UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

DATE: January 3, 2012

SUBJECT: Science Review of the AEATF II Aerosol Human Exposure Monitoring Study.

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This memorandum presents the EPA/OPP Antimicrobials Division (AD) science review of the human exposure aerosol study submitted by the Antimicrobial Exposure Assessment Task Force II (AEATF II). The dermal and inhalation exposure data as represented in this review are acceptable and, subject to the considerations described below, are recommended for use for pesticide handler exposure assessments.

EXECUTIVE SUMMARY

This document represents the USEPA, Office of Pesticides Program, Antimicrobials Division (AD) review of the Antimicrobial Exposure Assessment Task Force II (AEATF II) aerosol study. The aerosol study investigators monitored inhalation and dermal exposures to 18 workers spraying surfaces using a 19 ounce aerosol can. EPA confirms that the data meet the study design objective outlined in the AEATF II Governing Document and are considered the most reliable data for assessing exposures from spraying surfaces with an aerosol can. The reader is referred to Section 3.0 for a discussion on the data limitations and use of the data as surrogate.

EPA intends to use this AEATF II aerosol dataset instead of the Chemical Manufacturers Association (CMA) and/or the Pesticide Handlers Exposure Database (PHED) datasets to assess exposure for persons using an antimicrobial product while spraying surfaces with an aerosol can. The exposure data in the AEATF II aerosol scenario represent the application of an antimicrobial product pre-packaged in an aerosol can. The scenario does not cover the subsequent wiping of the aerosol spray solution. The potential exposure to the subsequent wiping of the sprayed solution can be determined by combining the results of this study with the results of the previously AEATF II conducted ready-to-use (RTU) wipe study. This aerosol study did not monitor the activity of wiping because there are some products that are labeled to be sprayed-on with no wiping.

Select summary statistics for the "unit exposures" normalized to pounds active ingredient handled are presented in Table 1 for inhalation exposure as well as for 3 clothing configurations. Each worker wore both inner and outer whole body dosimeters (WBD) that were sectioned and analyzed separately for each body part (e.g., lower leg, upper leg, lower arm, upper arm, etc). Therefore, the analyses of residues on the dosimeters worn by each individual worker allow for the estimation of dermal exposure for the following 3 clothing configurations:

(1) "Long-Long" or "Long Dermal"= long pants, long-sleeved shirt, and no gloves;
(2) "Long-Short" or "Long Short Dermal"= long pants, short-sleeved shirt, and no gloves; and
(3) "Short-Short" or "Short Dermal" = short pants, short-sleeved shirt, and no gloves.

For comparison, results from the earlier CMA and PHED studies for aerosols are also presented. It has been EPA's practice to use the PHED dataset for the aerosol can scenario rather than the CMA aerosol can data. The summary statistics reported in Table 1 for the AEATF II data are estimated using the lognormal mixed model while the CMA and PHED results are empirical estimates (Note: CMA results are in footnote "a" in Table 1).

Table 1. Unit Exposures: Aerosol Scenario				
Exposure Route	**Clothing**	**PHED[a]**	**AEATF II[b, c] (n=18)**	
		Arithmetic Mean	**Arithmetic Mean[d]**	**95th Percentile[e]**
Dermal (mg/lb ai)	Long pants/long-sleeves, no gloves	190 (n=15)	248 (185, 339)	552 (359, 845)
	Long pants/short-sleeves, shoes/socks, no gloves	Not Available	367 (287, 472)	735 (511, 1050)
	Short pants/short-sleeves, shoes/socks, no gloves	220 (n=15 hands, 30 body)	661 (537, 820)	1220 (894, 1670)
Inhalation (Total)	Breathing Zone (mg/lb ai) [f]	1.3 (n=15)	25.1 (19.8, 32.0)	49.4 (34.8, 69.8)
	Breathing Zone (mg/m^3/lb ai)	Not Available	60.3 (47.2, 77.6)	121 (84.1, 128)
Inhalation (100 µm)	Breathing Zone (mg/m^3/lb ai)	NA	48.1 (37.2, 63.0)	99.5 (67.9, 145)
Inhalation (10 µm)			25.5 (18.9, 35.1)	57.4 (37.0, 88.7)

[a] PHED data has been used to assess exposures to antimicrobial products packaged in aerosol cans. PHED data are based on an insecticide product which was sprayed as a crack and crevice treatment. As a comparison, the mean CMA exposure data for aerosols from applying the disinfectant in motels, dental offices, etc, using 19 oz cans (plus one 24 oz can) of a 0.1% ai product indicate the dermal UE (no glove scenario) of 144,000 mg/lb ai of which hand exposure was only 922 mg/lb ai (n=6) and inhalation UE of ~6,000 mg/lb ai (n=8; where all air samples were ND; LOD ranged from 0.294 to 74.8 mg/m^3 and sampling pumps ran from 1 to 26 minutes).

[b] AEATF II dermal UE includes corrections for removal efficiencies of 90.3% for hands and 89.4% for face/neck.

[c] Lower and upper 95% confidence intervals reported in "( )"; statistics are estimated using a variance component model accounting for correlation between measurements conducted within the same field study (i.e., measurements collected during the same time and at the same location). Additional model estimates (e.g., empirical and simple random sample assumptions) are described in Appendix A.

[d] Arithmetic Mean (AM) = GM * $\exp\{0.5*(\ln GSD)^2\}$

[e] 95th percentile = GM * $GSD^{1.645}$

[f] Inhalation (mg/lb ai) = (air conc (mg/m^3) / lb ai) * breathing rate (1 m^3/hour) * spray duration (hours/day)

The following important points with respect to these data are noted:

- The AEATF II data and associated unit exposures are considered superior to the existing aerosol datasets (i.e., CMA and PHED data). AEATF II efforts represented a well-designed, concerted process to collect reliable exposure data in a way that takes advantage of and incorporates a more robust statistical design, better analytical methods, and improved data handling techniques.

- The AEATF II study report containing dermal and inhalation exposure results are considered scientifically complete. No additional monitoring data are required at this time.

- The data are applicable for assessment of exposure to non-volatile pesticides. The cutoff for volatility is reviewed on a case-by-case basis (rule of thumb is that <E-4 mmHg @ 20° C is considered non-volatile).

- The statistical analysis provides evidence of direct proportionality (1:1) between dermal exposure and pounds of active ingredient (ai) handled (i.e., the confidence intervals for the slope of log exposure against log ai include 1 but not zero in Table 10 below), and the analysis shows that dermal exposure tends to increase with pounds of ai handled (AaiH) as described in Section 2.4 below. However, for inhalation exposure, the statistical analysis provides evidence against proportionality, although inhalation exposure tends to increase with pounds of ai handled (AaiH).

To assess the risks resulting from aerosol spray exposures, EPA will combine appropriate unit exposure (UE) values with chemical-specific inputs (e.g., maximum labeled application rates, dermal absorption rates, and toxicological endpoints of concern) and default inputs (e.g., high end area treated or volume applied) in the standard pesticide handler inhalation and/or dermal exposure algorithm: Potential dermal or inhalation exposure = [UE (mg/lb ai or mg/m^3/lb ai)] x [dermal absorption (%) if applicable] x [maximum label rate (lb ai/gallon or ounces)] x [volume (gallons or ounces)].

1.0 Background

The AEATF II is developing a database representing inhalation and dermal exposure during a number of antimicrobial handler scenarios. A scenario is defined as a pesticide handling task based on activity (e.g., application) and equipment type (e.g., aerosol cans, ready-to-use wipes, mop & bucket, pressure treatment of wood facilities, painting, etc). The AEATF II is monitoring both inner and outer dosimeters which will allow the EPA to estimate exposures to various clothing configurations (e.g., long pants, long-sleeved shirt or long pants, short-sleeved shirt or short pants, short-sleeved shirts, plus shoes, socks, and no gloves). Prior to conducting intentional exposure studies in humans, the protocols are reviewed by the Human Studies Review Board (HSRB). The HSRB reviewed this aerosol exposure study protocol in October 2009.

1.1 Aerosol Scenario Defined

The aerosol scenario in this study is defined as spraying various horizontal and vertical surfaces such as sinks, shower stalls, walls, etc in hotel rooms using a hand-held pressurized aerosol can containing a formulated antimicrobial product. The application is a spray and leave-on; no wiping of the treated surfaces occurred. Subjects sprayed as they normally would do. Subjects wore whole body dosimeters (WBD) underneath long-sleeved shirts, long pants, and no gloves (plus a personal air sampler). The conditions under which the study participants handle the pesticide as they are monitored are referred to as the scenario. Both inner and outer dosimeters were worn by the monitored study participants, and both inner and outer dosimeters were analyzed for residues.

1.2 Study Objective

The AEATF II's study objective is to monitor inhalation and dermal exposures to be used as inputs in exposure algorithms to predict future exposures to persons spraying surfaces with an antimicrobial product packaged in an aerosol can. Dermal and inhalation exposure monitoring was conducted while study participants sprayed various surfaces (walls, sinks, toilets, etc) for use in exposure assessments, as "unit exposures".

"Unit exposure" (UE) is defined as the expected external chemical exposure an individual may receive (i.e., "to-the-skin" or "in the breathing zone") per weight-unit of chemical handled and is the default data format used in pesticide handler exposure assessments. Mathematically, unit exposures are expressed as "handler" exposure normalized by the amount active ingredient handled by participants in scenario-specific exposure studies (e.g., mg exposure/lb ai handled). EPA uses these UEs generically to estimate exposure for other chemicals having the same or different application rates.

Criteria for determining when a scenario is considered complete and operative have been developed (Christian 2007). Outlined in the AEATF II Governing Document, the criteria can be briefly summarized as follows:

- The AEATF II's objective for this study design is to be 95% confident that key statistics of normalized dermal exposure are accurate within 3-fold. Specifically, the upper and lower 95% confidence limits should be no more than 3-fold (K=3) higher or lower than the estimates for each the geometric mean, arithmetic mean, and 95th percentile dermal unit exposures. To meet this objective AEATF II proposed an experimental design with a 3 cluster by 6 monitoring events (MEs).

- EPA also plans to use the data to evaluate the presumption of proportionality between exposure and amount of active ingredient handled. EPA used a log-log regression test to distinguish complete proportionality (slope = 1) from complete independence (slope = 0), with 80% statistical power, achieved when the width of the 95th confidence interval of the regression slope is 1.4 or less.

1.3 Protocol Modifications, Amendments, and Deviations

1.3.1 Protocol Modifications Subsequent to EPA/HSRB Review

EPA required one science-based modification to the aerosol protocol (EPA 2009). The EPA review of the protocol noted that the AEATF II needs *"…to indicate the course of action if the benchmark accuracy goals (i.e., k=3) are not achieved."* The AEATF II responded at the time of the protocol review that they *"…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."*

The HSRB provided written discussion on a number of *"…perceived inadequacies…"* of the aerosol review. Shah (2010a and 2010b) responded to the HSRB inquiries on the behalf of the AEATF II in letters to EPA (see Appendix B for letters). The HSRB issues and EPA responses and discussion are summarized below:

- ***Use of the results*** – The HSRB noted that *"…other variables can affect rates of exposure, including different nozzle sizes, spray and ejection rates, the size of the particles generated, and the generation of nonvolatile active ingredients."* The HSRB comment also stated it is unclear if occupational exposures could be used to estimate exposures to consumers.

  EPA acknowledges that ideally it would be more accurate to have performance data on all types of antimicrobial products packaged in aerosol cans (e.g., particle sizes generated, ejection rates, etc). However, EPA agrees with the AEATF II's pre-testing provided in the aerosol protocol, along with the fact that individual applicator behaviors while applying will equally affect exposure such that it may confound the spray nozzle information, and concludes they are sufficient rationales to accept the use of the product selected. If data generated in the future provide additional information about the effects of ejection rates on exposure, additional limitations can be considered by comparing ejection rates measured in this study (~1 gram/second). To directly compare and evaluate occupational exposures to those of consumers, most of the scenarios to be monitored by

the AEATF II would need to be based on two studies. If a sufficient rationale is available to suggest logical differences in exposures experienced by the two populations, the need for two studies could be rationalized. However, for the aerosol scenario, spraying a pre-packaged aerosol can products onto surfaces does not inherently suggest differences (both populations routinely use this device and no training is provided). Moreover, reading through the study observations (Appendix L starting on page 474 of the study report) supports the idea that workers are not more skilled or careful compared to a consumer when applying a product from an aerosol can.

- ***Sample size & analysis*** – The HSRB noted that *"…no statistical analyses have been planned. Sample size adequacy cannot be judged without a statistical analysis plan. …additional subjects may need to be enrolled."*

  EPA agreed with the AEATF II Governing Document (ACC, 2011) which provides the following description of sample size adequacy: *"In an ideal situation the determination of sample size would be based on an objective statistical approach. This approach would leverage existing data to estimate the variability that must be accounted for to specified confidence requirements. Such an approach was used for the initial few studies of the AEATF II. However, as the AEATF II began to work on implementing additional studies it became evident that either such data did not exist or that it was not relevant to current practices and methodologies. Attempts to use existing data from poor quality or only marginally relevant studies produced sample sizes that were logistically impractical to implement and unaffordable for the task force to complete. There is also concern that post collection analysis of newly collected data would indicate more samples had been collected than required to meet the confidence requirements. This would imply that subjects had been unnecessarily used and exposed in the data collection process.*

  As a result, the determination was made that a new, relevant, high quality "base set" of data needs to be created prior to applying a more statistically rigorous design process. To inform this approach, the AEATF II is relying on existing EPA guidelines on exposure studies (Series 875 - Occupational and Residential Exposure Test Guidelines). These guidelines call for essentially three groups of five observations per group. It is the intention of the AEATF II to collect 15 to 20 MEs per scenario to create a base-case data set. The exact number will depend on the number of levels of key factors that are considered likely to impact exposure.

  It is anticipated in some cases that after the base case is collected no additional data collection will be necessary as the data will be sufficient to meet regulatory needs. In other situations, the task force, in consultation with regulatory agencies, may determine that additional data are required. At that point, more rigorous statistical methods as used in the first few studies, and outlined in Appendix E [of the Governing Document], *may be applied. The exact steps will be determined after this joint evaluation, and with consideration for how the data will be used."*

  EPA has analyzed the aerosol scenario to see if the data meet the relative 3-fold accuracy goal (i.e., K = 3) for determining sample size. See Section 2.4 below for details of the analysis of the relative 3-fold accuracy. In summary, the aerosol data met the goal of

relative 3-fold accuracy for all 3 clothing configurations (Long Dermal, Short Dermal, Long Short Dermal) and for the inhalation exposure (mg/m^3/lb ai and mg/lb ai). On this basis, EPA concludes that the sample sizes used were adequate according to the previously established criteria.

- ***Application of spray*** – The HSRB noted that the researchers need to better clarify the sampling design aspects of the spraying (e.g., will the subjects need to keep spraying in a room if the room has been treated before the target number of cans are sprayed? What is the sampling interval between sites? Empty apartments or motel rooms? Effect of exhaust vents on exposure?

  The AEATF II provided the following responses in a letter submitted by Shah (2010a): "*We will clarify in the protocol the target numbers of cans sprayed in each location by each worker on each day. Workers will be given full cans as well as half full cans, as specified in the protocol. A worker does NOT need to continue spraying a room if the target application is met. Two monitoring events can occur within the same building, but not the same room within ONE DAY. The next day the same room could be used. Regarding the use of apartments rather than motel rooms, we have surveyed the Fresno area and have found a number of motels with full kitchens. We will be using hotels/motels exclusively for the study and will not be using apartments.*" A description of the effect of exhaust vents on exposure is not apparent in the AEATF II's documentation. EPA notes that the air exchange rates are 0.6 to 2 ACH.

- ***QA/QC improvements*** – The HSRB indicated that more thought was needed on the air monitoring methods such as equipment used, differences in orifice diameters and flow rates, because these parameters could affect aerosol collection efficiencies. HSRB also noted that minimal fortification levels should be increased to 2x to 4x the LOQ. Other variables were also mentioned by the HSRB: are surfaces wet or dry during treatment? Did subjects accidentally wipe surfaces as this action is not part of this study? Limit the number of workers to 2 for any given day in the same location.

  In response to the HSRB discussions the following EPA discussions are noted. The available literature studies indicate that the Respicon matches the thoracic and respirable sampling conventions fairly closely while significantly under sampling the inhalable convention. These studies generally suggest that the under sampling is consistent and can be addressed by using correction factors that range from 1.5 to 1.8. The reader is referred to Appendix C for further details of the literature (summary) and Section 4.0 (see Figure 10 for a comparison of the results). The minimal field fortification levels were modified by the AEATF II in the study; increased to 4x the LOQ as suggested. The surfaces were dry prior to the application events. The study observations did not make note of any subjects accidentally wiping surfaces as part of a routine for spray & wipe (as opposed to spray & leave-on). Finally, as evident in Tables 7, 8, and 9 of the study report (pages 116, 117, 118) there were no more than 2 MEs per sampling date.

1.3.2 Protocol Amendments

The study report (page 103) lists 4 protocol amendments. The amendments included the offering to the subjects the voluntary use of respirators; change of study dates; change in personnel including the Study Director/Principal Investigator and QA personnel; included a GLP analysis of the test substance and formulated product; lengthened the storage stability time from 6 to 18 months; revisions to the appendices dealing with recruiting subjects and informed consent form; revised procedures for removing subjects' socks; and revised sponsors contact information (office location move).

1.3.3 Protocol Deviations

A total of 8 protocol, 2 method, and 8 SOP deviations were noted in the study (study report pages 103-104). The deviations included, but not limited to, order in which socks were removed from subjects, subject in "fair" health was enrolled but not selected when the criteria was "good" health; not all of the field fortification samples were analyzed; order in which cans were sprayed for two MEs were switched; some of the laboratory QC samples were out of the range; extraction solvent expired (date) but used for some dosimeters; etc. For a detailed description of the protocol deviations the reader is referred to the study report. EPA accepts the study author's conclusion that these deviations did not adversely affect the outcome of the study.

1.4 Material & Methods

The following is a summary of the field aspects of the study:

- ***Study Location:*** The aerosol spray study was conducted in Fresno County, CA. Each of the 3 clusters was a different building. The buildings were all hotels (Marriott, Piccadilly Inn, and Hilton). Photos and schematics of the hotels and rooms are located in Appendices I, J, and K starting on page 460 of the study report.

- ***Pesticide Tested:*** The test substance monitored was n-alkyl dimethyl benzyl ammonium chloride (ADBAC), CAS number 68424-85-1. ADBAC was formulated in a product known as Clorox Commercial Solutions Clorox Disinfecting Spray (EPA Reg No. 67619-3). This product also contained 3 other Quats, DDAC, ODAC, and DODAC. ADBAC, DDAC, ODAC, and DODAC are in Clorox Disinfecting Spray at 0.252%, 0.0945%, 0.189%, 0.0945%, respectively. The C14 ADBAC was quantified in the analytical phase of the study. ADBAC consists of 50% C14, 40% C12, and 10% C16.

- ***Test System:*** The aerosol cans each contained 19 ounces (538 grams) of product (page 36 of study report). The discharge rates of the cans were measured for both batches of products using triplicate cans from each batch and each can sprayed three times for 10 seconds. The discharge rates averaged 0.991 and 1.19 g/second for the two batches of products. A photo of the aerosol product is presented below in Figure 1.

Figure 1. Aerosol Can Used In Study.

- ***Sequence of Events:*** A table listing the chronological order of key events for the study (e.g., test site selection, IIRB approval, first subject enrolled, monitoring dates, etc) is reported on pages 107-108 of the study report.

- ***Sample Size:*** The study consisted of 3 clusters and 6 MEs per cluster for a total of 18 monitoring events (ME). Each ME is a different subject.

- ***Treatment Solutions:*** The aerosol cans were obtained pre-packaged, no dilution by the researcher was necessary. The nominal percent active ingredient for the C14 ADBAC is 0.126%. The measured percent of C14 ADBAC in the two batches of products was 0.124% and 0.104%. Nominal amounts of C14 ADBAC sprayed (i.e., 0.124%) were used in normalizing the exposures from the first batch. Actual amounts of C14 ADBAC sprayed (i.e., 0.104%) were used in normalizing the exposures from the second batch.

- ***Duration & AaiH:*** For each of the 3 clusters, the MEs were randomly assigned to 1 of the 6 purposively selected number of cans sprayed. The pre-determined number of cans sprayed were:

- 1 to 1.5 cans
- 1.5 to 2 cans
- 2 to 2.5 cans
- 2.5 to 3 cans
- 3 to 3.5 cans
- 3.5 to 4 cans

The total sampling times for Cluster 1 ranged from 32 to 119 minutes; for Cluster 2 times ranged from 42 to 125 minutes; and for Cluster 3 times ranged from 25 to 115 minutes. The actual time spent spraying (i.e., finger on the nozzle) was measured with a stop watch and recorded. The sampling time included movement of the subject within the room, moving from one room to the next, changing cans, breaks, etc. The sampling duration was used to calculate the volume of air sampled (m^3) and the corresponding air concentration (mg/m^3). The amount of active ingredient (AaiH) sprayed onto surfaces was measured by weighing the cans prior to and subsequent to the monitoring event. The AaiH for Cluster 1 ranged from 704 to 2400 mg; for Cluster 2 it ranged from 613 to 2000 mg; and for Cluster 3 it ranged from 577 to 2010 mg. The AaiH as well as the spraying times (sampling and spraying) for individual MEs are reported in Table 2 below.

- ***Spraying Procedures***: Appendix L on pages 474 to 507 of the study report records the observation notes taken during each ME. The workers were generally allowed to spray as they would normally do. Note: In Cluster 2 subject number AE4 was told to lighten up the spray pattern by the study director (page 488 of study report). Typical surfaces sprayed included countertops, railings, shelving, tile walls, sinks, appliances, toilets and tubs, and mirrors. Procedures/observations were that the subjects would shake the spray can and spray, roughly 6 to 12 inches above the various surfaces using random/erratic spray patterns, zig-zag patterns, from left to right, and from top to bottom. Subjects used a light to heavy spray pattern, sometimes until surfaces were visibly dripping wet and at other times not uniformly wet.

- ***Environmental Conditions*:** Environmental conditions (humidity and temperature) are reported for the MEs on pages 116 to 118 of the study report. The humidity averaged in the 50% range. Temperatures averaged in the low 70º F range. The heating ventilation air conditioning (HVAC) system descriptions such as total cubic feet per minute (CFM), fresh air CFM, room volumes, air changes per hour (ACH), etc are reported on pages 119 and 120 of study report. ACH ranged from 0.6 to 2.0. Lighting levels were not measured.

2.0 Results

2.1 QA/QC Recovery Results

Controls: The non-fortified field and laboratory control samples were all less than the limit of quantification (LOQ), except for one sample, which indicates no background contamination. The exception was for one field control sample in Cluster 3 for the outer dosimeter. This control

sample indicated 38.2 µg/sample. The LOQs for the various matrices are air sampling tubes 25 ng/sample, neck/face wipe 100 ng/sample, WBD sections 3 µg/sample, and hand wash 0.05 µg/sample (1.0 ng/mL).

Laboratory Recoveries: Most of the concurrent laboratory recovery values range within 70 to 120 percent. Exceptions outside of this range include 3 low level fortifications of 131, 136, and 66.7 percent for face/neck, outer dosimeter, and outer dosimeter, respectively. A summary of the overall concurrent laboratory recovery samples, for each monitoring matrix, by cluster, is reported in the study report starting on page 70 (individual recovery values can be viewed starting on page 122). The mean recoveries for all matrices are approximately in the 90 to 100 percent range.

Field Recoveries: Most of the individual field fortified recovery values range within 70 to 120 percent. Exceptions include 2 low level fortifications of 757 and 295 percent for the outer dosimeters in Cluster 3 (see pages 88 and 158 of study report). Both of these values were considered to be outliers and not used for corrections or reported in mean recoveries based on the laboratories SOPs. According to the study report (page 88), *"The Study Director determined that these recoveries did not impact the study as the residues in the subject outer dosimeters in these sets were 9 to 166 times higher than the low fortification level."* A summary of the overall field fortified recovery samples, for each monitoring matrix, by cluster, is reported starting on page 73 of the study report (individual recovery values can be viewed starting on page 128). The mean recoveries for all matrices are approximately in the 90 percent range. All exposure/field matrices were corrected for the field fortified recovery results.

2.2 Calculating Unit Exposures

Dermal Unit Exposure: Dermal exposure is measured using 100% cotton inner and outer whole body dosimeters (WBD). The inner WBDs were worn underneath normal work clothing (i.e., long-sleeved shirt and long pants). The normal work clothing worn over the inner WBDs were also analyzed and reported as outer dosimeters. In addition, dermal exposures also included hand washes (collected at the end of the day and during breaks), and face/neck wipes. Because the subjects wore respirators, the results of the face wipes were corrected for the area covered by the respirator (1.43 correction factor). The inner and outer WBDs are sectioned and analyzed by body part (i.e., upper and lower arms, front and rear torso, and upper and lower legs). All of the inner WBD sections were analyzed because all of the outer dosimeter sections tested above the LOQ. All samples are adjusted as appropriate according to recovery results from field fortification samples.

Dermal exposures to the hands and face/neck are also corrected for sampling efficiency (see study report pages 61 to 63 for equations). A removal efficiency study (previously conducted study purchased by the AEATF II) for wipes (4x4 inch 6-ply dressing sponges, moistened with 5 mL isopropanol) was performed using the test substance, alkyl dimethyl benzyl ammonium, as the saccharinate salt (ADBAS, CAS 39387-42-3) (Boatwright 2008, MRID 48656201). The hand wipe removal efficiency for ADBAS is 88 ± 1.71% for the low fortification level (70 µg) and 90.5 ± 3.88% for the high fortification level (1,300 µg). In the second hand removal efficiency study for DDAC (cited in previous AEATF II studies) showed a

recovery efficiency of 90.3%. The hand measurements in this aerosol study were corrected for the 90.3% DDAC removal efficiency while the face/neck wipes were corrected using the results of the low level fortification for the ADBAS wipe efficiency. Although the ADBAS study reports the recovery efficiency as 88.2%, a value of 89.4% was cited in the aerosol study and used to correct the samples. See Section 3.0 below for further discussion on the limitations of the removal efficiency studies.

Total dermal exposure is calculated by summing exposure across all body parts for each individual monitored. The following WBD sections are summed to calculate the clothing configuration of long pants, long-sleeved shirts (Long-Long) plus face/neck wash and hand wash:

- inner lower and inner upper arms,
- inner front and inner rear torso, and
- inner lower and inner upper legs.

The following WBD sections are summed to calculate the clothing configuration of long pants, short-sleeved shirts (Long-Short) plus face/neck wash and hand wash:

- outer and inner lower arm,
- inner upper arm,
- inner front and inner rear torso, and
- inner lower and inner upper leg.

The following WBD sections are summed to calculate the clothing configuration of short pants, short-sleeved shirts (Short-Short) plus face/neck wash and hand wash:

- outer and inner lower arm,
- inner upper arm,
- inner front and inner rear torso,
- inner upper leg, and
- inner and outer lower leg.

Dermal unit exposures (i.e., mg/lb ai handled) are calculated by dividing the summed total exposure by the amount of active ingredient handled. The AEATF II's study report normalized the dermal exposures by milligrams (mg) of active ingredient applied. EPA recalculated the exposures and expressed the results as mg/lb ai applied. EPA prefers the normalization by pounds to coincide with the English units reported on pesticide labels (e.g., pounds, ounces).

Inhalation Exposure: Inhalation exposure is measured using a personal air sampling pump and an OSHA Versatile Sampler (OVS) tubes with a separate pump that was used to run the Respicon Particle Sampler. The OVS tube was attached to the worker's collar to continuously sample air at a target rate of 2.0 Lpm from the breathing zone while the Respicon Particle Sampler (3.1 Lpm) was physically attached to the tube (both samplers were in the breathing zone). Collected residue, per standard practice, is adjusted for recovery from field fortification samples.

The results from the OVS tubes are reported herein as the "total" air concentration monitored (i.e., no sizing of particles). The OVS tube collects all particles that could physically deposit on the tube when facing downwards with air drawn in by the pump (mimicking nostrils). The results of the Respicon Particle Sampler are reported as air concentrations with 50 percent cut size diameter of 100 µm, 10 µm, and 2.5 µm. As per the Respicon sampler's brochure, http://www.ajabrams.com/pdf/tsi/resp_bro.pdf, the following was used by EPA to report/calculate the air concentration results for the inhalable, thoracic, and respirable sized particulates:

- Inhalable (100 µm) = results of 100 µm + 10 µm + 2.5 µm filters;
- Thoracic (10 µm) = results of 10 µm + 2.5 µm filters;
- Respirable (2.5 µm) = results of 2.5 µm filter.

Inhalation unit exposures (i.e., mg/m^3/lb ai handled) are calculated by dividing the air concentrations by the amount of ai handled. When the need arises for the unit inhalation exposures to be expressed in units of mg/lb ai (e.g., when assessing inhalation risks using an oral toxicological endpoint) the inhalation daily exposure is calculated as the (air conc (mg/m^3) / lb ai) * breathing rate (1 m^3/hour) * aerosol spray duration (hours/day).

2.3 Dermal and Inhalation Exposure Results

Results -- A summary of the dermal results of the 18 MEs is presented in Table 2 for the clothing configurations of long pants and long sleeved-shirts (Long-Long), long pants and short-sleeved shirts (Long-Short), and short pants and short-sleeved shirts (Short-Short). Table 3 reports the results for the inhalation monitoring. These tables report the results for each individual worker along with empirical statistical summaries of each cluster and overall exposures. **Note:** The recommended unit exposures in this review are based on the results of the lognormal mixed model, not the empirical summaries provided in Tables 2 and 3. The individual ME results are reported for others to analyze (if desired) and because the empirical results are easily understood.

Appendix A provides statistical models to estimate the unit exposure summary statistics, including:

- Empirical simple random sampling model (see Appendix A, Tables 1 and 2);
- Lognormal simple random sampling model (see Appendix A, Tables 4 through 11); and
- Lognormal mixed model (see Appendix A, Table 3 for a summary, and Appendix A, Tables 4 through 11 for detailed results).

The results of the lognormal mixed model have been selected to best represent the summary statistics for the unit exposures (for summary results of recommended unit exposures see Table 1 above, which is taken from Appendix A, Table 3). For a detailed discussion of the lognormal mixed model calculations and results (along with a discussion of the HSRB-suggested quadratic models) the reader is referred to Appendix A.

Observations -- This aerosol study includes the recorded individual participant activities by observers. The study report indicates… "*There were always three to four study personnel following the subject during a given monitoring event",* with one being the *"observer"* (page 41 of study report). Detailed observations recorded during each ME capturing the notable events that occurred during the aerosol can applications can be viewed in the study report's Appendix L starting on page 474. Although a review of these observations indicate that subjects occasionally touched or brushed against treated surfaces or had overspray near body (e.g., page 478 of study report) or wiped hands on body (e.g., page 486, 492), these types of exposures are expected based on the task and are not considered outliers in the data. The following observations are highlighted:

- Cluster 2, AE3 – This subject received the highest hand exposure in the study (571 mg/lb ai). According to the observations recorded (page 486 of study report), *"…liquid is observed pooling on subject's spray hand and on spray nozzle of can; possibly due to subject's finger or can malfunction."*

- Cluster 1, AE18 – This subject received the highest dermal exposure in the study (850, 953, and 1179 mg/lb ai for Long-Long, Long-Short, and Short-Short, respectively). See Table 2 below for a comparison of these results to the other MEs. The observation notes for AE18 (page 479 of study report) indicate that this subject *"…stood close to surfaces with possible overspray onto self; stands in bathtub to spray; sprays toward self; crouches down and may have over sprayed on lower pants; leans on edge of counter that was already sprayed; sprays on wall over head while in the shower;"* etc. These behaviors may have contributed to the higher exposure. However, none of these behaviors appear to be grossly negligent. It is of interest to note that 3 of the 6 inner WBD sections are higher than the corresponding outer WBD. This is perplexing and did not happen in any of the other MEs. The study authors surmised that the subject had residues on their skin prior to the study, perhaps by bathing in a product containing ADBAC (page 24 of study report). EPA is not aware of any ADBAC products for bathing. One other possible explanation for the inner residues greater than the outer residues (for the upper arm, front torso, and back torso) is that the subject sprayed overhead and that spray may have settled down around the inside of the collar getting more residues on these inner WBD sections. This ME is not considered an outlier in the analysis. Nonetheless, EPA ran the models again without subject AE18 and the resulting unit exposures did not change more than ~10 percent.

Impact of Non-detects -- All of the inhalation monitors, hand samples, and dermal outer WBD sections were above the LOQ. The only non detect samples monitored (other than the controls) were for ~13 percent of the inner WBD sections (i.e., 14 of the 108 inner WBD samples were non detect). Samples with results less than the limit of quantification (LOQ) are included in the calculation of total exposure as ½ LOQ. Since the number of non-detects was small, and since all of those non-detect inner dosimeter values were at least a factor of 10 lower than the unusually high inner dosimeter values for subject AE18 mentioned above, the impact of the non-detects is negligible.

Table 2. Aerosol: Summary (Empirical) of Dermal Monitoring Results – Various Clothing Configurations and No Glove Scenario.

Cluster	Subject	AaiH (lb)	Surface Area (sq ft)	Time (min) Sampling and [Spraying]	Hands Only (mg/ lb AI)	Dermal Unit Exposures (mg/lb ai)		
						Long-Long	Long-Short	Short-Short
1	AE2	0.001552	707	32 [17]	122	177	261	411
	AE5	0.002403	1184	57 [29]	54.1	88.3	142	248
	AE33	0.002734	1673	63 [25]	259	345	443	837
	AE18	0.003219	410	52 [28]	178	850	953	1179
	AE22	0.004674	2419	112 [43]	75.7	97.5	150	325
	AE29	0.005291	2146	119 [79]	117	157	250	471
	Mean	**0.003312**	**1423**	**73 [37]**	**134**	**286**	**366**	**579**
	Std	**0.001417**	**797**	**35[22]**	**74.4**	**291**	**307**	**358**
2	AE3	0.001351	731	48 [13]	571	606	688	992
	AE27	0.002099	1014	42 [16]	143	229	399	742
	AE4	0.002646	1084	46 [21]	155	253	404	844
	AE32	0.003439	1422	68 [28]	60.2	173	249	479
	AE10	0.003858	1706	108 [44]	128	182	272	542
	AE30	0.004409	2408	128 [38]	121	249	430	780
	Mean	**0.002967**	**1394**	**73 [27]**	**196**	**282**	**407**	**730**
	Std	**0.001146**	**601**	**35 [13]**	**187**	**162**	**157**	**191**
3	AE9	0.001272	417	25 [9]	86.5	140	249	492
	AE21	0.002097	716	41 [14]	54.4	100	183	351
	AE24	0.002513	848	55 [21]	131	301	477	818
	AE17	0.003219	1115	64 [22]	105	204	380	811
	AE12	0.004145	1618	86 [29]	81.8	136	242	555
	AE28	0.004431	1459	115 [42]	174	240	412	884
	Mean	**0.002946**	**1029**	**64 [23]**	**105**	**187**	**324**	**652**
	Std	**0.001219**	**457**	**32 [11]**	**42.1**	**75.6**	**115**	**216**
Overall	Mean	0.003075	1282	70 [29]	145	252	366	653
	Std	0.001201	623	32 [16]	118	191	200	257
	Median	0.002976	1150	60 [27]	122	193	326	648
	GeoMean	0.002836	1132	63 [25]	121	208	324	602
	95th %le	0.004766	2410	120 [49]	306	643	728	1020

Table 3. Aerosol: Summary (Empirical) of Inhalation Monitoring Results.

Cluster	Subject	AaiH (lb)	Sampling Time (min)	Air Concentration as Measured in Field		Air Concentration Normalized by AaiH ((mg/m3)/lb AI)			
				Total (mg/m3)	<100 um (mg/m3)	Total	<100 µm	<10 µm	<2.5 µm
1	AE2	0.001552	32	0.128	0.143	82.5	92.1	48.4	17.0
	AE5	0.002403	57	0.124	0.126	51.6	52.4	27.6	8.4
	AE33	0.002734	63	0.122	0.095	44.6	34.7	12.9	5.2
	AE18	0.003219	52	0.294	0.284	91.3	88.2	30.2	14.2
	AE22	0.004674	112	0.100	0.096	21.4	20.6	11.5	7.5
	AE29	0.005291	119	0.153	0.129	28.9	24.4	15.8	8.5
	Mean	**0.003312**	**73**	**0.154**	**0.146**	**53.4**	**52.1**	**24.4**	**10.1**
	Std	**0.001417**	**35**	**0.071**	**0.070**	**28.2**	**31.5**	**14.1**	**4.47**
2	AE3	0.001351	48	0.043	0.056	31.4	41.1	27.7	10.8
	AE27	0.002099	42	0.118	0.089	56.2	42.5	27.6	13.0
	AE4	0.002646	46	0.302	0.221	114	83.5	61.0	25.8
	AE32	0.003439	68	0.202	0.124	58.7	36.1	17.1	7.97
	AE10	0.003858	108	0.188	0.104	48.7	27.0	9.65	4.18
	AE30	0.004409	125	0.103	0.066	23.4	14.9	7.48	2.98
	Mean	**0.002967**	**73**	**0.159**	**0.110**	**55.4**	**40.8**	**25.1**	**10.8**
	Std	**0.001146**	**35**	**0.091**	**0.060**	**32.0**	**23.3**	**19.6**	**8.29**
3	AE9	0.001272	25	0.145	0.116	114	91.2	57.4	36.8
	AE21	0.002097	41	0.122	0.102	58.2	48.7	17.0	4.52
	AE24	0.002513	55	0.174	0.108	69.2	43.0	14.4	6.19
	AE17	0.003219	64	0.269	0.175	83.6	54.4	36.4	15.1
	AE12	0.004145	86	0.169	0.121	40.8	29.2	18.7	9.90
	AE28	0.004431	115	0.232	0.146	52.4	32.9	15.5	4.48
	Mean	**0.002946**	**64**	**0.185**	**0.128**	**69.7**	**49.9**	**26.6**	**12.8**
	Std	**0.001219**	**32**	**0.055**	**0.028**	**26.2**	**22.3**	**17.2**	**12.4**
Overall	Mean	0.003075	70	0.166	0.128	59.5	47.6	25.3	11.3
	Std	0.001201	32	0.071	0.054	28.1	25.0	16.1	8.54
	Median	0.002976	60	0.149	0.119	54.3	41.8	17.9	8.46
	GeoMean	0.002836	63	0.151	0.119	53.3	41.9	21.3	9.06
	95th %le	0.004766	120	0.295	0.230	114	91.3	58.0	27.5

2.4 Evaluation of Scenario Benchmark Objective

Benchmark Objective -- The data from the study has been analyzed to see if the aerosol scenario meets the AEATF II objective of a relative 3-fold accuracy (i.e., K = 3). Using the SAS code originally developed by the Agricultural Handler Exposure Task Force (AHETF) and independently confirmed by the Health Effects Division (HED) (and now modified by AD), EPA has determined, and presents, the analysis that the aerosol study results meet the 3-fold relative accuracy objective. Appendix A provides the detail benchmark analysis which is summarized as follows:

Benchmark Objective: fold Relative Accuracy (fRA)

The benchmark objective for AEATF II scenarios is for select statistics – the geometric mean (GM), the arithmetic mean (AM), and the 95th percentile (P95) – to be accurate within 3-fold with 95% confidence (i.e., "fold relative accuracy"). EPA has analyzed the data using various statistical techniques to evaluate this benchmark. First, to characterize the unit exposures (also referred to as "normalized exposure"), lognormal probability plots of dermal and inhalation UEs (adjusted for residue method collection efficiencies) are provided in Figures 2 to 5 for the 3 clothing configurations as well as inhalation exposure. These plots support the assumed lognormal distributions for the normalized exposure. Note: The figure titles are provided both above and below the graphs because they were cut and pasted as file images. Also note that all logarithms defined in this review are natural logarithms.

Quantile plot normalized long dermal exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled

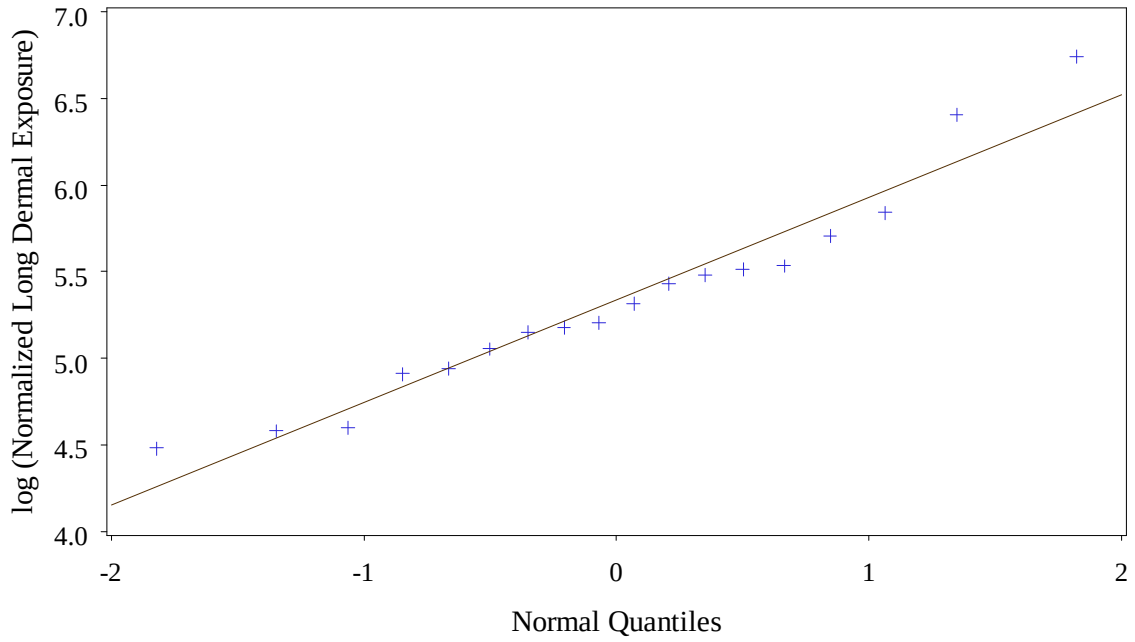

Figure 2. Quantile plot of normalized long dermal exposure data with a lognormal distribution normalized by pounds of Active Ingredient handled.

Quantile plot normalized short dermal exposure data with a lognormal distribution Normalized by Pounds Active Ingredient Handled

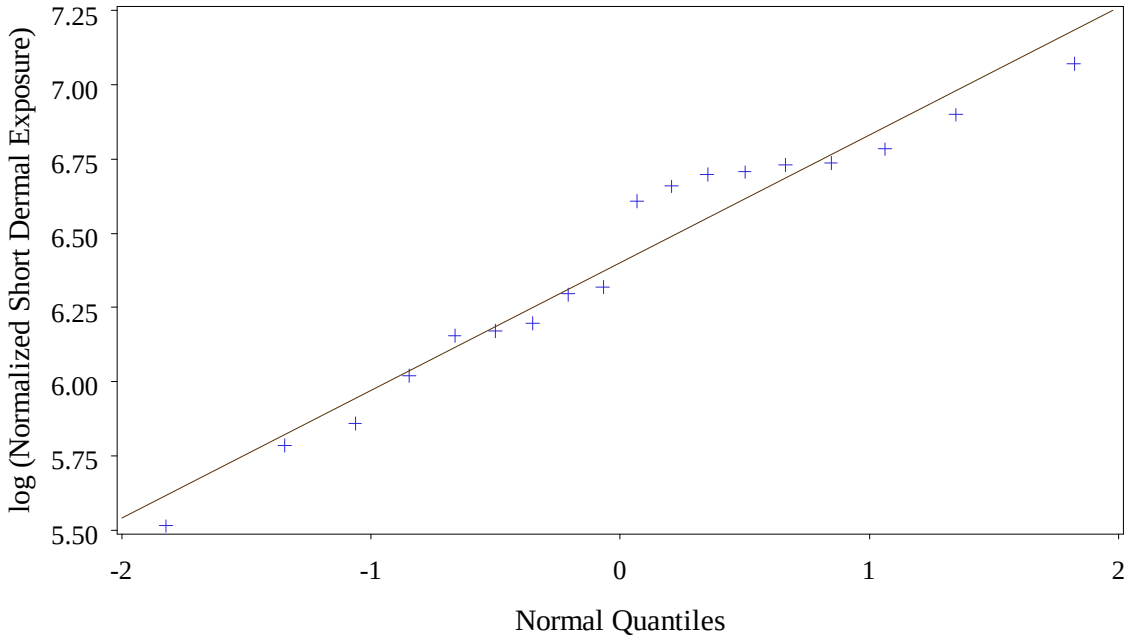

Figure 3. Quantile plot of normalized short dermal exposure data with a lognormal distribution normalized by pounds of Active Ingredient handled.

Quantile plot normalized long short dermal exposure data with a lognormal distribution Normalized by Pounds Active Ingredient Handled

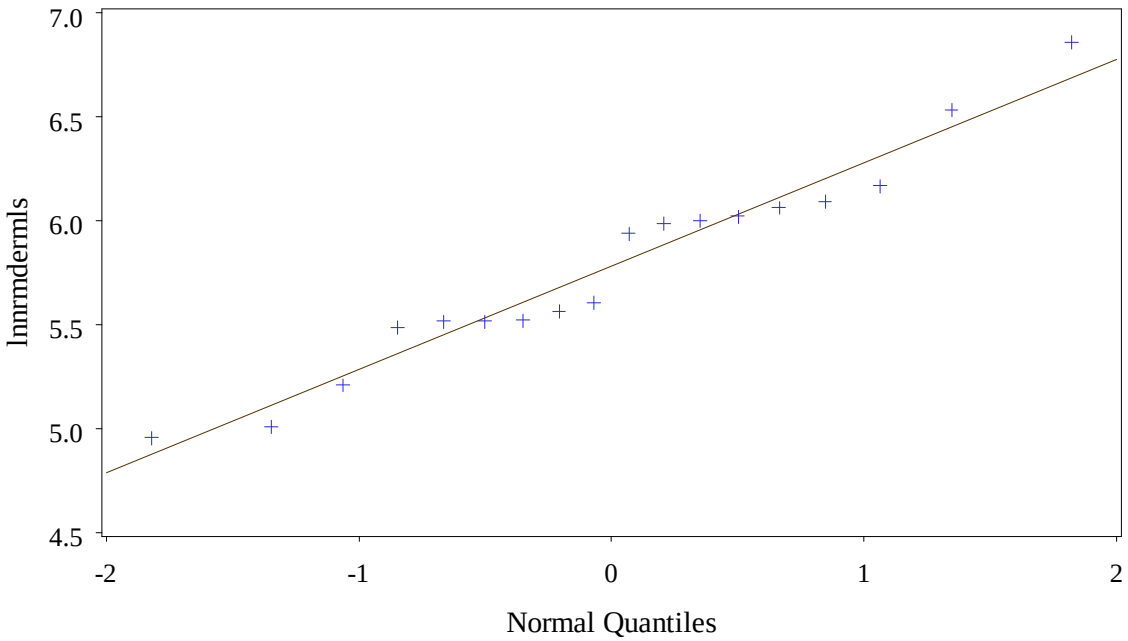

Figure 4. Quantile plot of normalized long short dermal exposure data with a lognormal distribution normalized by pounds of Active Ingredient handled.

Quantile plot normalized inhalation conc exposure data with a lognormal distribution Normalized by Pounds Active Ingredient Handled

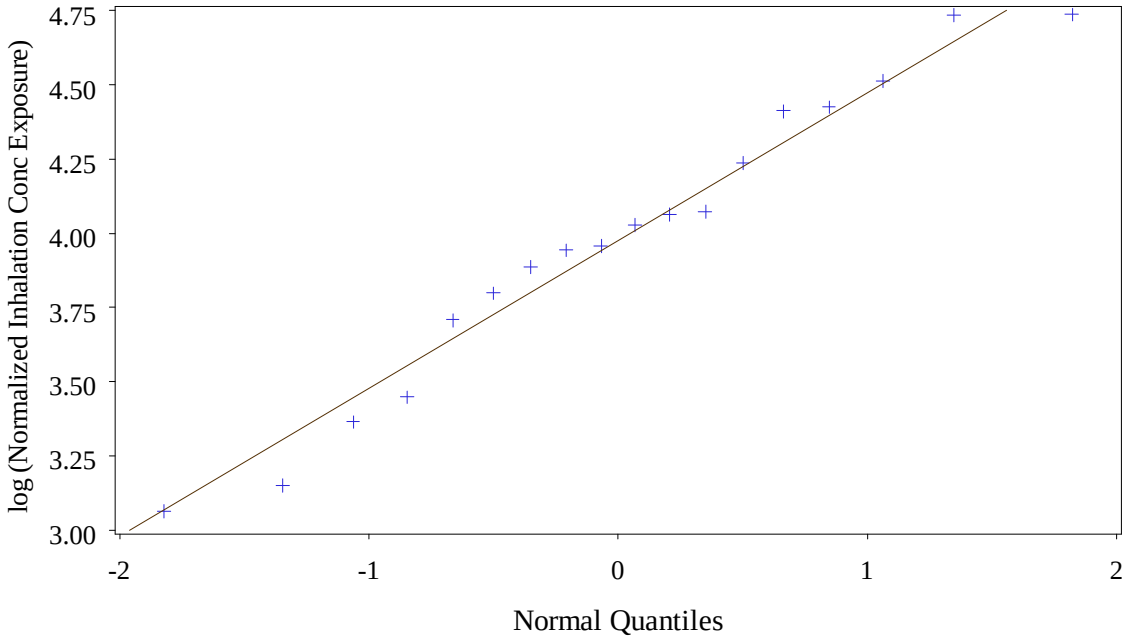

Figure 5. Quantile plot of normalized total inhalation exposure data with a lognormal distribution normalized by pounds of Active Ingredient handled.

Next, EPA calculated estimates of the GM, AM and P95 based on three different calculation methods:

- Empirical estimates;
- Assuming a lognormal distribution and a simple random sample (SRS); and,
- Hierarchical variance component modeling to account for potential ME correlations.

The 95% confidence limits for each of these estimates were obtained by generating 10,000 parametric bootstrap samples. Then, the fRA for each was determined as the maximum of the two ratios of the statistical point estimates with their respective upper and lower 95% confidence limits. Table 4 below presents the results for the aerosol scenario, for the long pants, short-sleeved shirt and the inhalation exposures. The results of the benchmark analysis for the other clothing configurations are reported in Appendix A Table 4 (long pants, long-sleeved shirt) and Appendix A, Table 5 (short pants, short-sleeved shirt).

Table 4: Results of Primary Benchmark Analysis for Long Pants, Short-sleeved Shirt and Inhalation.						
	Dermal Exposure			Inhalation Exposure		
Statistic	**Unit Exposure Estimate (mg/lb ai)**	**95% CI**	**fRA**	**Unit Exposure Estimate (mg/m^3/lb ai)**	**95% CI**	**fRA**
GM_S	324.0	257.5 – 409.1	1.3	53.3	42.3 – 67.2	1.3
GSD_S	1.6	1.4 – 1.9	1.2	1.6	1.4 – 1.9	1.2
GM_M	324.0	257.5 – 409.1	1.3	53.3	42.3 – 67.2	1.3
GSD_M	1.6	1.4 – 2.0	1.2	1.6	1.4 – 2.0	1.2
ICC	0.0	0.0 – 0.4	NA	0.0	0.0 – 0.4	NA
GM_S = geometric mean assuming SRS = "exp(average of 18 ln(UE)) values" GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 18 ln(UE)) values" GM_M = variance component model-based geometric mean GSD_M = variance component model-based geometric standard deviation ICC = intra-cluster correlation						
AM_S	365.7	285.6 – 466.3	1.3	59.5	46.9 – 76.6	1.3
AM_U	366.7	287.2 – 471.1	1.3	60.3	47.2 – 77.4	1.3
AM_M	366.7	287.4 – 472.4	1.3	60.3	47.2 – 77.6	1.3
AM_S = average of 18 unit exposures AM_U = arithmetic mean based on GM_S = GM_S*exp{0.5*(ln(GSD_S)^2} AM_M = variance component model-based arithmetic mean = GM_M* exp{0.5*(ln(GSD_M)^2}						
$P95_S$	953.4	509.9 – 1417.9	1.9	114.2	83.8 – 233.0	2.0
$P95_U$	734.6	509.1 – 1038.7	1.4	120.7	83.7 – 170.7	1.4
$P95_M$	734.6	511.6 – 1050.9	1.4	120.7	84.1 – 172.7	1.4
$P95_S$ = 95th percentile (i.e., estimated as the maximum unit exposure from the 18 unit exposures) $P95_U$ = 95th percentile based on GM_S = GM_S * GSD_S $^{1.645}$ $P95_M$ = variance component model-based 95th percentile = GM_M* GSD_M $^{1.645}$						

Tables 4, 5, 6 and 8 of Appendix A also present confidence intervals computed using a non-parametric bootstrap approach instead of the bootstrap parametric approach, as suggested by HSRB reviewers of the previous mop study. The parametric bootstrap approach assumes that the exposure data were generated from the fitted lognormal mixed model. The non-parametric bootstrap approach assumes that the data were generated using a simple random sample from each cluster. The parametric and non-parametric bootstrap confidence intervals were similar for these clothing configurations and inhalation exposure.

The benchmark of 3-fold accuracy for dermal and inhalation unit exposures has been met for all 3 clothing configurations and inhalation exposures for all 3 statistical models, using both the parametric and non-parametric bootstrap methods.

Presumption of Proportionality -- EPA evaluated the presumption of proportionality between exposure and amount of active ingredient handled (AaiH). EPA tested proportionality using a statistical benchmark to be able to distinguish, with 80% statistical power, complete proportionality from complete independence between exposure and amount of active ingredient handled.

To evaluate the relationship for this scenario EPA performed regression analysis of log(exposure) and log(AaiH) to determine if the slope is not significantly different than 1 – providing support for a proportional relationship – or if the slope is not significantly different than 0 – providing support for an independent relationship. If slope is positive, not zero and not 1 then the exposure tends to increase with the AiaH but not proportionally, so that, for example, doubling the AiaH will not tend to double the exposure. If the slope confidence interval excludes both 1 and 0 then the statistical evidence rejects both proportionality and independence and shows that the exposure tends to increase with the AiaH but not proportionally. **Note: the slope measures the change in log mg dermal exposure for each unit change in log lb ai. A slope of one implies that the log of the unit exposure (mg/lb AI) is equal to a constant plus a random error, so that the unit exposure has the same mean for any amount of ai, and thus the mg dermal exposure is proportional to the lb ai.**

A simple linear regression, a mixed-effect regression, and a more complex "repeated measures" model (see Appendix A page 47 for more details) were used to analyze the data to take into account the clustered nature of the data and were used to evaluate the relationship between exposure and AaiH. Appendix A also provides an analysis of the proportionality for each of the three clothing configurations for each scenario. The statistical analyses of all three clothing configurations showed proportionality and rejected independence. The estimated slopes were all at least 0.81 (proportionality is when the slope is one for the underlying population of all potential janitor exposures). The results of the proportionality analysis for the three clothing configurations should be consistent on physical grounds; either all or none of the clothing configurations should show proportionality to AaiH. To investigate the proportionality issues further, an alternative model ("repeated measures") was developed to fit the data from all of the clothing configurations. The reader is referred to Appendix A and the SAS code for specific details on this repeated measures model.

For inhalation exposure, the statistical analyses rejected proportionality and did not reject independence. The estimated slope was 0.4.

The resulting regression slope and confidence intervals are summarized in Table 5 and in Figures 6 and 7 for the long pants, short-sleeved shirt dermal exposure and for inhalation exposure (the two slopes in Figures 6 and 7 are identical; and therefore, only show on the graph as one slope/line). To calculate the confidence intervals, the Kenwood-Rogers method was used to estimate the denominator degrees of freedom for the repeated measures models and would have been used for the mixed-effect regressions with a non-zero estimated ICC. However, in the aerosol study, the mixed effects models for the three clothing configurations and the inhalation exposure had a zero estimated ICC. **Following comments from HSRB reviewers of the mop study analyses, we used the containment method to estimate the denominator degrees of freedom in those cases, since when the estimated ICC is zero, the Kenwood-Rogers method ignores the uncertainty of the estimated ICC and produces a confidence interval that is too narrow.**

Note that a confidence interval width of 1.4 (or less) indicates at least 80% statistical power, which was achieved for the short pants and short sleeves dermal exposure, for the long pants and short sleeves dermal exposure, and for inhalation exposure, and almost achieved (width = 1.47) for the long pants and long sleeves dermal exposure. For the dermal models, the slopes are positive and the results indicate that exposure is directly proportional (1:1) to AaiH (i.e., the confidence interval includes 1) and also indicate that exposure is not independent of AaiH (i.e., the confidence interval does not contain 0). The results for the inhalation models

indicate that exposure is not directly proportional (1:1) to AaiH (i.e., the confidence interval does not include 1) and suggest that exposure is independent of AiaH (i.e., confidence interval contains 0). For more details including results for other exposure measures and other normalizing variables, the reader is referred to Appendix A, Tables 13, 13b, and 13c.

Table 5. Results of Analysis of Proportionality for Dermal and Inhalation Exposure.

Exposure Route	Clothing	Model	Slope	Confidence Interval	Confidence Interval Width
Dermal (mg)	Long pants and long sleeves	Mixed	0.87	0.08 – 1.54	1.47
	Short pants and short sleeves	Mixed	1.01	0.47 – 1.55	1.07
	Long pants and short sleeves	Mixed	0.87	0.25 – 1.48	1.24
Inhalation (mg/m^3)		Mixed	0.43	-0.11 – 0.97	1.08

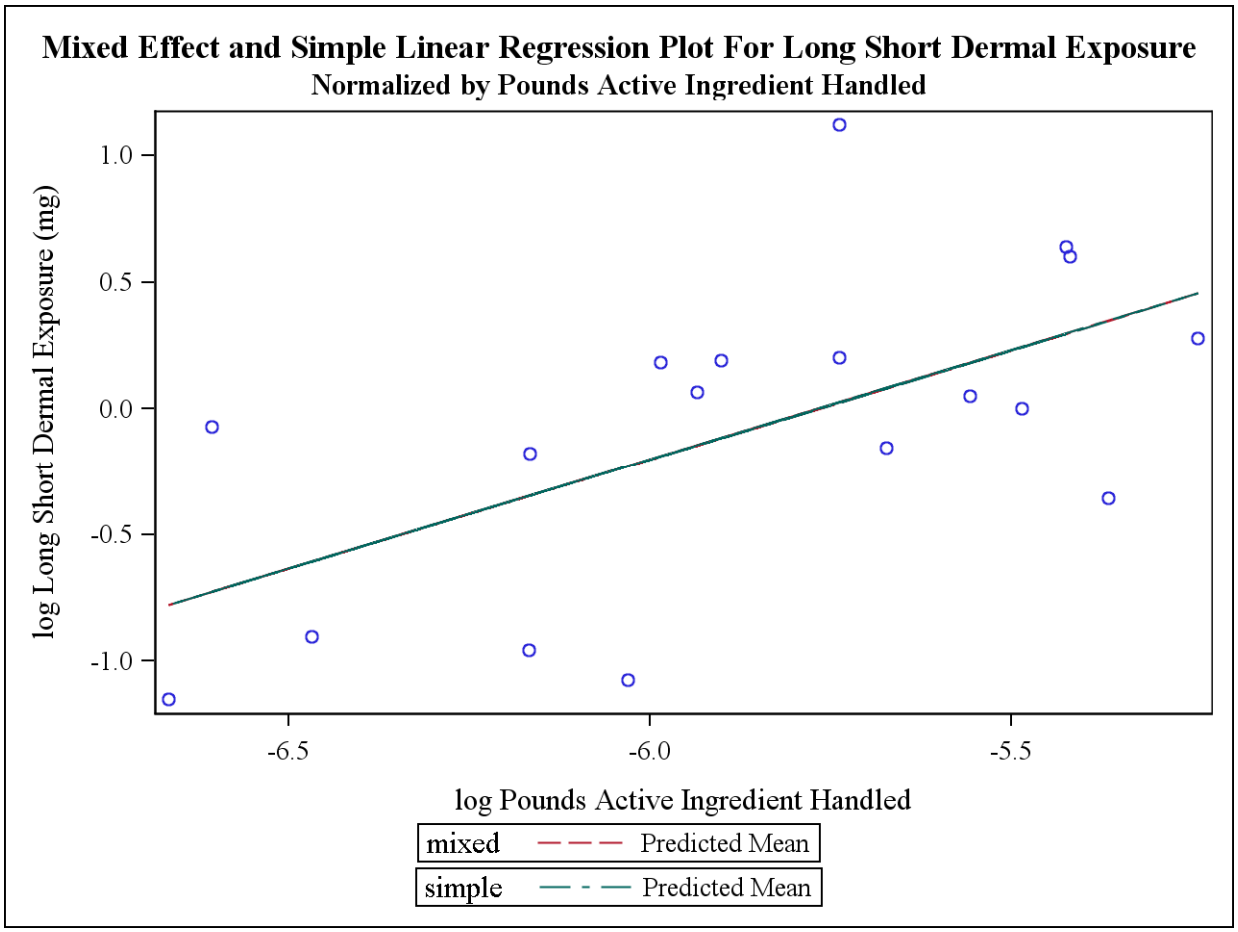

Figure 6. Mixed and simple linear regression plots for long short dermal exposure

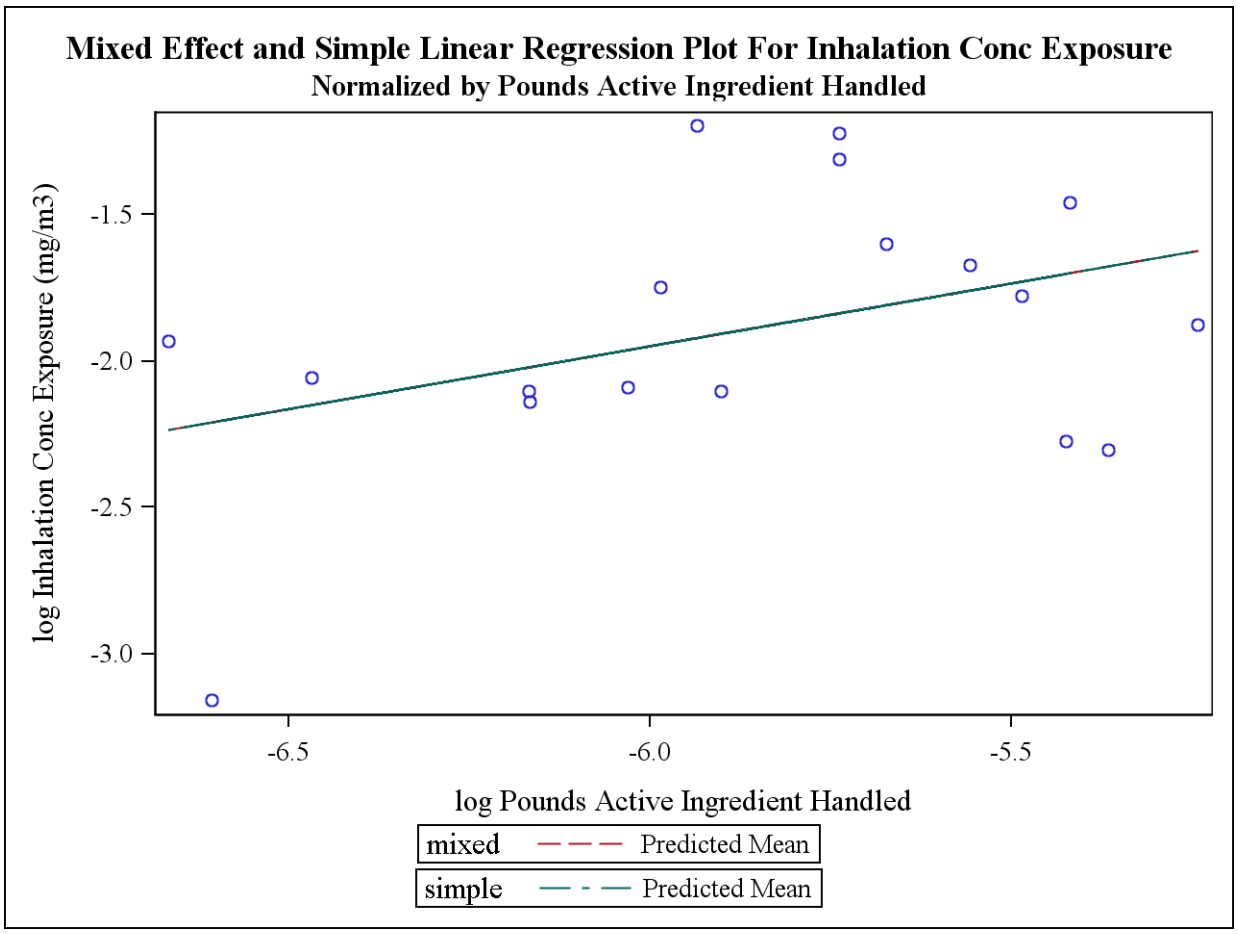

Figure 7. Mixed and simple linear regression plots for inhalation exposure.

Threshold of AaiH for Over- or Under-Predicting Exposure – The mixed model regresses the log exposure against the log lb ai with an unknown slope. The proportionality model is the mixed model where the slope of log exposure against log lb ai is assumed to equal to 1. It is shown in Appendix A that if the mixed model formulation is correct and the estimated regression slope is less than one, then the mean exposure will be over-predicted if the proportionality model is extrapolated to high levels of the amount of active ingredient and the exposure will be under-predicted at low levels of the amount of active ingredient.

As an exception, for the short pants and short sleeves clothing configuration, the slope was higher than one, and in this case the mean exposure will be under-predicted if the proportionality model is extrapolated to high levels of the amount of active ingredient and the exposure will be over-predicted at low levels of the amount of active ingredient. However, since the estimated slope for the short pants and short sleeves clothing configuration is only slightly greater than one, the two models predict nearly the same mean exposures and the over-prediction will be very small.

Table 6 gives the minimum amount of active ingredient handled for which the proportionality model will over-estimate the expected exposure (under-estimate if the slope is greater than 1). Figures 8 and 9 show the statistical models and thresholds for the long pants and short sleeves and inhalation exposures. These figures display the 18 measured exposure values (6 in each cluster) together with the predicted mean exposure calculated using the proportionality model (where the slope of log exposure against log ai is assumed to be one) and using the more general

mixed model (where the slope of log exposure against ai is estimated). The threshold is where the two predicted means are the same. The proportionality model uses unit exposures to estimate the exposure for a given amount of active ingredient, and this is a "conservative" overestimate, compared to the more general mixed model, when the amount of active ingredient is higher than the threshold.

Table 6. Minimum Pounds of Active Ingredient for Which Normalized Exposure Model Over-Predicts Dermal and Inhalation Exposure.

Exposure Route	Clothing	Model	Slope	Threshold Level (lb AiaH)
Dermal (mg)	Long pants and long sleeves	Mixed	0.81	0.00295
	Short pants and short sleeves	Mixed	1.01	0.00174*
	Long pants and short sleeves	Mixed	0.87	0.00297
Inhalation (mg/m^3)		Mixed	0.43	0.00272

*For this case, slope > 1 and so the proportionality model under-predicts exposure for pounds of active ingredient above the threshold. Since the slope is only 1.01, the under-prediction is small.

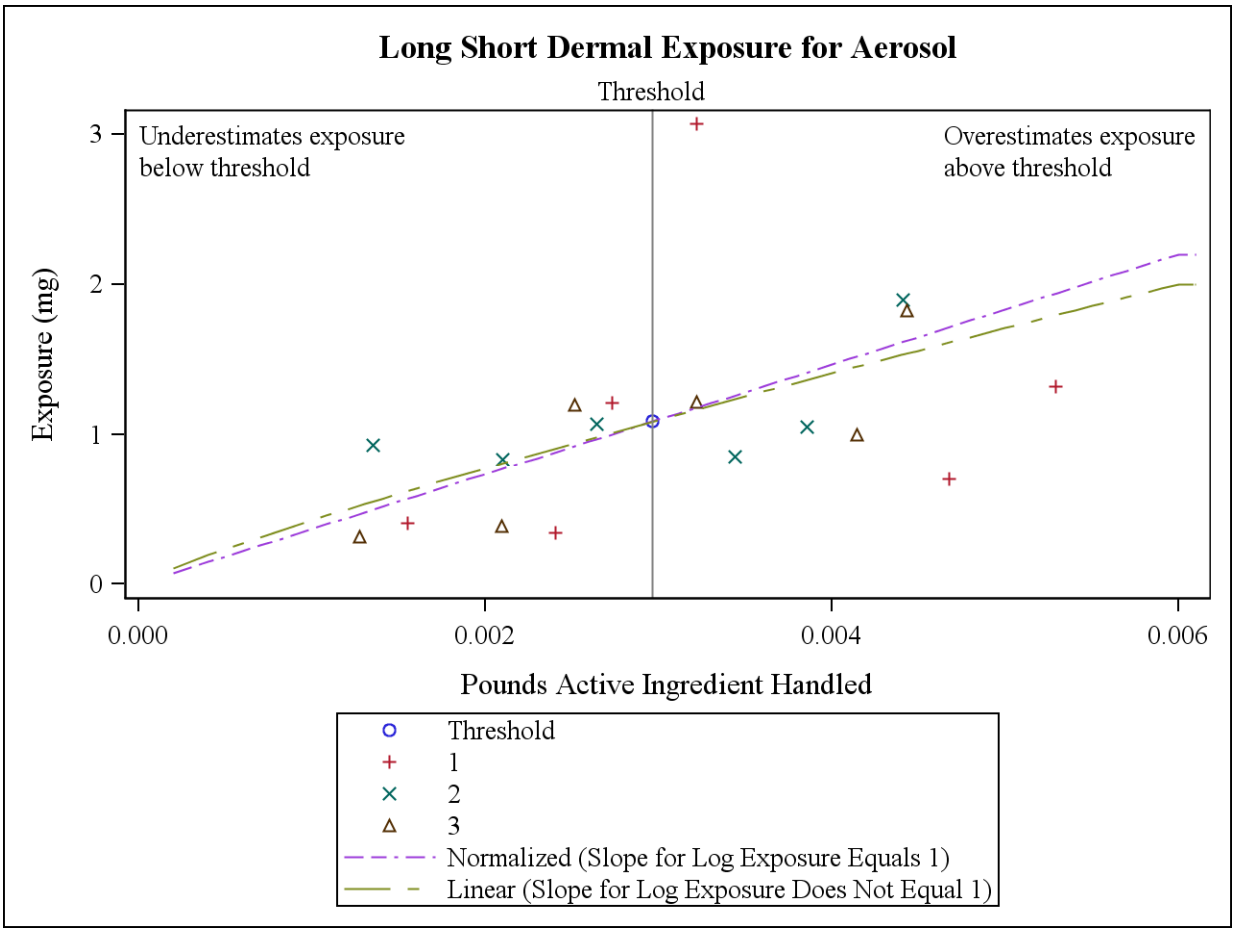

Figure 8. Predicted means for exposure with long pants and short sleeves using the proportionality and non-proportionality models; threshold value.

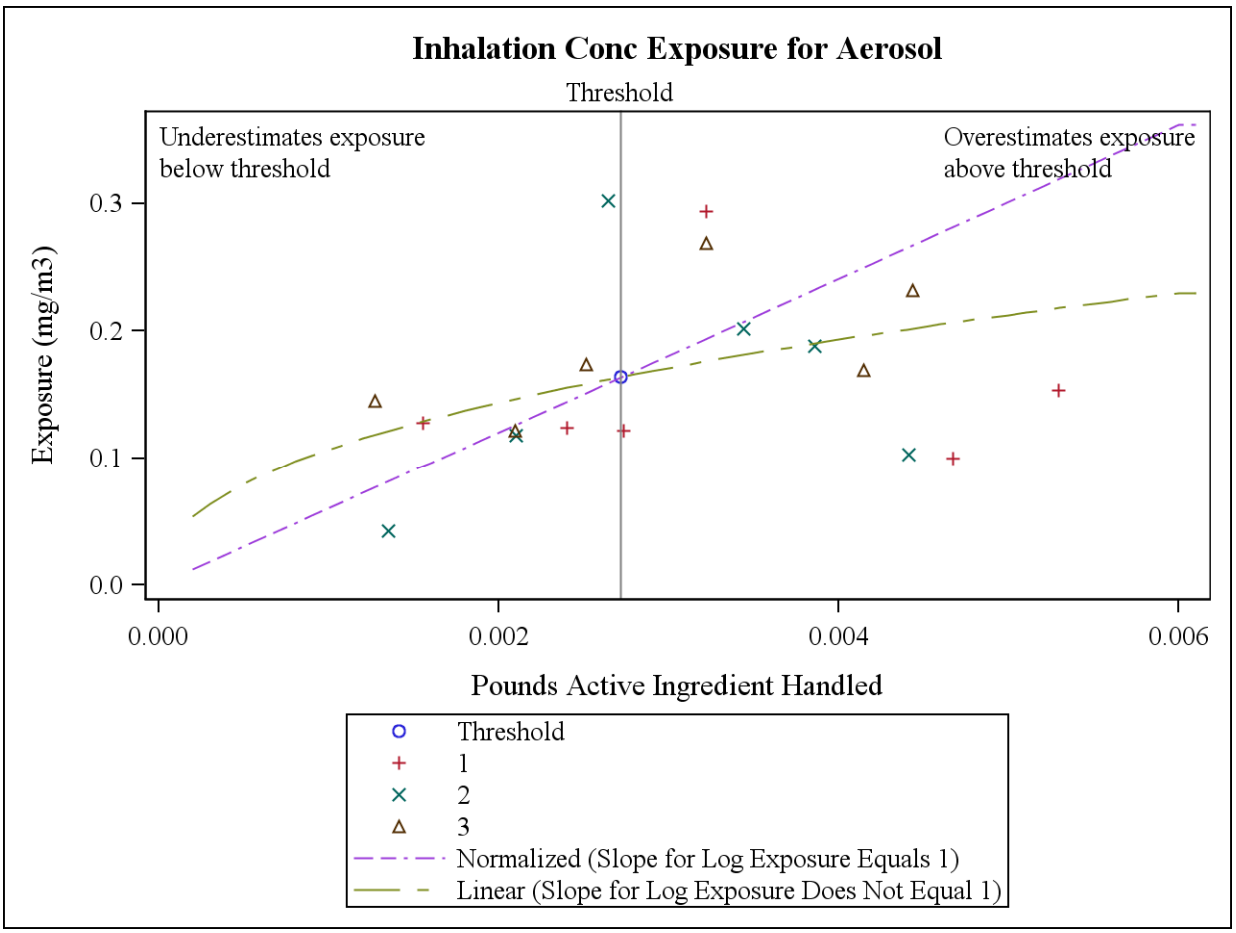

Figure 9. Predicted means for inhalation exposure using the proportionality and non-proportionality models; threshold value.

3.0 Discussion of Data Generalizations and Limitations

The regulatory need for a generic data base of pesticide handlers for antimicrobial pesticide products has been discussed previously (Christian 2007). This aerosol study was designed to represent the high end of potential exposure for workers spraying surfaces using an antimicrobial product packaged in an aerosol spray can. The study design also incorporated random diversity selection where feasible. Such a study design requires a discussion of how the data can be generalized and the limitations of the results. The following items are provided to characterize the results of this sampling effort:

(1) The study purposively selected Fresno, CA, as the study location. This selection criterion, rather than a random selection of sites across the country, limits to some degree the statistical generalizations of the data. Thus we cannot determine whether these results provide unbiased estimates of exposure distributions from the spraying of an aerosol can in locations other than Fresno, CA, and it is not possible to use these data to estimate the potential bias or the geographic variability. To generalize these results to the whole country requires an assumption that the exposure distribution for these scenarios is independent of the geographic location. The statistical limitations of the purposive site selection are deemed acceptable by the Joint Regulatory Committee (JRC). It is reasonable to assume

that the mechanics of spraying an aerosol can onto surfaces inside hotels in Fresno are not substantially different than spraying an aerosol can onto surfaces inside other hotels throughout the country. It is also reasonable to assume that the spraying inside hotels would also not be substantially different from spraying in other types of buildings that have similar HVAC systems. Given a limited set of resources for the overall AEATF II monitoring program, the assumption that indoor spraying of surfaces using an aerosol can does not vary geographically was sufficiently reasonable to forgo the random site selection (of all buildings in the country) in favor of spending the limited resources to monitor additional distinctly different scenarios (e.g., pouring of liquids, painting, metal working fluids, pressure treatment of wood, etc).

(2) The removal efficiencies for the hand wash and face/neck wipes were both conducted using quaternary ammonium products (i.e., DDAC and ADBAS, respectively) from previously conducted studies rather than for ADBAC itself. At least 2 uncertainties need to be acknowledged and discussed. First, the solubility of the test materials may affect the removal efficiencies. According to the study report (page 61 – 62)… *"With the known chemical similarity between the quaternary salts used as in the removal efficiency studies and the test material for this study, it is expected that the 89.4% dermal removal efficiency for ADBAS via wiping will apply to ADBAC as well. In the same manner, the 90.3% removal of DDAC via washing should apply to ADBAC also. In an ongoing study at Golden Pacific Laboratories, the solubility of ADBAS, ADBAC and DDAC is being evaluated in IPA as well as IPA/water (50/50) solvents (GPL Study No. 110388). Preliminary results of these experiments show solubility of both salts of ADBA as well as the chloride salt of DDA in these solvents to be much greater than levels observed in subject samples. This complete solubility data will support the measured high removal efficiencies reported by Boatwright (above), and validate the planned correction of hand wash results from this study for a 90.3% removal efficiency and correction of face/neck wipe results by a 89.4% removal efficiency."* EPA acknowledges the high removal efficiencies for hand washes of the various studies available (DDAC and ADBAS), and will wait for the submission of the solubility testing to further comment on the solubility results.

Second, the sampling (wash and wipe) procedures may also affect the removal efficiency. The DDAC removal efficiency study used a hand wash procedure less vigorous then the AEATF II SOP (which may tend to overestimate the correction factor). The dry time of the DDAC on the hands was 30 minutes compared to the average sampling time of 70 minutes in this aerosol study (which may tend to underestimate the correction factor). Of note is that the ADBAS wipe efficiency is 88.2 percent while the DDAC wipe efficiency was ~60 percent. Contributing to this difference may be that the ADBAS wipes were moistened with isopropanol (IPA) while the DDAC study used a 50/50 IPA/water solution (as did this aerosol study). Finally, there is a potential discrepancy in the ADBAS wipe removal efficiency (88.2% reported in study versus 89.4% used as the correction) and EPA will consult with the AEATF II for clarification. EPA has weighed the uncertainties of the available removal efficiency data against the need for an additional study to help clarify hand removal efficiencies. Although EPA views the removal efficiency studies as having limitations, we are not recommending a new study be conducted prior to using the unit exposures generated in this study. EPA considerations were given to the low dermal absorption of these chemicals; to the potential minor changes to the unit exposures based on recovery efficiencies; the time and resources necessary to conduct a new removal efficiency study; and the use of additional human test subjects.

(3) The data generated in this study are acceptable to use as surrogate for assessing other chemicals considered to have low volatility (i.e., vapor pressures less than ~1E-4 mmHg @ 20ºC). This "rule-of–thumb" for the vapor pressure threshold is reviewed by EPA on a case-by-case basis, particularly for those antimicrobial pesticides with vapor pressures that are near to this threshold. For example, for those chemicals with vapor pressures of ~1E-4 mmHg, EPA reviews the pesticide application method for the potential for aerosol generation and the available inhalation toxicity data to see if the toxicity studies were performed as a gas or with an aerosol.

(4) The data generated in this study are acceptable to use as surrogate to assess pesticide labeled uses of spraying surfaces using an aerosol can.

(5) The dermal exposures that resulted from the spraying of the product packaged in an aerosol can generated in this study are acceptable to use for clothing configurations of long pants, long-sleeved shirts, and no gloves; long pants, short-sleeved shirts, and no gloves; as well as short pants, short sleeved-shirts, and no gloves.

(6) The small sample size by itself does not cause statistical limitations since the confidence intervals for the summary statistics were reasonably narrow (in most cases meeting 2-fold relative accuracy or better). More important is the fact that the original sets of subject participants, locations, and dates from which the subjects, clusters, and sampling dates were chosen were limited and hence might not be representative of all Fresno users of aerosol cans (e.g., those that use aerosol cans but did not volunteer), buildings (e.g. only hotels were eligible for this study), and time periods (e.g., winter versus summer, night versus day, etc.). In other words, the most significant limitation is that these data were not derived from a stratified random sample of MEs even though the statistical analyses made that assumption. At a minimum this increases the uncertainty of the estimates (so the calculated confidence intervals are too narrow) and there may also be some bias (e.g., study participants not in the volunteer pool might be more or less prone to exposure than the selected group).

(7) EPA will continue using exposures normalized by AaiH as a default condition. The results of the aerosol study scenario are not inconsistent with the proportionality assumption that dermal exposure tends to increase proportionally with AaiH. The choice of normalizing variable of AaiH is based upon considerations of suitability for product labeling and consistency between scenarios. The results for inhalation exposure are inconsistent with proportionality. However, for inhalation exposure, the use of this inconsistent assumption of direct proportionality of exposure to AaiH when extrapolating to the high end of AaiH – the EPA regulates on the high end of AaiH – tends to overestimate the exposure, resulting in conservative risk assessments and human health protective regulatory decisions. Table 6 above provides for the minimum amount of AaiH for the normalized exposures to be over-predicting exposures (i.e., protective of human health). Data will continue to be collected by the AEATF II to add to the knowledge base of normalized exposures.

4.0 Conclusions

EPA has reviewed the AEATF II aerosol study and concludes that the AEATF II made the appropriate changes to the protocol proposed by the EPA and HSRB and has executed the study successfully. The protocol deviations that occurred and were reported on have not adversely impacted the reliability of these data. The EPA recommends that the inhalation and

dermal UE generated in this aerosol study be used provided the data are used within the boundaries set forth in this review.

The following is a summary of our conclusions.

- The AEATF II data for inhalation and dermal exposures represent reliable data for assessing the spraying of surfaces using an aerosol can. This scenario does not include the subsequent wipe with a rag. The "wiping" portion of this type of an application does not always occur; some products are "leave on" applications. Exposures occurring while wiping are available in a previously submitted AEATF II study. Alternative data sources or special circumstances will be considered on a case by case basis.

- The inhalation exposure monitoring results are available as total particles, inhalable particles (<100 µm), thoracic particles (<10 µm), and respirable particles (<2.5 µm). These results are graphically illustrated in Figure 10. EPA will consult with the JRC and inhalation toxicologists to determine which inhalation exposure monitoring results from this study are best suited to each individual assessment (e.g., a chemical that is an irritant causing no systemic toxicity might be best represented by the results of the inhalable particles). EPA will also continue to review the potential correction factors for the inhalable particle results (i.e., ranging from 1.5 to 1.8) as noted in Appendix C. Any advice from the HSRB on the Respicon results will also be considered

- Estimates of the GM, AM, and P95 were shown to be accurate within 3-fold with 95% confidence for all the analyses of the three clothing configurations and of inhalation exposure.

- The data provided 80% statistical power to distinguish complete proportionality or independence between exposure and AaiH for both dermal and inhalation routes of exposure.

- A direct proportionality (1:1 relationship) between dermal exposure and AaiH was established.

- A direct proportionality (1:1 relationship) between inhalation exposure and AaiH was not established but the trend of inhalation exposure increases as AaiH increases.

- Additionally, Table 6 provides a threshold that is the minimum AaiH value where exposure will be over-estimated when extrapolating the normalized exposure (mg dermal/lb ai or mg/m^3 inhalation/lb ai) to other chemical assessments (i.e., using these unit exposures as surrogates to assess other chemicals that handle more active ingredient than the threshold).

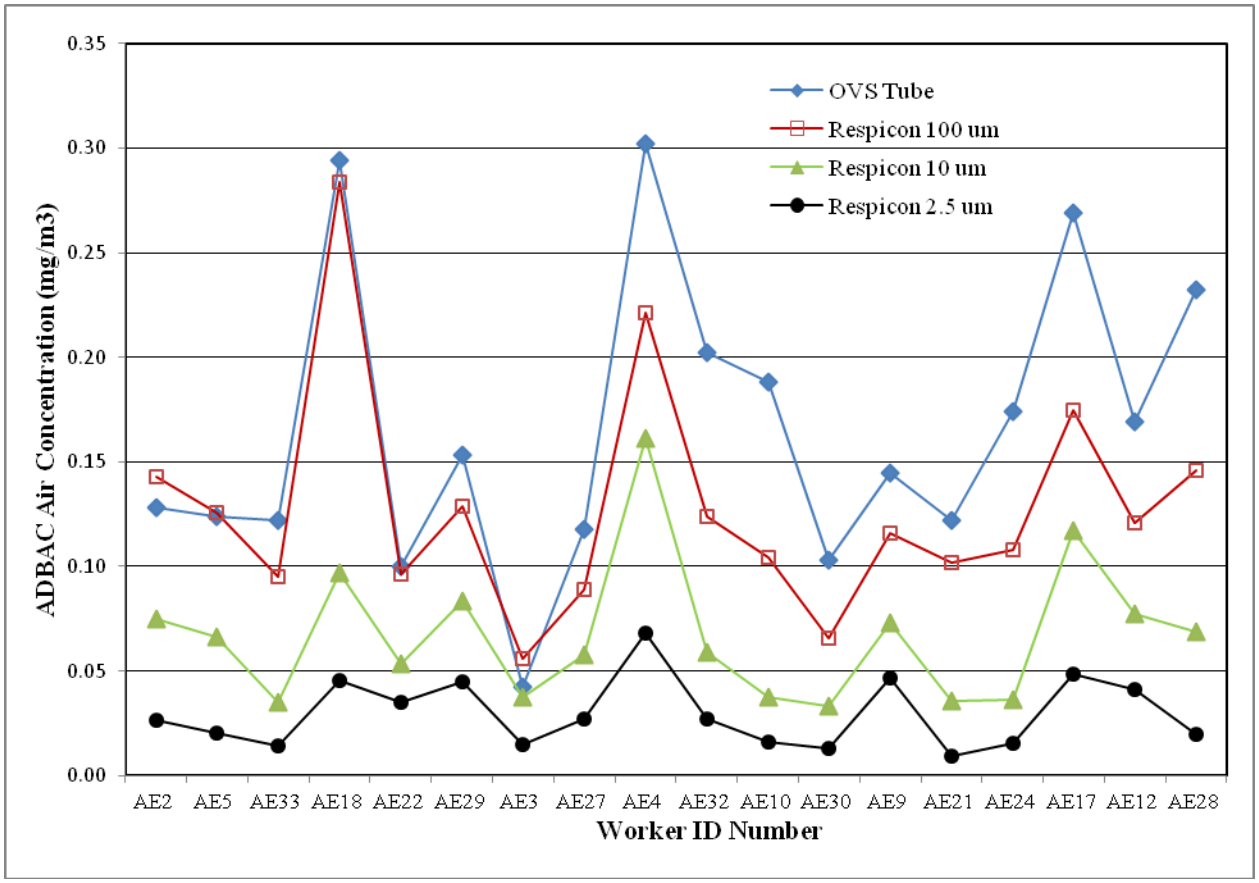

Figure 10. Comparison of ADBAC Air Concentrations Measured Using the OVS Tube and the Respicon Sampler.

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Appendix A

Statistical Review of the AEATF II Aerosol Study

(To be included as a separate electronic file)

Appendix B

AEATF II Letters in Response to HSRB Protocol Review Comments

(To be included as two separate electronic files)

Appendix C

Respicon Air Sampler Information

Respicon Air Sampler Information

Introduction

The Respicon sampler is a multi-stage, virtual impactor that traps airborne particles onto three individual filters. The first impactor stage separates out and collects particles smaller than 2.5 um. The second stage collects particles below 10 um while the third stage collects the remaining particles. The filters from the three stages can be added to together as follows to represent the inhalable, thoracic and respirable sampling conventions for airborne aerosols:

- Inhalable (50% cutoff at 100 um) : Stages 1 + 2 + 3
- Thoracic (50% cutoff at 10 um): Stages 1 + 2
- Respirable (50% cutoff at 2.5 um): Stage 1

Literature Study Test Results

Li et al, 2000. The Respicon sampler was compared to five other inhalable aerosol samplers including the IOM sampler. This evaluation was conducted in a wind tunnel operated at 0.55 and 1.1 m/sec and the samplers were oriented at 0, 90 and 180 degrees to the wind. The test aerosol was generated as monodisperse solid particles with aerodynamic diameters ranging from 5 to 68 um. The results indicated that the Respicon matched the inhalation convention very well at 0.55 m/sec and oversampled at 1.1 m/sec, matched the thoracic convention very well except for under-sampling of 5 um particles due to inner particle loss and matched the respirable convention very well except for under-sampling of the 1.6 micron particles which was due to non-uniformity of the test particles. The authors mentioned that since the average wind speed in an indoor workspace is 0.3 m/sec (per Baldwin and Maynard, 1998), the result at 0.55 m/sec is more relevant.

Koch et al, 2002. The Respicon sampler was compared to the IOM sampler and a stainless steel mannequin (i.e. the CALTOOL) that is designed to simulate human breathing. The comparison to IOM sampler was done using side by side personal sampling of workers in nickel refining operations. Each worker wore IOM and Respicon samplers for a full work shift and a total of 132 pairs of samples were collected. The comparison to CALTOOL was done using side by side area samples in workplace environments or a test chamber. Regression analysis of the area sample resulted indicated that the IOM and the CALTOOL inhalable results were 1.51 and 1.83 times greater than the Respicon inhalable results. This data also suggested that the CALTOOL and IOM results were not greater than the Respicon results when the particle size was less than 10 microns. Analysis of the IOM and Respicon personal sample results indicated that the IOM results are generally higher than the Respicon results; however, some of this difference might be due to known vulnerability of the IOM sampler to contamination by non-airborne material.

Linnainmaa et al, 2003. The Respicon sampler was compared to seven other inhalable aerosol samplers including two IOM samplers (with or without foam filters for respirable aerosols). This evaluation was conducted under laboratory conditions in a chamber with an airflow of 0.1 m/sec or under field conditions in a talc production plant. The test aerosol for the laboratory evaluation consisted fine quartz dust. The laboratory study indicated the Respicon yielded inhalable, thoracic and respirable aerosol levels that were 50%, 60% and 125% of those measured using the IOM sampler. The field study indicated that the Respicon yielded inhalable, thoracic and respirable levels that were 75%, 60% and 100% of the IOM results.

Feather and Chen, 2003. The Respicon sampler was compared to the IOM sampler in a small chamber that was designed to maintain calm air conditions where the air velocities do not exceed 20 cm/sec. This velocity was chosen based on the study by Baldwin and Maynard, 1998 of wind speeds in the workplace. The test aerosol consisted of monodispersed fluorescence-tagged polymer in either aqueous or powder form with aerodynamic diameters of 2.0, 6.1, 16.4, 30.7 and 69.7 um. The test aerosol was dispersed into top of the chamber and allowed to settle to the bottom where it was collected by isokinetic reference probes and the IOM and Respicon samplers. The results indicated that the IOM sampler was close to 100 percent efficient at all of the particle sizes while the Respicon matched the conventional respirable and thoracic convention curves but undersampled the inhalable fraction.

Rock et al, 2009. The Respicon sampler was compared to five other aerosol sampler types including Anderson cascade impactors, total suspended particulate (TSP) samplers, PM10 samplers, and laser light scattering particle monitors. This evaluation was conducted in a controlled test chamber (wind speed not reported) using poly-disperse fly ash with a mass median aerodynamic diameter of 11.77 um and a geometric standard deviation of 2.06 um. The results indicated that the Respicon underestimated total suspended PM by 43 percent when compared to the TSP samplers. The Anderson samplers had 17% and 85% more thoracic and respirable mass, respectively, than the Respicon and this was determined to be from particle bounce in the Anderson samplers.

Conclusion

The literature studies indicate that the Respicon matches the thoracic and respirable sampling conventions fairly closely while significantly undersampling the inhalable convention. These studies generally suggest that the undersampling is consistent and can be addressed by using correction factors that range from 1.5 to 1.8.

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