ng/sample and 10 µg/sample
Inner Dosimeter Section	12 µg/sample and 1.0 mg/sample
Outer Dosimeter Section	12 µg/sample and 1.0 mg/sample
Respicon Fiberglass Filters	100 ng/filter and 2.0 µg/filter



- d) *Considering other variables that may influence the measurement of exposure, including whether the surface being treated is dry or wet at the time of the next spray application, and whether the applicant accidentally wiped the surface after spraying. Data accumulated during gross deviations from the protocol should also be excluded. Finally, the protocol should indicate that there will be a maximum of two workers on any given day in the same location.*

See Random Selection of Facilities as Monitoring. Section 8 B, page 26.

No more than 2 MEs per day could be monitored at a given site on a given day, and will depend upon the number of rooms available as well as on the number of canisters assigned. Rooms at a given site will only be used once per day.

See Assignment of Amount of Active Ingredient Handled to MEs. Section 8D, page 27.

The total number of qualified subjects will each be assigned a consecutive number, starting at AE1. The numbers will then be randomized using a research randomizer program accessible at the following internet website: <http://randomizer.org>. The first 24 numbers in the generated randomized list will determine the participating subjects, while the remaining subjects will be held as alternates, their order for potential entry into the study being determined by the randomization process. The 24 subjects will be split into three groups, each corresponding to the location of one of the three experimental sites. The first set of eight numbers (AE1-AE8, where AE indicates the randomized order list) will be grouped into location A, the second set of eight numbers (AE9-AE16) will be grouped into location B, and the third set of eight numbers (AE17-AE24) will be grouped into location C. There will be six different aerosol spraying durations for assigned monitoring events (MEs). Within each group of eight, the first six subjects will be assigned the durations listed under section 8.C in the protocol (AE1 1 to 1.5 canisters; AE2 1.5 to 2 canisters; AE3 2 to 2.5 canisters; AE4 2.5 to 3 canisters; AE5 3 to 3.5 canisters; AE6 3.5 to 4 canisters). The last two subjects in the group of eight will be considered as alternates and will be on hand if any subject does not show up. If additional subjects above the 24 initially selected are required, AE25 will be contacted followed by AE 26 and so on, until a total of 18 MEs are completed for the study.

Once the subjects have been randomized into three clusters, subjects from the first cluster will be scheduled into the study. Every attempt will be made to schedule two subjects per day. No more than two subjects will be monitored in one day. An example schedule could look as follows:

Day	ME	No. of Canisters	ME	No. of Canisters
1	AE6	3.5 to 4	AE1	1 to 1.5
2	AE5	3 to 3.5	AE2	1.5 to 2
3	AE4	2.5 to 3	AE3	2 to 2.5
4	AE7	alternate	AE8	Alternate



Every attempt will be made to schedule the subjects with the longest duration first. If this is not possible because of work or scheduling conflict, subjects with the longest MEs will be assigned to the earliest time slot available. If the subject with the longest ME cannot finish his or her application volume, subsequent subject with a shorter unfilled application volume will be asked to complete the longest ME. As long as the six subjects achieve the target spraying amount, the process is continued and six ME have been obtained one for each of the six strata. If this is not achieved, because two subjects ended up with the same spray amount, alternate subjects will be asked to participate in the study and fill the missing ME.

3. Changes in the Ethics Section

- a) *Possible subjects for this study may be undocumented immigrants. Recruitment materials should state that government-issued identification is necessary for enrollment in this study.*

The Principal Investigator or designee will check the potential subject's driver license or government-issued identification card to verify identity as required by California DPR. See Subject Recruitment, Section 9 ii, page 32.

- b) *A valid government-issued form of identification is necessary for enrollment. Volunteers who lack proper identification are excluded from study participation but no other action is taken, minimizing any social risks to undocumented workers from disclosure of their status to law-enforcement or immigration authorities.*

Volunteers who lack proper identification will not be enrolled in the study. No other action will be taken. Language added to the protocol. See Subject Recruitment, Section 9 ii, page 32.

- c) *The Board agrees with the EPA ethics review that the informed consent form should read: "We will pay for needed medical treatment that is not paid for by your own insurance or the insurance of a third party under which you are covered."*

The revised language now reads: AEATF will cover the cost of reasonable and appropriate medical attention for a study-related injury or illness that is not covered by your own insurance or insurance provided through your employer. This includes deductible costs and any out-of-pocket expenses, including co-payments you might have. The Study Director, in consultation with the on-site medical professional will decide if you have an illness or injury that is due to your participation in this study. See Appendix B, page 78.



- d) *As some possible subjects for this study may be undocumented immigrants, recruitment materials should more explicitly state that a valid government-issued form of identification is necessary for enrollment.*

The following was added to the recruitment flyer: subject must “have a valid photo ID.” See Subject Recruitment, Section 9 ii, page 32.

- e) *The protocol provides for use of a community notification flyer. However, one neglected community includes persons who might be staying in the hotels where the study is conducted. The flyer should be revised so that it communicates the goals of the study and risks to that group. These flyers, in both English and Spanish, should also be posted in locations so that the hotel guests are likely to see it. Alternatively, the researchers should consider conducting the research in areas away from hotel guests.*

A second ‘Notice to Hotel/Motel Guests’ flyer is now added under Community Involvement, Section 6 D, page 18 and Appendix H, page 127.

- f) *The exclusion criteria should be revised to eliminate some groups that might be at higher risk of physical harm but are not presently excluded. This might include subjects who might be immunosuppressed for a variety of reasons, those with severe diabetes, and those with other conditions that pose a health risk.*

Section added to protocol: (Under Exclusion Criteria, Section 9 A iii, page 35):

- Severe diabetes
- Immunologically suppressed (e.g. undergoing chemotherapy, transplant patients)

Added under Subject Self-Reporting Demographic Form, Appendix D, page 107:

Do you have any of the following conditions?

- | | | |
|--------------------------------------|------------------------------|-----------------------------|
| Moderate or severe asthma, emphysema | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Cardiovascular disease | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Severe diabetes | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Immunologically suppressed | <input type="checkbox"/> Yes | <input type="checkbox"/> No |



4. Justification for the separating monitoring activities between clusters from seven days to two days.

The seven day waiting period originally arose out of applications in agricultural settings which could be influenced by weather conditions and other outdoor settings.

Most antimicrobial exposure monitoring studies, including the aerosol study, will be conducted indoors and weather changes are not expected to have any type of impact on monitoring events. In addition, there are no specific parameters that would be expected to change significantly with time, two vs. seven days. Furthermore, based on professional judgment and the experience of the AEATF in mop and wipe studies, it is anticipated that any increase in “diversity” that may come with a seven day time span between clusters will have minimal to no impact on the variation estimate when compared to other factors such as new subjects or a new application scenario. In AEATF’s judgment, based on previous experience, it is much easier to sign up and retain subjects into a study with a shorter waiting period between enrollment and study participation. Thus, the Task Force proposes a minimum of two days between clusters as adequate time to get ready for monitoring the next cluster in more practical and cost effective manners.

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If you have any questions, please contact me at (703) 741-5637 or via email at has_shah@americanchemistry.com.

Sincerely,



Hasmukh Shah
Manager, AEATF

Cc: John Carley
Kelly Sherman

