UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: October 9, 2012

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

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This memorandum presents the EPA/OPP Antimicrobials Division (AD) science review of the human exposure liquid pour 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) liquid pour study. The protocol for this completed study was previously reviewed by the EPA and the Human Studies Review Board (HSRB) for ethical and scientific design. Both EPA and HSRB approved the protocol and provided recommendations for some minor modifications (discussed within this memo). This memo contains the scientific review, recommended unit exposures, and study limitations to be considered by users. The ethics review is contained in a separate memo. Both of these reviews are to be presented to the HSRB on November 1, 2012.

The liquid pour study investigators monitored inhalation and dermal exposures to 18 workers each pouring liquid products packaged in conventional product containers and in containers engineered as reduced splash. Two different active ingredients were used in the study to separate the monitoring results of conventional versus reduced splash containers. Various size product containers, receiving containers, amounts poured, and pour heights were employed. EPA confirms that the data are considered the most reliable data for assessing handler exposures from pouring liquid antimicrobial products. 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 liquid pour dataset instead of the Chemical Manufacturers Association (CMA) and/or the Pesticide Handlers Exposure Database (PHED) datasets to assess exposure for persons pouring a liquid antimicrobial product in various settings. The exposure data in the AEATF II liquid pour scenario represent the pouring of a liquid antimicrobial product in the commercially available size containers (e.g., small containers up to 5 gallon buckets that can be poured manually) into receiving containers of various sizes. The scenario does not cover the subsequent application of the treatment solution. The total potential exposure from pouring and the subsequent application of the treatment solution can be determined by combining the results of this study with the results of the studies AEATF II has previously conducted or plans to conduct. There are also antimicrobial uses of liquid pour that require no additional application (e.g., pouring products into pulp & paper water systems).

The AEATF II designed the study to develop unit exposures for conventional pour (CP) and reduced splash (RS) containers, regardless of the product container size. The results of the study, as reported herein, indicate that the exposures for the monitoring events (MEs) using the spray bottle as the receiving container are statistically significantly different from the exposures for the MEs that involve pouring directly from the product container into other, larger types of receiving containers. Thus EPA's review provides an additional unit exposure for pouring liquids into spray bottles (spray bottles such as those used for disinfectants).

Select summary statistics for the "unit exposures" normalized to pounds active ingredient handled are presented in Table 1 for dermal and inhalation exposure. Although 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), the unit exposures for the various clothing configurations were atypical (i.e., increasing exposure with more layers of clothing, this statistical quirk is discussed below). Therefore, the dermal unit

exposures provided in Table 1 are to be used for any combination of long/short pants/sleeves and no gloves. Confidence intervals for these unit exposures are presented in Table 9 of Appendix A.

For comparison, results from the PHED studies for liquid pour are also presented in Table1. The summary statistics reported in Table 1 are estimated using the lognormal mixed model while the CMA and PHED results are empirical estimates.

Table 1. Unit Exposures (UE) for Liquid Pour Scenarios

Exposure Route	Clothing	PHED ("best fit")[a]	AEATF II[b, c] (n=6 Bottle and 18 CP & RS)		
			Scenario	Arithmetic Mean[d]	95th Percentile[e]
Dermal (mg/lb ai)	Long pants/long-sleeves, no gloves	2.9 (n=53 to 122)	Bottle	299	1110
			Conventional (CP)	10.0	36.9
			Reduced Splash (RS)	3.1	11.6
Inhalation	Breathing Zone (mg/lb ai) [f]	0.0012 (n=85)	Bottle	0.012	0.033
			Conventional (CP)	0.0017	0.0046
			Reduced Splash (RS)	0.00091	0.00242
	Breathing Zone (mg/m^3/lb ai)	Not Available	Bottle	0.047	0.128
			Conventional (CP)	0.016	0.042
			Reduced Splash (RS)	0.0049	0.0132
	Breathing Zone (8 hr TWA mg/m^3/lb ai)[g]	Not Available	Bottle	0.0016	0.0041
			Conventional (CP)	0.00021	0.00057
			Reduced Splash (RS)	0.00011	0.00030

[a] Historically PHED data has been used to assess the open liquid pour exposures to antimicrobial products. The PHED "best fit" measure is the median and/or geometric mean for the various individual body parts.

[b]Dermal UE include corrections for removal efficiencies for hands and face/neck. Dermal and inhalation UEs are corrected for field recoveries. Bottle refers to pouring into spray bottles (where both CP and RS containers were used), Conventional or CP is conventional pour containers, and Reduced Splash or RS is reduced splash containers. The UE for Long-Long are to be used for any combination of long/short sleeves/pants with no gloves.

[c] Statistics are estimated using a variance component model accounting for correlation between the two measurements on each worker and different geometric means for each group 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) * pouring duration (hours/day)

[g] 8-Hour Time Weighted Average ((mg/m^3)/lb ai) = air conc ((mg/m^3) / lb ai) * pouring duration (hours/day) / 8 (hours)

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 liquid pour datasets for antimicrobial uses (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 dermal unit exposures recommended in Table 1 are based on the long sleeved shirt, long pants, and no gloves. The clothing scenarios for various configurations of short sleeves and short pants are not reported in Table 1 and are not recommended for regulatory purposes (these unit exposures are provided in the analyses below (Tables 7, 8, 9) and discussed in detail in Appendix A (Tables 9, 12-18)). The variance component model estimated decreasing exposure with less clothing. These results would appear to be contrary to the fact that the calculated exposures for short sleeves versus long sleeves are higher due to the outer dosimeter for the lower arm, and the calculated exposures for short pants versus long pants are higher due to the outer dosimeter for the lower leg. These results occurred because the estimated arithmetic mean based on the lognormal mixed model is given by the formula GMm×exp(½ V) where GMm is the estimated geometric mean and V is the estimated variance. Even if the estimated geometric mean increases, the estimated variance can decrease, producing a net decrease in the estimated arithmetic mean even though the true arithmetic mean must increase. For this reason we regard this issue as a statistical "quirk" attributable to large uncertainty in the fitted models for dermal exposure.
- The design of this study was to develop unit exposures for conventional pour and reduced splash containers. Based on the results of the monitoring, EPA has identified a third unit exposure scenario –pouring into spray bottles ("bottle" scenario – See Section 2.1 for additional justification). Although separating out the bottle scenario decreases the number of MEs in each scenario, EPA believes this to be the best use of the data. The estimated unit exposures for the bottle scenario can be used by EPA when assessing certain disinfectant uses (i.e., products with directions for application in trigger pump and spray for hard surfaces). If the bottle scenario was not separated out, the exposures involved with pouring concentrates into trigger pump and spray bottles would tend to be underestimated and exposures for the other types of pouring liquid scenarios would tend to be overestimated.
- The statistical analysis (Section 2.5) provides evidence of log-log-linearity with a slope of 1[1] between inhalation 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). Log-log-linearity with a slope of 1 supports the use of unit exposures. The analysis also shows that inhalation exposure tends to increase with pounds of active ingredient handled (AaiH) as described in Section 2.5 below.
- The statistical analysis (Section 2.5) for dermal exposure and pounds ai handled provides evidence against log-log-linearity with a slope of 1, and the estimated slopes are negative, although not statistically significant. Various alternative methods were used, unsuccessfully, to try to identify potential data points causing the negative slopes. The exposure driver appears to be the random drips and/or spills on the worker's hands rather than how much product was poured. The EPA will still normalize the liquid pour data by

[1] The statistical analysis of log-log-linearity tests whether the slope of log exposure against log ai is 1. We now refer to these analyses as the log-log-linearity analyses. In the Governing Documents and in previous reviews of the AEATF II studies we have referred to these analyses as a "proportionality" analysis, but this has caused some confusion because the statistical models do not assume that the exposure is directly proportional to the AI but instead assume that the logarithm of the exposure is linear in the logarithm of AI with a slope of 1, which is a related finding but a very different model, as explained in more detail in Appendix A. We have therefore changed the terminology from "proportionality" to "log-log-linearity."

AaiH because logically each drip and/or spill on the hands is a given volume of liquid, and the potential exposure is dependent upon the concentration of ai in that drip and/or spill. The study could not be designed to vary the concentration of ai to further investigate this assumption because higher concentrations of ai would require the use of chemical resistant gloves. The use of this inconsistent assumption 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.

- Although EPA is prepared to use the data as recommended in Table 1, EPA will work with the AEATF II once it completes its other planned studies, to determine whether it would be useful to conduct additional monitoring to increase the number of samples in the bottle scenario.
- 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).

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

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 or mixing/loading) 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 residues on 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 liquid pour exposure study protocol in October 2011.

1.1 Liquid Pour Scenario Defined

The liquid pour scenario in this study is defined as manually pouring pesticide out of conventional and reduced splash containers of various sizes from various heights into various size receiving containers, with and without pre-measurements of the product being poured. Subjects poured 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. For reasons described below, only the inner dosimeters, represented by long sleeved shirt and long pants are recommended for regulatory purposes.

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 manually pouring a liquid antimicrobial product packaged in conventional and reduced splash containers. Dermal and inhalation exposure monitoring was conducted while study participants poured liquid products using various methods (containers, heights, pre-measurements or not, etc) for use in exposure assessments, as "unit exposures". The study was designed to provide results for two distinct unit exposures: conventional containers and reduced splash containers. However, based on the results, a third unit exposure value, for pouring into spray bottles, was deemed by EPA to be appropriate as discussed below.

"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 (SAP 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 3 size groups of product containers by 6 monitoring events (MEs) for each of the conventional and reduced splash scenarios.

- EPA also plans to use the data to evaluate whether the mean exposure is a multiple of the amount of active ingredient handled; that multiple is the estimated unit exposure. EPA evaluated this hypothesis using a log-log-linearity test based on the slope of the straight line relating the logarithm of the exposure to the logarithm of the amount of active ingredient handled. A slope of 1 supports this hypothesis. EPA used a log-log regression test to distinguish a slope of 1 from complete independence (slope = 0).

1.3 Protocol Modifications, Amendments, and Deviations

1.3.1 Protocol Modifications Subsequent to EPA and HSRB Reviews

EPA required 4 science-based modifications to the liquid pour protocol (EPA 2011). The EPA review of the protocol noted that the AEATF II needs to make the following modifications (specific changes to the protocol made by the AEATF II in response to EPA's review are provided in subsequent sections):

- Allow random selection for two additional items: (1) randomize the order in which the randomly-selected product container sizes are poured; and (2) randomize the selection of which three subjects will use a measuring cup in Group 2.
- Allow subjects to fill the spray bottles from the product container and with water in the order they *would normally do* as opposed to the researchers directing them to fill with water after pouring the concentrate from the measuring cup.
- Provide a description of how the different size product containers will be randomly assigned to each ME.
- Provide details about how the airflow in the laboratory room will be measured and what the target airflow will be (e.g., will the airflow be minimized?).

The HSRB also provided written discussion on a number of issues pertaining to the review of the liquid pour study. AEATF II provided EPA with responses to the HSRB inquiries. The HSRB issues [identified below by "Lines" of the HSRB report] and AEATF II responses are reproduced below from AEATF II's January 18, 2012 correspondence to EPA (verbatim):

HSRB Lines 49 to 53 – The Board pointed out two limitations not identified in the protocol or by the Agency: 1) the wider range of exposures that could occur while pouring products outdoors than only indoors as proposed; and, 2) the unknown impact of potential differences in exposures between consumers and professionals.

AEATF Response: Exposure data indicate that the handling and use of chemicals indoors tend to result in higher exposures than outdoors due to the restricted potential for dilution of airborne residues. Since the majority of the uses of antimicrobial products occur indoors (e.g. cleaning and sanitizing of equipment and surfaces; water treatment; wood treatment; pulp and paper manufacturing; textile manufacturing), the study was designed to capture the majority of the uses of antimicrobial products. We suspect that the use of these data to predict exposures to people pouring antimicrobial products outdoors may actually result in slightly overestimated risks. The AEATF agrees that the impact of using only professionals versus consumers on exposure potential is unknown and that this may be a limitation. However, although potential differences may exist, the impact of the differences is unknown. Pouring is not a skill used only for handling antimicrobials. Even for professionals, pouring is only a small part of their job, and there is no reason to believe that they can do it any better than a typical consumer. In the absence of any supporting data, it is impossible to know if consumer exposure would higher.

HSRB Lines 352 to 368 – The Agency proposed that the protocol be revised to randomize the use of a measuring cup by participants in monitoring Group 2. The HSRB anticipates that the effect of using a measuring cup as currently described in the protocol will have little effect on exposures. The HSRB suggested two alternative ways to assess the effect of using a measuring cup: 1) have half the participants in Group 2 use a measuring cup to transfer all of their assigned source product into the receiving container(s), and the other half not use the cup at all; or 2) no one in Group 2 uses a measuring cup, but instead test for a difference in the unit exposure values between Group 1 (all of whom use a measuring cup) and Group 2 (all of whom do not use a measuring cup).

AEATF Response: The purpose of including the use of a measuring cup was to increase diversity by capturing the range of possible activities associated with the pouring of an antimicrobial product. The purpose was not to compare exposure with and without the use of a measuring cup. The use of a measuring cup is not something that can be regulated by a product label. The act of measuring out a specific amount with a measuring cup is typically done only once during the transfer of a product, not continuously for the entire contents of a container. Requiring participants to transfer their entire assigned source product with a measuring cup would mean they would have to measure and pour up to 225 times (1,800 fl oz divided into 8 oz aliquots) which is not realistic or practical. For these reasons, scripting of two pours per source container per participant with a measuring cup was included in the protocol. With respect to suggestion 2, because the receiving containers are vastly different between Groups 1 and 2, attempting to compare exposures between these groups based on the use of a measuring cup or not would not provide meaningful results. The AEATF will keep the current study design and randomize the use of the measuring cup for 3 of the participants in Group 2 as recommended by the Agency.

HSRB Lines 370 to 383 – The Agency indicated that the protocol should be changed to allow the participants in Group 1 to fill the spray bottles from the source container and with water in the order they normally would do as opposed to the researchers directing them to fill with water after pouring the chemical. The HSRB noted that the Agency should ensure that the protocol directs the handlers to follow label directions. However, it was also noted that since the participants will be using pre-diluted test material none of the labeling instructions that would normally be present on the original container will be present in the pouring containers used in the study. The protocol should be amended to specify what label information will be made available to study participants.

AEATF Response: The protocol will be changed to allow for the participants to fill the trigger spray bottles with water and product in any order that they would like. A product data sheet and MSDS will be generated for each of the two diluted test substances being used in the study. These will be appended to the protocol and will be available should a participant request to see it. As is typical for dilute (<1%) consumer products, consumer labels do not contain pouring or dilution instructions as they are already diluted and ready to use. The protocol specifies that label safety information will be explained to study participants.

HSRB Lines 384 to 391- In addition to the recommendation by the Agency that a description of how the different size containers will be randomly assigned to each ME, the HSRB suggested adding statistical constraints to the randomization process to avoid statistical outliers.

AEATF Response: A description of how the different size containers will be randomly assigned to each ME will be added to the protocol along with the provision that if the random array results in 80% (8 out of 10 conventional or 12 out of 15 reduced-splash) or more of the source containers being the same size, that random array will not be used.

HSRB Lines 393 to 420 – The agency requested that details about how the airflow in the laboratory will be measured and what the target airflow will be (will it be minimized?) be added to the protocol. The HSRB added that the main focus should be on the local air flow between the pouring operation and the handler. The pattern of air flow should be measured before or/and after exposures and the orientation between the source and each handler should be documented for each ME. Alternatively the room's set up and orientation between the source and handler could be varied (e.g. rotated 90 degrees) either within or among MEs. It was also pointed out that the airflow through laboratories is generally more than what would be expected in many other work rooms in which such pouring would take place; therefore some steps to minimize the air flow should be considered.

AEATF Response: More details about how the airflow will be measured will be included in the protocol. From a design perspective, varying the orientation of the MEs may be difficult. Although the rooms measure 12 ft by 24 ft, the built-in counters and benches limit the area where the participant can be located. As such, the orientation of each test subject in the room with respect to the direction of air flow and the containers he is pouring will be documented. The subject will be free to position himself/herself relative to the receiving container(s) within the room. The airflow rate in the rooms is about 10 to 12 air exchanges per hour which is higher than some other locations, but similar to that in medical offices and lower than that in such locations as mills, factories, laundries, and restaurants where antimicrobial products are also used. Since this study is characteristic of antimicrobial use in all situations, the AEATF does not view the somewhat higher airflow rate as a negative and no steps to minimize the HVAC flow will be taken.

It is important to emphasize that the primary goal of the monitoring program is to characterize the range and magnitude of worker exposures and not all ancillary parameters can, or should, be controlled. Given the very short duration of a pouring event, the air flow will, in a practical sense, have little impact.

HSRB Lines 427 to 438 - It was suggested that a provision be put in the protocol that the study observer can decide if someone's dosimeters should be changed between the two monitoring events if the dosimeter becomes visibly wet during the first ME. The concern is that if the dosimeter becomes locally saturated by a significant spill or splash, its ability to retain further chemical may be compromised. This should be done in such a way as to not cause change in the participant's behavior.

AEATF Response: This is a good idea and will be added to the protocol.

HSRB Lines 438 to 441 – No rationale was given for using DDAC in the conventional pour scenario and ADBAC in the reduced-splash pour scenario versus randomizing the two antimicrobial agents between the conventional and reduced-splash containers.

AEATF Response: A rationale will be added to the protocol. Because we want to quantify the exposure of pouring from conventional containers and reduced-splash containers, while minimizing the number of participants, the test substance in the conventional containers must be different from the test substance in the reduced-splash containers. Since exposure to an active ingredient of the same formulation type is generic and does not have an influence on exposure, there was no reason to randomize the two test substances between the conventional and reduced-splash containers. For simplicity's sake, it was decided that DDAC will be used in the conventional containers and ADBAC in the reduced splash containers.

HSRB Lines 445 to 452 – There was some concern noted regarding the lack of description or list of candidate source containers that would be used in the study.

AEATF Response: Since this study is to be representative of people pouring from a wide range of container sizes and shapes, we did not want to restrict what we would use other than providing the target container capacities to ensure we had diversity in the source containers. A description of the containers used in the study along with photographs will be in the final report.

HSRB Lines 537 to 539 – Both the Agency and the Board agree that AEATF should identify the recruiting newspapers and specify "Spanish" rather than a "second alternative language" in the protocol.

AEATF Response: These changes will be made.

HSRB Lines 557 to 558 – The HSRB agrees with the Agency's suggestion to clarify the steps that participants should take if they have an adverse reaction within 24 hours of participating in the study.

AEATF Response: This will be added to an SOP.

HSRB Lines 572 to 637 – Various edits to the ICF have been recommended.

AEATF Response: All of the recommendations will be incorporated. Based on the discussion at the HSRB meeting, the AEATF has decided to remove the language regarding returning individual research results to the participants.

As recommended by EPA and the HSRB, changes were made to the protocol by the AEATF II and submitted to EPA. The changes are detailed below as submitted by the AEATF II in their January 18, 2012 correspondence (verbatim):

AEATF Response: A number of changes were made to the liquid pour protocol since it was reviewed and approved by the IIRB on July 20, 2011. These changes are based on comments received from the US EPA in its science and ethics review dated September 23, 2011 and suggestions received from the EPA HSRB (Human Studies Review Board) meeting on October 19-20, 2011. Some additional changes have been made by the AEATF, the majority of which are a result of increased knowledge about the available containers, products, and the practical aspects of implementing this protocol. None of these changes alter the fundamental design of the study or its objectives and most of these changes have been coordinated with EPA prior to incorporating them in a revised protocol. The changes are grouped as "Changes Based on EPA and/or HSRB Suggestions" and "Changes Based on a Final AEATF Review".

Changes Based on EPA and HSRB Suggestions

1. The order in which each participant pours his/her set of source containers will be up to the individual participant. The set of 10 conventional pour or 15 reduced-splash pour containers will be placed in a group, not a line, so that there will be no influence as to the order that they should be picked up.
2. The 3 subjects out of the 6 in Group 2 who will use a measuring cup will be randomly selected.
3. The participants will be allowed to fill the trigger spray bottles with water and product in any order that they would like.
4. A description of how the different size source containers will be randomly selected for each ME was included (note this applies only to groups where there are multiple container sizes). In addition, a provision was added that if the random array results in 80% (8 out of 10 conventional or 12 out of 15 reduced-splash) or more of the source containers being the same size, that particular random array will not be used
5. Details regarding the test room air flow measurements and target airflow were added.
6. The newspapers used for the recruiting advertisements were identified.
7. References to an "alternative second language" have been replaced with "Spanish"
8. A statement was added to the consent form which indicates that if a test subject experiences symptoms within 24 hours after participating in the study and he/she believes they are related to participation in the study, he/she should contact the Study Director. The procedure for handling and documenting such a call was incorporated into an existing SOP.
9. A new product data sheet was generated for each of the two diluted test substances being used in the study since the registered product labels are for the undiluted products. The product data sheets and MSDSs are appended to the protocol and will be available should a participant request to see them. The protocol specifies that label safety information will be explained to study participants.
10. The orientation of each test subject in the test room with respect to the direction of air flow and the containers he is pouring will be documented in the raw data. The subject will be free to position himself/herself relative to the receiving container(s) within the test room.
11. The procedures for monitoring study participants were changed to allow the study observer to decide if someone's dosimeters should be changed between the two

monitoring events if the dosimeter becomes visibly wet during the first ME. The changing of the dosimeter would occur once this ME is complete. The concern is that if the dosimeter becomes locally saturated by a significant spill or splash, its ability to retain further chemical may be compromised. This should be done in such a way as to not cause change in the participant's behavior. The changing of the dosimeter would entail removal of the affected outer dosimeter (shirt or pants, or both if both are visibly wet) and the inner dosimeter if that has also become visibly wet. New dosimeters would be placed on the subject prior to him starting his next ME.

12. A rationale was added for assigning DDAC in the conventional pour scenario and ADBAC in the reduced-splash pour scenario versus randomizing the two antimicrobial agents between the conventional and reduced-splash containers.

13. An explanation was added to explain why there is a lack of description or list of candidate source containers.

14. A few edits were made to the consent form to improve clarity.

15. Based on the discussion at the HSRB meeting, the AEATF has elected to remove the language regarding returning individual research results to the participants.

16. The ICF was updated to include breach of confidentiality associated with photographs taken or video recorded as a potential risk associated with study participation.

Changes Based on a Final AEATF Review

1. The receiving containers will be evenly split between the MEs in each container size group. For example, in Group 1 there will be 6 MEs, and they will use either the spray bottle or the 2 gallon bucket as the receiving container. Three MEs will be randomly selected to use the spray bottles and 3 MEs will use the 2 gal bucket. The same procedure will be used for Group 2 where 2 MEs will use the 2 gal buckets, 2 MEs will use the 4 gal buckets, and 2 MEs will use the large basins.

2. The 4th row in Group 2 (indicating that ten 180 oz containers would be poured) was removed from Tables 2 and 3. This allows the 6 MEs to be evenly divided among the three source container/receiving container combinations. This was inadvertently left in Tables 2 and 3.

3. There will be no restriction on where potential test subjects reside. The sentence limiting recruitment only to people living in Lake County was revised. People living in counties surrounding Concord, Ohio can apply to participate in the study.

4. The recruitment period was changed from 4 weeks to 2 weeks because it is anticipated that by placing the ad in 4 media outlets (hard copy and on-line when possible), 22 interested respondents will be identified rapidly.

5. All source containers will be provided to the test subjects with their lids on.

6. The hoods in the test rooms will be turned off and closed during the MEs. In addition, the doors to the test rooms will be closed during the monitoring.

7. The Exposure Observations section was updated to include instructions to record all activities associated with spills and clean-up and that rags or paper towels should be available to the study participants in case they want to use them.

8. Correction of incorrect minimum volume to be poured on page 11.

9. The container sizes in Group 2 (medium containers) for conventional pour have been changed from 96, 128, and 180 oz to 128, 202 (6 liter), and 256 oz (2 gallon).

Member companies were asked to provide new, empty containers for use in the study. No one could provide 96 oz or 180 oz containers, and we were told these were odd sizes. More typical sizes sold by member companies were substituted. The goal of including a range of container sizes in the study was to add diversity to the study design. The actual sizes used in the study reflect the range of sizes of containers used for antimicrobial products.

10. The container size in Group 1 (small containers) for reduced-splash is 64 fl oz. At the time the draft protocol was written, a range of 60 to 64 fl oz was stated to allow for some flexibility. The size of the containers is now known.

11. Maquat DS 1412 10% (EPA registration number 10324-25) was replaced by Maquat 1412-10% FCS (EPA registration number 10324-111). Both products contain the same active ingredient, 10% ADBAC. Maquat 1412-10% FCS is a water-based formulation whereas Maquat DS 1412 10% contains EDTA and other additives. The reason for substituting Maquat 1412-10% FCS is because the registrant (Mason Chemical Company) did not have any Maquat DS available in their production facility at the time that the chemical was ordered for the analytical pre-study method work. Rather than making up a special small batch just for this study, they suggested that we use Maquat 1412-10% FCS as it is essentially the same thing. Since the AEATF focus is on the active ingredient, not the other components of the formulation, this substitution was considered acceptable.

12. Large rigid polyethylene low-walled water troughs of 50 gallon capacity will be used as the large receiving containers for part of Group 2 and all of Group 3 rather than baby swimming pool-type containers for practical reasons. The non-rigid structure of a child's plastic swimming pool, its small size, and the tendency for tearing, makes this a poor option. Based on the total volume of liquid poured in Group 3 (20 to 30 gallons), a 50 gallon receptacle is appropriate. The large water troughs would provide a good simulation for pouring into a swimming pool or spa or an industrial vat.

13. Field fortification events will take place every other day of monitoring, starting on the first day of monitoring. It is anticipated that monitoring will occur on consecutive days over a period of 6 to 10 days, not a minimum of 9 days as stated in the draft protocol.

14. Information missing from the field recovery and analytical sections regarding reference standards, internal standards, and fortification solutions has been added. Information on the methods and field fortifications has been updated as necessary based on method development work that has occurred since July, 2011.

1.3.2 Protocol Amendments

The study report (page 74) lists 5 protocol amendments. The amendments comprised of specifying where subject's shoes would be removed; no calibration of the bathroom scale to weigh subjects; wrapping of face/neck wipes instead of the use of glass jars; identifying which phase of the report the monitored residues would be corrected for field recoveries; and identifying the extraction solvents.

1.3.3 Protocol Deviations

A total of 7 protocol and 2 SOP deviations were noted in the study (study report pages 74 & 75). The 9 protocol and SOP deviations included the following: (1) bathroom scale not calibrated to GLP standards as per SOPs; (2) order in which the shoes were removed from test subjects; (3) 400 ml instead of 500 ml was used for the hand wash; (4) one test subject removed their own shoes (Subject G, conventional ME 16 and reduced splash ME 7); (5) one subject unbuttoned 2 top buttons of shirt (Subject F, conventional ME 1 and reduced splash ME 10); (6) diluted standard stock solution instead of the stock solution was analyzed; (7) internal standards of DDAC and ADBAC were shipped and received prior to initiation of the protocol; (8) SOP 8E.1 specifies fortifying the OVS tube in through the glass fiber filter but instead it was fortified onto the surface of the glass fiber filter; and (9) SOP 8C.2 specifies the use of 8 ply cotton pads and instead 12 ply was used. 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 liquid pour study was conducted in two rooms in a laboratory in Concord, Ohio. Both test rooms measured 12ft x 24ft with a 13.5ft ceiling. Photos and schematics of the laboratory & test rooms are located in Appendix C starting on page 150 of the study report.

- ***Pesticides Tested:*** The two test substances monitored were didecyl dimethyl ammonium chloride (DDAC, CAS number 7173-51-5) in the conventional pour containers and tetradecyl dimethylbenzyl ammonium chloride (C14-ADBAC, CAS number 139-08-2) in the reduced splash containers. Maquat 1412-10% and Maquat WP were diluted by the study researchers to make the batches of product concentrate of 0.2 percent active ingredient. To avoid confusion, the 0.2 percent ADBAC is equivalent to 0.1 percent C14-ADBAC as C14-ADBAC is 50 percent of ADBAC.

  Test System: The study was designed to test two types of containers, conventional and reduced splash, in various packaging sizes. As described in the study report, *"Each subject conducted two distinct sets of pouring events sequentially, one with conventional pour containers and one with reduced-splash (or "no-glug") containers. The consecutive use of the two active ingredients allowed for simultaneous analysis of the same set of samples. This allowed each test subject to conduct both monitoring events sequentially without the need to change dosimeters between container types."* The conventional and reduced splash containers were both separated into 3 groups. Table 2 provides the size of the product containers, the size/type of receiving containers to which the subjects poured the product, and the number of containers poured. Group 1 has been further subdivided by EPA within this review to make a distinction between the receiving containers. EPA is making this distinction because the act of pouring the product into the small opening of the spray bottles in Group 1a greatly increased the hand exposures (see

statistical analysis below). Figure 1 provides example photos from the liquid pour study showing the various containers and pouring events.

Table 2. Test System Design.

Group	Container Type	Product Container Size	Number of Product Containers Poured per ME	Receiving Container
1a	Conventional (CP)	24, 32, 64 oz	10	32 oz spray bottles
	Reduced-splash (RS)	64 oz	15	
1b	Conventional (CP)	24, 32, 64 oz	10	2 gallon buckets
	Reduced-splash (RS)	64 oz	15	
2	Conventional (CP)	128, 202, 256 oz	10	2 or 4 gallon buckets, or 50 gallon troughs
	Reduced-splash (RS)	96, 128, 180 oz	15	
3	Conventional (CP)	5 gallons	4	50 gallon troughs
	Reduced-splash (RS)		6	

Note: The study report (Tables 7 & 8, pages 85 & 86) lists the specific containers assigned to each of the individual 18 MEs.

Figure 1. Liquid Pouring, Examples Photos from AEATF II Study Report.

Figure 1. Liquid Pouring, Examples Photos from AEATF II Study Report (cont.)

Figure 1. Liquid Pouring, Examples Photos from AEATF II Study Report (cont.)

- ***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 78 & 79 of the study report.

- ***Sample Size:*** The study consisted of 3 groups and 6 MEs per group for a total of 18 monitoring events (ME) for each of the conventional and reduced splash containers (n=18 for conventional; and n=18 for reduced splash). Each ME within a scenario is a different subject; but each subject performed both a conventional pour and a reduced splash pour (i.e., total of 18 test subjects, not 36 test subjects).

- ***Treatment Solutions:*** The product containers did not come pre-packaged. The study researchers diluted a concentrated product down to 0.2 percent active ingredient and filled the various size containers prior to providing those containers to the subjects. The nominal 0.2 percent active ingredient for both ADBAC (C14 ADBAC is 50 percent of ADBAC) and DDAC was prepared by the researchers using Maquat 1412-10% FCS (EPA Reg. Nos. 10324-111) and Maquat WP (EPA Reg. No. 10324-91), respectively.

The dilute solution was prepared in 55 gallon drums prior to filling the conventional and reduced splash containers. The nominal concentration was confirmed for each batch. The measured concentration used in the determination of AaiH per ME was 0.19 and 0.11 percent for DDAC and C14 ADBAC, respectively.

- ***Duration & AaiH:*** The sampling times for the conventional containers ranged from 3 to 14 minutes (average 8.5 minutes); for the reduced splash containers the sampling times ranged from 8 to 22 minutes (averaged 13.1 minutes). The duration of the sampling pump run times were used as the duration of the ME and to calculate the volume of air sampled (m^3) and the corresponding air concentration (mg/m^3). The sampling time durations in some of the study report tables are incorrectly switched for some of the MEs. The AEATF II provided EPA with the sampling times correctly matched to the individual MEs and will submit an amendment to the study report once the HSRB review is complete. The sampling times are presented correctly in the EPA analyses and in this review (e.g., Tables 5 and 6).

  The amount of active ingredient handled (AaiH) was measured by weighing the containers prior to and subsequent to the monitoring event. The AaiH for the conventional containers ranged from 0.0045 to 0.269 with a mean of 0.168 lbs ai. The AaiH for the reduced splash containers ranged from 0.0039 to 0.260 with a mean of 0.141 lbs ai.

  The AaiH as well as the pouring times for individual MEs are reported in Tables 3, 4, 5 and 6 below.

- ***Pouring Procedures***: The test subjects were *"… given basic instruction of what needed to be poured into what; not to pour so much product into a bucket so that it overflows; and how many times to use the measuring cup and when to just pour from the container directly into the receiving containers."* The test subjects were instructed to pour as they would normally do. Appendix D, starting on page 163 of the study report, records the observation notes taken during each ME. There are a number of observations that note the solution overflowed onto the subject's hands or dripping down the sides of the containers.

- ***Environmental Conditions*:** Environmental conditions (humidity and temperature) are reported for the MEs on page 87 of the study report. The humidity ranged from ~12 to 34%. Temperatures ranged from ~67 to 78º F. The heating ventilation air conditioning (HVAC) system was operating and air flow rates were monitored just before and after the study. *"An Alnor Bolometer model 6463 Flow Capture Hood was used to measure the air flow at the supply vent and the exhaust vent by placing the hood of the instrument completely over the vent to get the maximum airflow through the Bolometer. Readings were taken over a 30 minute period. The fume hoods in the rooms were turned off and the doors shut when the readings were taken. Duplicate readings were taken for each room. The hourly air change rate in test room 1 (Room 245) on February 2 and 23 was 8.65 and 10.69 respectively. The hourly air change rate in test room 2 (Room 244) on February 2 and 23 was 7.66 and 6.77 respectively."*

2.0 Results

2.1 Scenario Justification (Statistical Significance)

This study was originally designed to provide only two distinct exposure scenarios for liquid pouring: conventional and reduced splash. However, based on the results of the study, EPA has determined that there are three exposure scenarios: pouring into spray bottles, conventional containers, and reduced splash containers. EPA has determined that the Group 1a (i.e., pouring into spray bottles) is a logical and statistically justified scenario. Spray bottles are to be used for applying disinfectant and/or sterilizer products according to directions commonly appearing on antimicrobial labels. Because this is a commonly specific label use, it is logical that the risk assessment supporting these claims can be tailored specifically to the pouring into spray bottles. In addition, there is statistical support to treat the three exposure scenarios separately.

To evaluate possible groupings, EPA first separated the measurements into 8 subgroups 1aCP, 1aRS, 1bCP, 1bRS, 2CP, 2RS, 3CP, 3RS, where for example 1aCP and 1aRS are the 3 measurements each in group 1a (pouring into spray bottles) for conventional pour and reduced splash containers, respectively. Summary statistics for these and other groupings are presented in Tables 1 to 7 of Appendix A. EPA fitted a statistical mixed model for the logarithm of the unit exposure:

Log(unit exposure) = subgroup + worker + error

so that each subgroup has a different geometric mean and the components of variance are the between-worker and within-worker random effects. P-values for various statistical comparisons are presented in Table 8 of Appendix A. A test of whether the geometric means for 1aCP and 1aRS are equal (p-value = 0.88 for Long-Long dermal exposure) showed no statistically significant difference (at the 5 percent level) for each dermal or inhalation unit exposure, which justifies combining the RP and CP data for group 1a. A test of whether the pairs of geometric means for 1bCP and 1bRS, 2CP and 2RS, and 3CP and 3RS are equal (p-value = 0.01 for Long-Long dermal exposure) showed a statistically significant difference for each dermal unit exposure and for inhalation concentration, which justifies separating the CP and RS data for other receiving containers. Similarly, other tests showed statistically significant differences between pouring into spray bottles and not pouring into spray bottles for conventional containers, and between pouring into spray bottles and not pouring into spray bottles for reduced splash containers (p-values < 0.005 for Long-Long dermal). These results justify separating the results of this study into the three exposure scenarios or groups: Bottles (group 1a); Conventional (subgroups 1bCP, 2CP, and 3CP); and Reduced Splash (subgroups 1bRS, 2RS, and 3RS).

2.2 QA/QC Recovery Results

Controls: The non-fortified field and laboratory control samples were all less than the limit of quantification (LOQ). The LOQs (LODs) for the various matrices are air sampling OVS tubes 10 (3) ng/sample, neck/face wipe 50 (15) ng/sample, WBD sections 3 (0.9) µg/sample, and hand wash 2 (0.6) ng/mL (hand wash samples were 500 mL per sample).

Method Validation: The method validation consisted of 7 samples for each monitoring matrix at 3 fortification levels. The C14-ADBAC for the 5 matrices ranged from 93±2 to 103±5 percent and DDAC ranged from 79±5 to 97±3 percent.

Laboratory Recoveries: The concurrent laboratory recovery values for all of the matrices for DDAC ranged from 74.7 to 113.5 percent and for C14-ADBAC ranged from 87.0 to 116.3 percent. A summary of the overall concurrent laboratory recovery samples, for each monitoring matrix is reported in the study report starting on page 90.

Field Recoveries: Most of the individual field fortified recovery values range within 70 to 120 percent. The DDAC exceptions include a high fortification level for one hand wash recovery (173.7 percent) where the researcher noted the fortifying sample contained the incorrect amount; and 2 face/neck wipe fortification levels (high fortification level) where the recoveries were 64.1 and 67.6 percent. The hand wash recovery of 173.7 percent was considered incorrect and not used for corrections or reported in mean recoveries. The C14-ADBAC exception was for one hand wash recovery of the high fortification level where the recovery was 178.4 percent. The researcher noted the incorrect amount was used in the fortifying solution and this recovery value was not used for corrections or reported in the mean recoveries. A summary of the field fortified recovery samples for DDAC and C14-ADBAC for each monitoring matrix is reported starting on page 95 of the study report. The mean recoveries for all matrices are approximately in the 90 to 100 percent range. All exposure/field matrices were corrected for the field fortified recovery results.

2.3 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 and face/neck wipes. 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 samples are adjusted as appropriate according to recovery results from field fortification samples.

The various analyses of residues on the dosimeters worn by each individual worker allow for the estimation of 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.

Dermal exposures to the hands and face/neck are also corrected for sampling efficiency. For details on the sampling efficiency studies and correction factors, see EPA reviews of the AEATF II studies for mop (DDAC) and aerosol can (ADBAC) that were previously reviewed by the HSRB.

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.

Inhalation Exposure: Inhalation exposure is measured using a personal air sampling pump and an OSHA Versatile Sampler (OVS) tubes. 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. 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).

Inhalation unit exposures are provided in 3 different methods:

(1) Air concentration normalized by AaiH (i.e., mg/m^3/lb ai handled) is calculated by dividing the air concentrations by the amount of ai handled.
(2) Air concentration expressed as an 8 hour time weighted average (TWA) and normalized by AaiH (i.e., mg/m^3/lb ai handled) is calculated as the air concentration ((mg/m^3) / lb ai) * exposure duration (hours/day) / 8 (hours / day).
(3) Inhalation exposure (mg/lb ai) or dose is calculated as the air concentration ((mg/m^3) / lb ai) * breathing rate (1 m^3/hour) * exposure duration (hours/day).

2.4 Dermal and Inhalation Exposure Results

Results -- A summary of the dermal results of the 18 MEs are presented in Table 3 for the MEs pouring into spray bottles (i.e., Group 1a) and Table 4 for the MEs pouring from the conventional and reduced splash containers 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). Also shown for comparison are the dermal results for the hand exposures only, demonstrating that most of the dermal exposures in these no gloves clothing configurations were to the hands. Tables 5 and 6 report the results for the inhalation monitoring. These tables report the results for each individual worker along with empirical statistical summaries of each group and overall exposures. **Note:** The recommended unit exposures summarized in Table 1 above are based on the results of the lognormal mixed model, not the empirical summaries provided in Tables 3, 4, 5, and 6. 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 through 7 for detailed summaries by group and subgroup, and Appendix A, Tables 12 to 18 for confidence intervals by group);
- Lognormal simple random sampling model (see Appendix A, Tables 12 through 18); and
- Lognormal mixed model (see Appendix A, Table 9 for a summary, and Appendix A, Tables 12 through 18 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 9). 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.

Study Observations – The liquid pour study includes the recorded individual participant activities by observers. Detailed observations recorded during each ME capturing the notable events that occurred during the liquid pouring can be viewed in the study report's Appendix D starting on page 163. Although a review of these observations indicate that the solution dripped

on hands, these types of exposures are expected based on the task and are not considered outliers in the data. The following observations are highlighted:

- From the text of the study report (page 37): *"A measuring cup was used for all Group 1 MEs and four out of six MEs in Group 2. The first volunteer that used a measuring cup (ME06 conventional pour and ME01 reduced-splash) used an 8 oz (1 cup) measuring cup. This measuring cup was made by Rubbermaid Commercial out of polycarbonate material and purchased from US Plastic Corp. Because it was discovered that this measuring cup did not have a spout or lip which made it difficult to pour into the narrow opening of the 32 oz spray bottles, all subsequent uses of a measuring cup were done using the 16 oz measuring cups that had been purchased for the study. The 16 oz measuring cups were purchased from Leslie's Poolmart and had a pouring spout."*

- Conventional pour (CP) MEs 6, 7, 8, 11, 12, and 13 had hand residues greater than 1 mg (1.2 to 3.8 mg) and reduced-splash (RS) ME 1 and 7 had 1.8 and 4.4 mg, respectively. Most of the other MEs had hand residues equal to or less than ~0.5 mg. Therefore, the two MEs that used the measuring cup without the spout (CP ME 6 = 1.8 mg and RS ME 1 = 1.8 mg) were among the MEs with the highest hand exposure, but not the highest.

- Many of the observational notes indicated incidental contact from dripping from the product containers. None of these incidents appear to have resulted from the subject being grossly negligent. These MEs are not considered outliers in the development of the unit exposures.

- During the HSRB review of the protocol, there was a discussion/concern that spills may occur which could potentially saturate the WBD. Tables 27 and 28 of the study report noted only one body part with greater than 1 mg. This one body part was for ME 13 in the conventional pour scenario where the outer dosimeter for the upper legs reports a value of 1.5 mg. The observational notes for this same ME (page 176 of study report) notes that when the lid was removed from the 5 gallon bucket some of the product spilled onto the pants. Overall, saturation of the WBDs did not appear to be problematic (and most of the exposure was to the hands).

Impact of Non-detects -- All of the hand samples were above the limit of quantification (LOQ). In fact, the hand exposure contributed to over 80 percent of the total dermal exposure (summed over face and neck, hands, and all the inner and outer dosimeters). For the Conventional Pour, 4 of the 18 face and neck measurements, 67 of the 108 outer dosimeter measurements, 107 of the 108 inner dosimeter measurements, and 6 of the 18 OVS measurements were below the LOQ. For the Reduced Splash, 0 of the 18 face and neck measurements, 41 of the 108 outer dosimeter measurements, 105 of the 108 inner dosimeter measurements, and 9 of the 18 OVS measurements were below the LOQ. All samples with results less than the LOQ are included in the calculation of total exposure as ½ LOQ. In Appendix A, Tables 10 and 11 we present arithmetic means and 95th percentiles calculated using substitutions of 0, ½ LOQ, and LOQ for values below the LOQ and also using a multiple

imputation method based on a fitted log-normal distribution. These alternative approaches changed the Long-Long unit exposures by no more than 7 percent. Since over 40 percent of the OVS measurements were less than the LOQ, the inhalation unit exposures were changed by up to 20 percent for the Conventional and Reduced Splash groups, but by more than 80 percent for the Bottle group (see Appendix A, Table 11). EPA will consider reassessing the inhalation unit exposures presented in Table 1 that are based on ½ LOQ in favor of using the multiple imputation method.

Table 3. Summary (empirical model arithmetic means) of dermal unit exposure estimates for pouring into spray bottles.

ME	Container	AaiH (lb)	Unit Exposure (mg/lb ai)			
			Hands	Long-Long	Long-Short	Short-Short
1	CP	0.0048	113.32	115.28	115.59	116.42
3	CP	0.0045	120.19	122.22	122.55	122.88
5	CP	0.0051	92.77	94.70	95.00	101.63
Mean	CP	0.0048	108.76	110.73	111.05	113.64
SD	CP	0.0003	14.27	14.31	14.33	10.90
1	RS	0.0039	456.92	459.47	461.15	464.55
3	RS	0.0043	97.27	99.48	99.83	100.18
5	RS	0.0044	38.30	40.36	40.70	41.04
Mean	RS	0.0042	197.50	199.77	200.56	201.92
SD	RS	0.0003	226.60	226.84	227.61	229.36
Mean	Overall	0.0045	153.13	155.25	155.80	157.78
SD	Overall	0.0004	151.60	151.80	152.34	153.06

Table 4. Summary (empirical model arithmetic means) of dermal unit exposure estimates for pouring from conventional and reduced splash containers.

		Conventional					Reduced Splash				
			Unit Exposure (mg/lb ai)					Unit Exposure (mg/lb ai)			
Group	ME	AaiH (lb)	Hands	Long-Long	Long-Short	Short-Short	AaiH (lb)	Hands	Long-Long	Long-Short	Short-Short
1	2	0.0536	10.0	10.1	10.3	11.1	0.0633	6.36	6.51	6.53	6.55
1	4	0.0388	13.7	13.9	14.0	14.0	0.0626	0.98	1.13	1.16	1.97
1	6	0.0505	35.0	35.2	35.2	40.0	0.0642	1.25	1.39	1.66	1.68
1	Mean	0.0476	19.6	19.8	19.8	21.7	0.0634	2.86	3.01	3.12	3.40
1	SD	0.0078	13.5	13.5	13.5	15.9	0.0008	3.03	3.03	2.97	2.73
2	7	0.2050	6.3	6.4	6.4	6.4	0.1413	31.31	31.39	31.48	32.24
2	8	0.1990	6.8	6.8	7.4	7.4	0.1246	3.20	3.28	3.34	3.48
2	9	0.2100	1.5	1.6	1.6	1.8	0.1373	1.85	1.92	1.93	1.97
2	10	0.2170	0.2	0.2	0.6	0.6	0.1199	2.79	2.88	2.89	3.64
2	11	0.2230	13.8	13.8	14.1	14.4	0.1424	0.84	0.90	0.93	1.06
2	12	0.2510	15.2	15.2	15.2	15.2	0.1448	4.05	4.33	4.43	4.47
2	Mean	0.2175	7.3	7.3	7.6	7.6	0.1351	7.34	7.45	7.50	7.81
2	SD	0.0185	6.1	6.1	6.1	6.1	0.0103	11.79	11.78	11.81	12.03
3	13	0.2690	13.5	13.6	13.6	16.1	0.2535	0.26	0.30	0.32	0.86
3	14	0.2400	0.8	0.8	0.8	0.9	0.2601	0.64	0.68	0.73	1.12
3	15	0.2670	1.1	1.1	1.2	1.2	0.2601	0.27	0.30	0.34	0.80
3	16	0.2580	1.4	1.4	1.4	1.6	0.2535	0.18	0.21	0.22	0.39
3	17	0.2560	3.6	3.6	3.6	3.7	0.2491	0.09	0.13	0.13	2.24
3	18	0.2650	1.4	1.4	1.4	1.4	0.2535	0.67	0.71	0.72	0.75
3	Mean	0.2592	3.6	3.7	3.7	4.1	0.2550	0.35	0.39	0.41	1.03
3	SD	0.0107	4.9	5.0	5.0	5.9	0.0043	0.24	0.25	0.25	0.64
Overall	Mean	0.2002	8.3	8.4	8.5	9.1	0.1687	3.65	3.74	3.79	4.21
Overall	SD	0.0823	9.2	9.3	9.3	10.4	0.0781	7.85	7.86	7.87	7.94

Table 5. Summary (empirical model arithmetic means) of inhalation unit exposure estimates for pouring into spray bottles.

ME	Container	AaiH (lb)	Duration (minutes)	Unit Exposure		
				Concentration (mg/m^3/lb ai)	Dose (mg/lb ai)	8-hour Time Weighted Average (mg/m^3/lb ai)
1	CP	0.0048	13	0.03988	0.00864	0.00108
3	CP	0.0045	13	0.04231	0.00917	0.00115
5	CP	0.0051	14	0.03433	0.00801	0.00100
Mean	CP	0.0048	13.3	0.03884	0.00861	0.00108
SD	CP	0.0003	0.6	0.00409	0.00058	0.00007
1	RS	0.0039	20	0.03224	0.01075	0.00134
3	RS	0.0043	22	0.02617	0.00959	0.00120
5	RS	0.0044	17	0.03311	0.00938	0.00117
Mean	RS	0.0042	19.7	0.03051	0.00991	0.00124
SD	RS	0.0003	2.5	0.00378	0.00074	0.00009
Mean	Overall	0.0045	16.5	0.03467	0.00926	0.00116
SD	Overall	0.0004	3.8	0.00577	0.00093	0.00012

Table 6. Summary (empirical model arithmetic means) of inhalation unit exposure estimates for pouring from conventional and reduced splash containers.

		Conventional					Reduced Splash				
				Unit Exposure					Unit Exposure		
Group	ME	AaiH (lb)	Duration (minutes)	Concentration (mg/m^3/lb ai)	Dose (mg/lb ai)	8-hour Time Weighted Average(mg/m^3/ lb ai)	AaiH (lb)	Duration (minutes)	Concentration (mg/m^3/lb ai)	Dose (mg/lb ai)	8-hour Time Weighted Average (mg/m^3/ lb ai)
1	2	0.0536	9	0.00509	0.00076	0.00010	0.0633	14	0.00279	0.00065	0.00008
1	4	0.0388	12	0.00532	0.00106	0.00013	0.0626	11	0.00359	0.00066	0.00008
1	6	0.0505	7	0.02590	0.00302	0.00038	0.0642	14	0.00273	0.00064	0.00008
1	Mean	0.0476	9.3	0.01210	0.00162	0.00020	0.0634	13.0	0.00304	0.00065	0.00008
1	SD	0.0078	2.5	0.01195	0.00123	0.00015	0.0008	1.7	0.00048	0.00001	0.00000
2	7	0.2050	12	0.00756	0.00151	0.00019	0.1413	17	0.00104	0.00029	0.00004
2	8	0.1990	12	0.03368	0.00674	0.00084	0.1246	17	0.00422	0.00120	0.00015
2	9	0.2100	5	0.03314	0.00276	0.00035	0.1373	12	0.00352	0.00070	0.00009
2	10	0.2170	7	0.01527	0.00178	0.00022	0.1199	12	0.01007	0.00201	0.00025
2	11	0.2230	12	0.01388	0.00278	0.00035	0.1424	14	0.00125	0.00029	0.00004
2	12	0.2510	12	0.00174	0.00035	0.00004	0.1448	9	0.00188	0.00028	0.00004
2	Mean	0.2175	10.0	0.01754	0.00265	0.00033	0.1351	13.5	0.00366	0.00080	0.00010
2	SD	0.0185	3.2	0.01321	0.00219	0.00027	0.0103	3.1	0.00338	0.00070	0.00009
3	13	0.2690	5	0.02018	0.00168	0.00021	0.2535	9	0.01070	0.00160	0.00020
3	14	0.2400	4	0.05705	0.00380	0.00048	0.2601	8	0.00361	0.00048	0.00006
3	15	0.2670	4	0.01313	0.00088	0.00011	0.2601	10	0.00223	0.00037	0.00005
3	16	0.2580	5	0.00191	0.00016	0.00002	0.2535	10	0.00794	0.00132	0.00017
3	17	0.2560	3	0.01285	0.00064	0.00008	0.2491	8	0.00347	0.00046	0.00006
3	18	0.2650	4	0.00813	0.00054	0.00007	0.2535	12	0.00707	0.00141	0.00018
3	Mean	0.2592	4.2	0.01887	0.00128	0.00016	0.2550	9.5	0.00584	0.00094	0.00012
3	SD	0.0107	0.8	0.01966	0.00133	0.00017	0.0043	1.5	0.00326	0.00056	0.00007
Overall	Mean	0.2002	7.5	0.01699	0.00190	0.00024	0.1687	11.8	0.00441	0.00083	0.00010
Overall	SD	0.0823	3.6	0.01508	0.00173	0.00022	0.0781	2.9	0.00307	0.00055	0.00007

2.5 Evaluation of Scenario Benchmark Objective

Benchmark Objective -- The data from the study has been analyzed to see if the liquid pour 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 liquid pour study results meet the 3-fold relative accuracy objective for dermal and inhalation exposures for the Conventional and Reduced Splash groups, for inhalation exposures for Bottles, but not for dermal exposures for Bottles based on the mixed model. 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 and for the group mean logarithm of exposure) 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

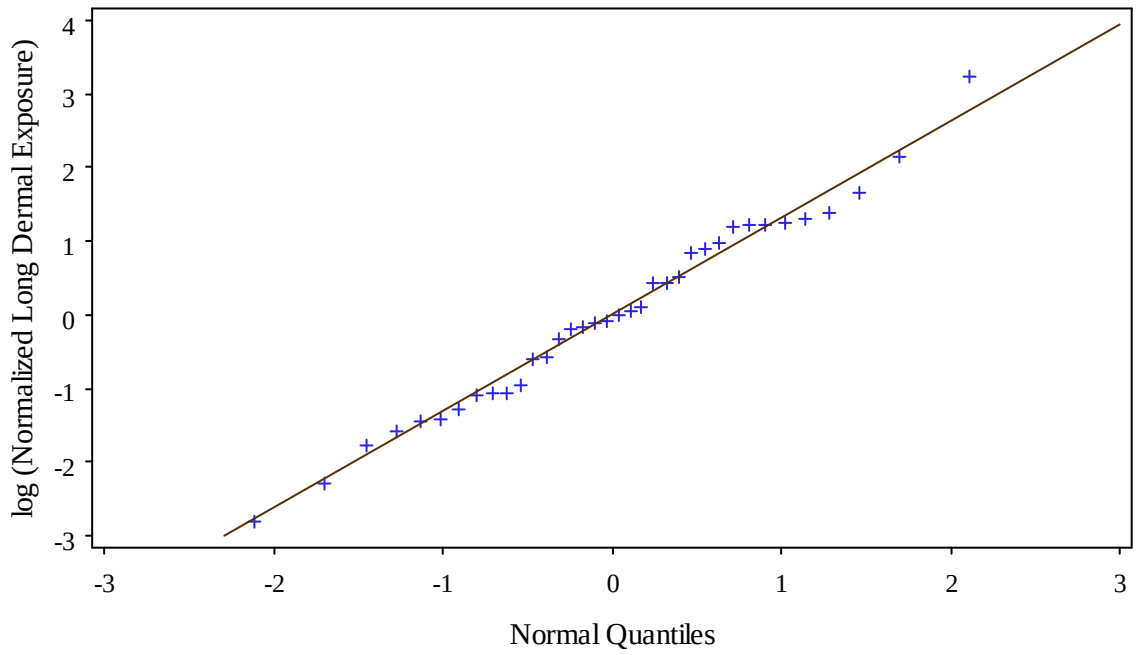

Figure 2. Quantile plot of normalized long dermal exposure data with a lognormal distribution normalized by pounds of Active Ingredient handled.

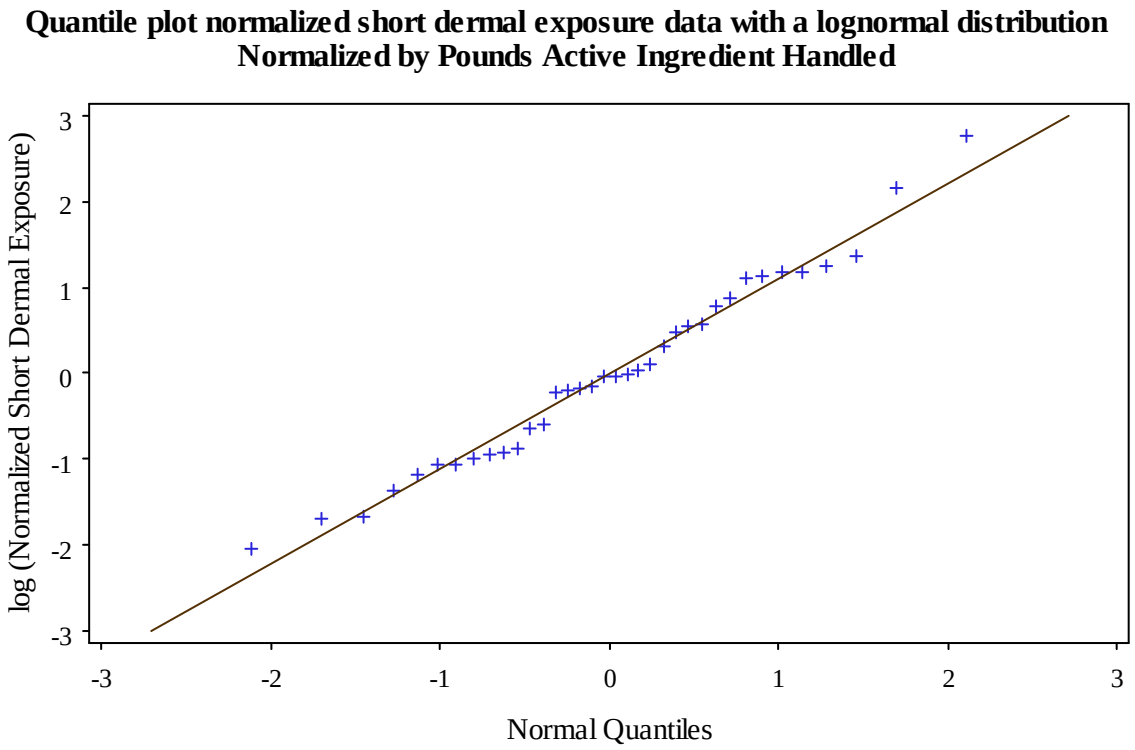

Figure 3. Quantile plot of normalized short dermal exposure data with a lognormal distribution normalized by pounds of Active Ingredient handled.

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

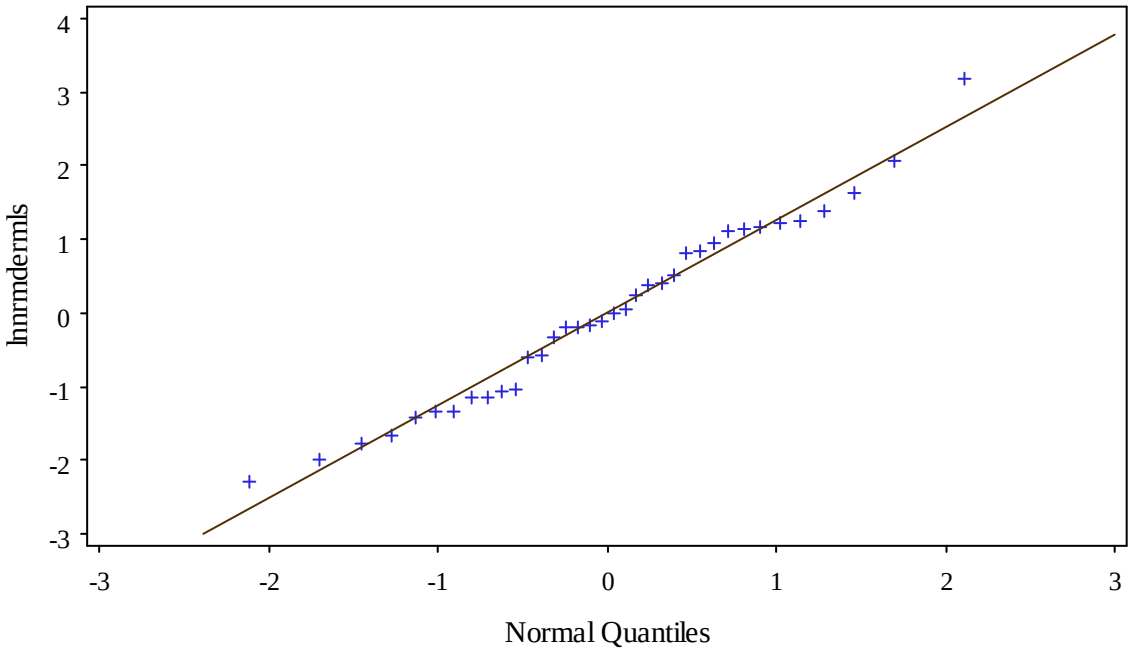

Figure 4. Quantile plot of normalized long short dermal exposure data with a lognormal distribution normalized by pounds of Active Ingredient handled.

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

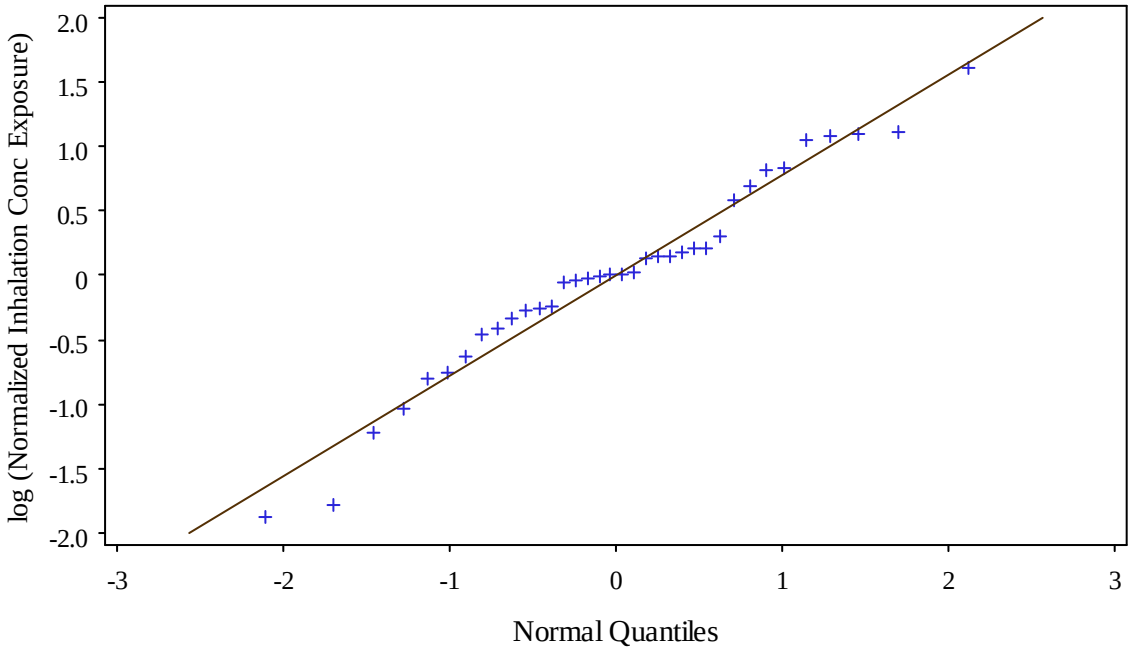

Figure 5. Quantile plot of normalized total inhalation exposure data with a lognormal distribution normalized by pounds of Active Ingredient handled.

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. Tables 7, 8 and 9 below presents the results for the liquid pour scenario, for the long pants, long-sleeved shirt and the inhalation concentration. The results of the variance component model are shaded within the tables as this model is the recommended approach to estimating the unit exposures. Results of the benchmark analysis for the other clothing configurations are reported in Appendix A, Table 14 (long pants, short-sleeved shirt) and Appendix A, Table 13 (short pants, short-sleeved shirt). Results for inhalation dose and inhalation 8-hour time weighted average are reported in Appendix A, Tables 17 and 18, respectively.

Table 7: Results of Primary Benchmark Analysis for the Bottle group: Long Pants, Long-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	116.2	39.5 – 376.4	3.2	0.0343	0.0180 – 0.0651	1.9
GSD_S	2.2	1.7 – 8.7	4.0	1.1858	1.3981 – 3.6254	3.1
GM_M	120.0	39.1 – 370.3	3.1	0.0343	0.0178 – 0.0655	1.9
GSD_M	3.9	2.8 – 5.4	1.4	2.2311	1.8484 – 2.7008	1.2
ICC	0.3	0.0 – 0.7	NA	0.0	0.0 – 0.48	NA
GM_S = geometric mean assuming SRS = "exp(average of 6 ln(UE)) values" GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 6 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	155.3	63.4 – 1007.6	6.5	0.0347	0.0220 – 0.0929	2.7
AM_U	158.1	70.1 – 1755.5	11.1	0.0348	0.0229 – 0.1045	3.0
AM_M	298.5	89.9 – 1005.7	3.4	0.0473	0.0240 – 0.0930	2.0
AM_S = average of 6 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 = $GM_M * \exp\{0.5*(\ln(GSD_M)^2\}$						
$P95_S$	459.5	132.4 – 4287.3	9.3	0.0423	0.0377 – 0.2912	6.9
$P95_U$	422.3	183.6 – 6158.5	14.6	0.0453	0.0453 – 0.3503	7.7
$P95_M$	1105.5	309.4 – 3817.5	3.6	0.1283	0.0613 – 0.2640	2.1
$P95_S$ = 95th percentile (i.e., estimated as the maximum unit exposure from the 6 unit exposures) $P95_U$ = 95th percentile based on $GM_S = GM_S * GSD_S^{1.645}$ $P95_M$ = variance component model-based 95th percentile = $GM_M * GSD_M^{1.645}$						

Table 8: Results of Primary Benchmark Analysis for the Conventional group: Long Pants, Long-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	4.1	2.0 – 8.0	2.0	0.0113	0.0076 – 0.0171	1.5
GSD_S	4.0	2.3 – 6.4	1.7	2,7484	1.6565 – 2.9691	1.7
GM_M	4.0	2.0 – 7.9	2.0	0.0113	0.0076 – 0.0171	1.5
GSD_M	3.9	2.8 – 5.4	1.4	2.2311	1.8484 – 2.7008	1.2
ICC	0.3	0.0 – 0.7	NA	0.0	0.0 – 0.48	NA
GM_S = geometric mean assuming SRS = "exp(average of 15 ln(UE)) values" GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 15 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	8.4	3.8 – 24.3	2.9	0.0170	0.0097 – 0.0245	1.8
AM_U	10.9	4.1 – 28.1	2.6	0.0189	0.0099 – 0.0253	1.9
AM_M	10.0	4.5 – 22.8	2.3	0.0156	0.0102 – 0.0243	1.6
AM_S = average of 15 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 = $GM_M* \exp\{0.5*(\ln(GSD_M)^2\}$						
$P95_S$	35.2	11.5 – 210.6	6.0	0.0571	0.0211 – 0.1184	2.7
$P95_U$	40.9	12.8 – 106.7	3.2	0.0598	0.0225 – 0.0785	2.7
$P95_M$	36.9	15.4 – 86.7	2.4	0.0424	0.0253 – 0.0705	1.7
$P95_S$ = 95th percentile (i.e., estimated as the maximum unit exposure from the 15 unit exposures) $P95_U$ = 95th percentile based on $GM_S = GM_S * GSD_S^{1.645}$ $P95_M$ = variance component model-based 95th percentile = $GM_M* GSD_M^{1.645}$						

Table 9: Results of Primary Benchmark Analysis for the Reduced Splash group: Long Pants, Long-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	1.2	0.6 – 2.5	2.0	0.0035	0.0024 – 0.0053	1.5
GSD_S	4.3	2.4 – 6.4	1.8	2.0072	1.6592 – 2.9904	1.5
GM_M	1.3	0.6 – 2.5	2.0	0.0035	0.0024 – 0.0053	1.5
GSD_M	3.9	2.8 – 5.4	1.4	2.2311	1.8484 – 2.7008	1.2
ICC	0.3	0.0 – 0.7	NA	0.0	0.0 – 0.48	NA
GM_S = geometric mean assuming SRS = "exp(average of 15 ln(UE)) values" GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 15 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	3.7	1.2 – 7.6	3.2	0.0044	0.0030 – 0.0076	1.7
AM_U	3.6	1.3 – 8.9	2.8	0.0045	0.0031 – 0.0079	1.8
AM_M	3.1	1.4 – 7.4	2.3	0.0049	0.0032 – 0.0076	1.6
AM_S = average of 15 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 = $GM_M * \exp\{0.5*(\ln(GSD_M)^2\}$						
$P95_S$	31.4	3.6 – 65.5	8.7	0.0107	0.0065 – 0.0373	3.5
$P95_U$	13.7	4.0 – 33.8	3,5	0.0111	0.0070 – 0.0249	2.2
$P95_M$	11.6	4.9 – 28.1	2.4	0.0132	0.0079 – 0.0223	1.7
$P95_S$ = 95^{th} percentile (i.e., estimated as the maximum unit exposure from the 15 unit exposures) $P95_U$ = 95^{th} percentile based on $GM_S = GM_S * GSD_S^{1.645}$ $P95_M$ = variance component model-based 95^{th} percentile = $GM_M * GSD_M^{1.645}$						

For the Conventional and Reduced Splash groups, the benchmark of 3-fold accuracy for dermal and inhalation unit exposures for the mixed model has been met for all 3 clothing configurations and inhalation exposures, using the parametric bootstrap method (non-parametric bootstrap approaches were not devised for this model). For the bottle group, the benchmark of 3-fold accuracy for dermal and inhalation unit exposures has been met for all inhalation exposures for the mixed model, but the benchmark of 3-fold accuracy was not met for the 3 clothing configurations. For the empirical and lognormal simple random sampling models, the benchmark of 3-fold accuracy was met in some but not all cases; this may be due to the fact that the confidence intervals and fold relative accuracy values were derived using the fitted mixed model.

Presumption of Log-log-linearity With Slope 1 -- EPA evaluated the presumption that the mean exposure is a multiple of the amount of active ingredient handled (AaiH). In the Governing Documents and in statistical reviews of previous AEATF II studies, this presumption

has been referred to as "proportionality" but we are now referring to this analysis as a "log-log-linearity" analysis to clarify that the statistical models do not assume that the exposure is directly proportional to the amount of active ingredient handled. If the log-log-linear model has a slope of 1, then the arithmetic mean exposure will be a multiple of the amount of active ingredient handled. The statistical test compares the slope of 1 with a slope of 0, where 0 corresponds to 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 of this log-log-linear model 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 AaiH but not proportionally, so that, for example, doubling the AaiH will not tend to double the exposure. If the slope confidence interval excludes both 1 and 0 but the slope is positive, then the statistical evidence rejects both proportionality and independence and shows that the exposure tends to increase with the AaiH 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 mixed-effect regression, and a more complex "repeated measures" model (see Appendix A page 51 for more details) were used to analyze the data to take into account the clustered nature of the data (due to within-worker correlations) and were used to evaluate the relationship between exposure and AaiH. The primary mixed effect regression model assumes that the slope is the same for all three groups (Bottle, Conventional, and Reduced Splash). The statistical analyses of all three clothing configurations supported independence (a slope of zero) and rejected a slope of 1. The estimated slopes were between -0.28 and -0.04 using all the data and were between -0.14 and 0.14 after excluding 3 potential outlier measurements with unusually high unit exposures. A true negative slope is unrealistic since it implies that increasing the amount of active ingredient tends to decrease the exposure. The upper bounds of the 95% confidence intervals were all less than one, showing that a slope of 1 is rejected. Alternative simple linear regression and mixed models that assumed different slopes for the three groups also produced negative slopes for some clothing configurations and container groupings (see Appendix A, Table 24).

The results of the log-log-linearity analysis for the three clothing configurations should be consistent on physical grounds; either all or none of the clothing configurations should show a slope of 1. To investigate the log-log-linear slopes 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.

The finding that these data support independence of exposure and the amount of active ingredient for dermal exposure is likely to be due to the fact that for liquid pour, the bulk of the dermal exposure occurs due to accidental splashes and spills on the hands. Over 80% of the total dermal exposure measured in this study was measured on the hands.

For inhalation exposure, the statistical analyses supported log-log-linearity with a slope of 1 and rejected independence. The estimated slope was 1.2 for the inhalation concentration and 0.92 for the inhalation dose and 8-hour time weighted average.

The resulting regression slope and confidence intervals are summarized in Table 10 and in Figures 6 and 7 (for the long pants, long-sleeved shirt dermal exposure and for inhalation exposure) below. To calculate the confidence intervals, the Kenwood-Rogers method was used to estimate the denominator degrees of freedom for the mixed and repeated measures models because of the covariance structure and the unbalanced data among the three container groups. For these log-log-linear mixed models, the three groups have different intercepts but the same slope.

For more details including results for other exposure measures, alternative statistical models, and after excluding some outlier data, the reader is referred to Appendix A, Tables 20 and 24.

Table 10.

Exposure Route	Clothing	Slope	Confidence Interval	Confidence Interval Width
Dermal (mg)	Long pants and long sleeves	-0.28	-1.06 – 0.49	1.5
	Short pants and short sleeves	-0.04	-0.68 – 0.60	1.3
	Long pants and short sleeves	-0.26	-0.99 – 0.48	1.5
Inhalation (mg/m^3)	NA	1.21	0.72 – 1.72	1.0

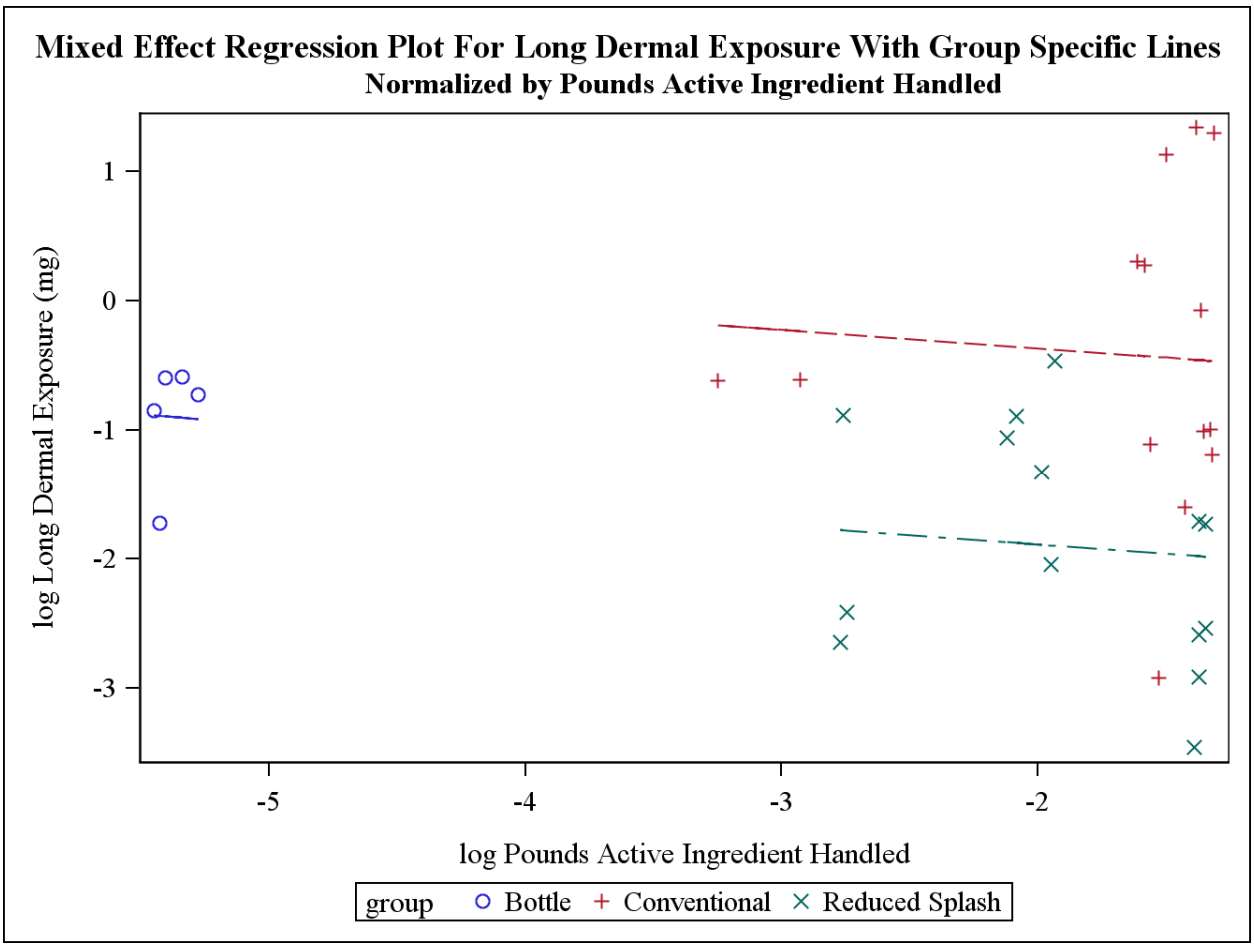

Figure 6. Mixed linear regression plots for long long dermal exposure

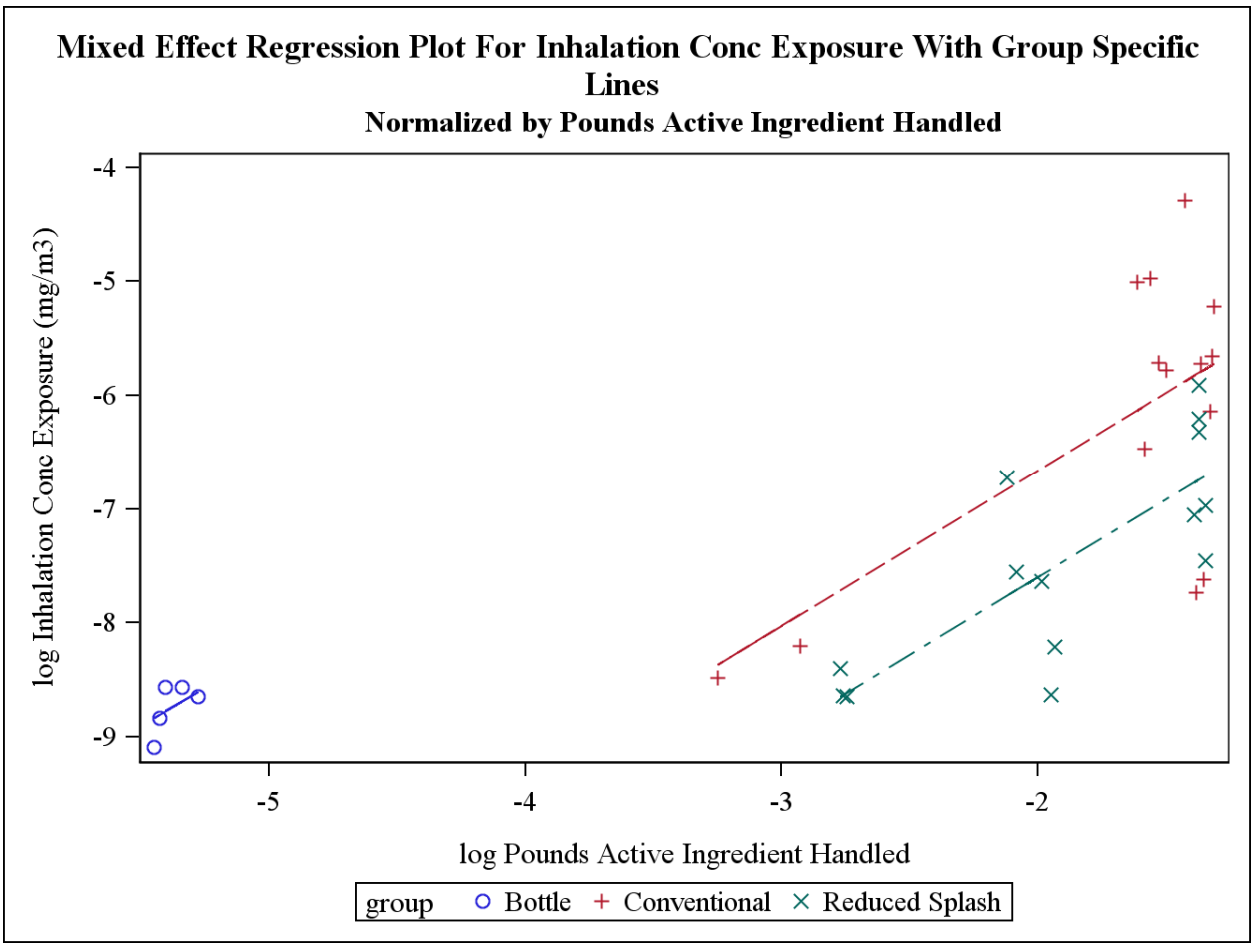

Figure 7. Mixed linear regression plots for inhalation exposure.

Threshold of AaiH for Over- or Under-Predicting Exposure – The log-log-linear mixed model regresses the log exposure against the log lb ai with an unknown slope and a different intercept for each group. The normalized exposure mixed model is the log-log-linear 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 arithmetic mean exposure will be over-predicted if the normalized exposure mixed model is extrapolated to high levels of the amount of active ingredient and the arithmetic mean exposure will be under-predicted at low levels of the amount of active ingredient.

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

Table 11 gives the minimum amount of active ingredient handled for which the normalized exposure mixed model will over-estimate the expected exposure (under-estimate if the slope is

greater than 1). Figures 8 through 13 show the statistical models and thresholds for the long pants and long sleeves and inhalation concentration exposures. Each group is plotted separately because the threshold depends upon the group (even though the slope does not depend upon the group). These figures display the measured values (6 for Bottle, 15 for Conventional, and 15 for Reduced Splash) together with the predicted arithmetic mean exposure calculated using the normalized exposure mixed 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 plotted points are labeled by the original group number, so that for Bottle, 1 denotes subgroup 1a, and for Conventional or Reduced Splash, 1, 2, and 3 denote subgroups 1b, 2, and 3, respectively. The normalized exposure mixed model calculation 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 (lower for inhalation concentration) than the threshold.

Table 11. Threshold levels for the minimum amount of active ingredient handled for which the normalized exposure mixed model will over- or under-estimate exposure.

Exposure Route	Clothing	Slope	Threshold Level (lb AiaH)		
			Bottle	Conventional	Reduced Splash
Dermal (mg)	Long pants and long sleeves	-0.28	1.14	1.43	0.38
	Short pants and short sleeves	-0.04	0.83	1.34	0.50
	Long pants and short sleeves	-0.26	1.07	1.42	0.37
Inhalation (mg/m^3)		1.21	0.00025*	0.00271*	0.00073*

*For this case, slope > 1 and so the normalized exposure mixed model under-predicts exposure for pounds of active ingredient above the threshold. Since the slope is only 1.21, the under-prediction is small.

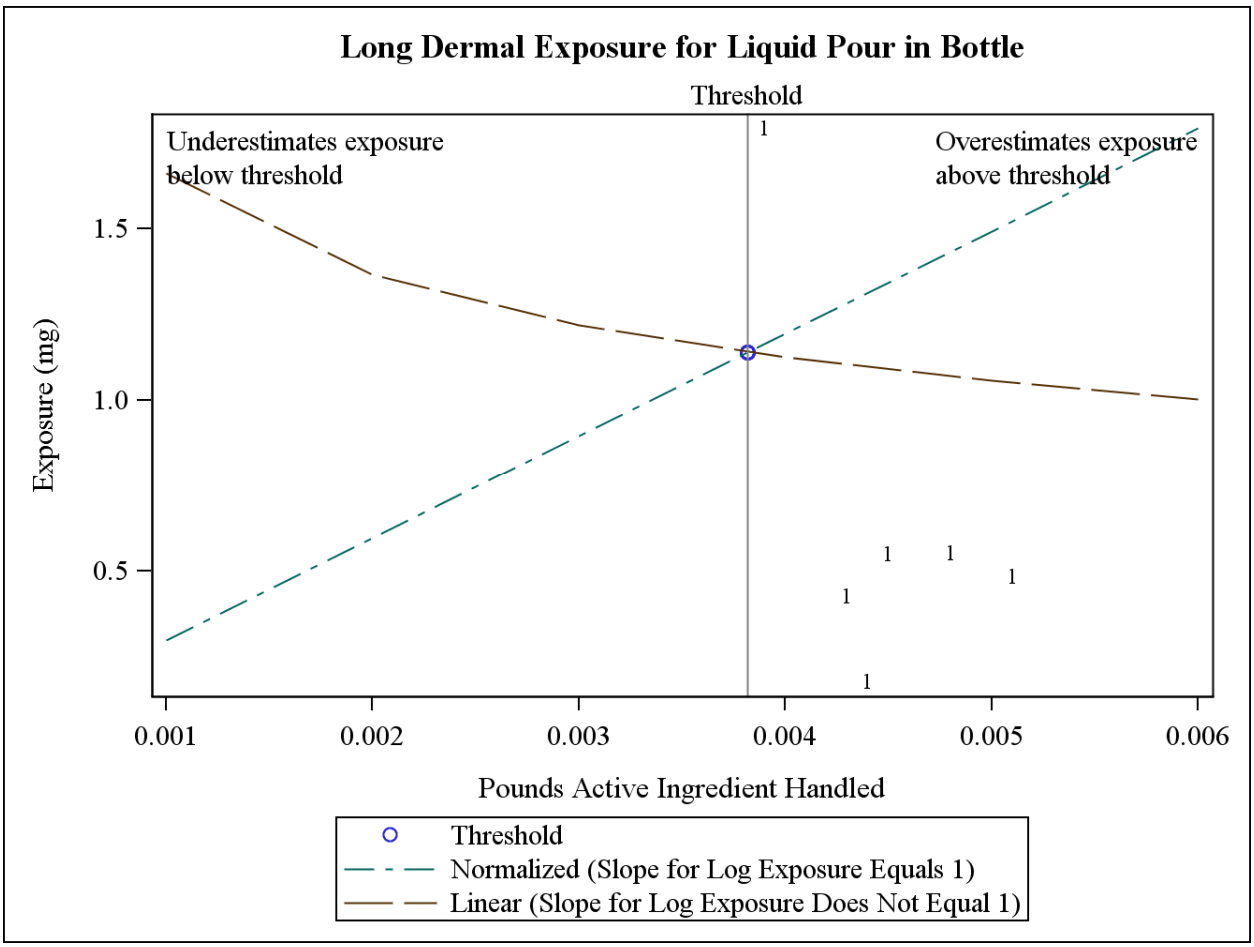

Figure 8. Predicted means for exposure from pouring into Bottles with long pants and long sleeves using the normalized exposure mixed model and general log-log-linear mixed model; threshold value.

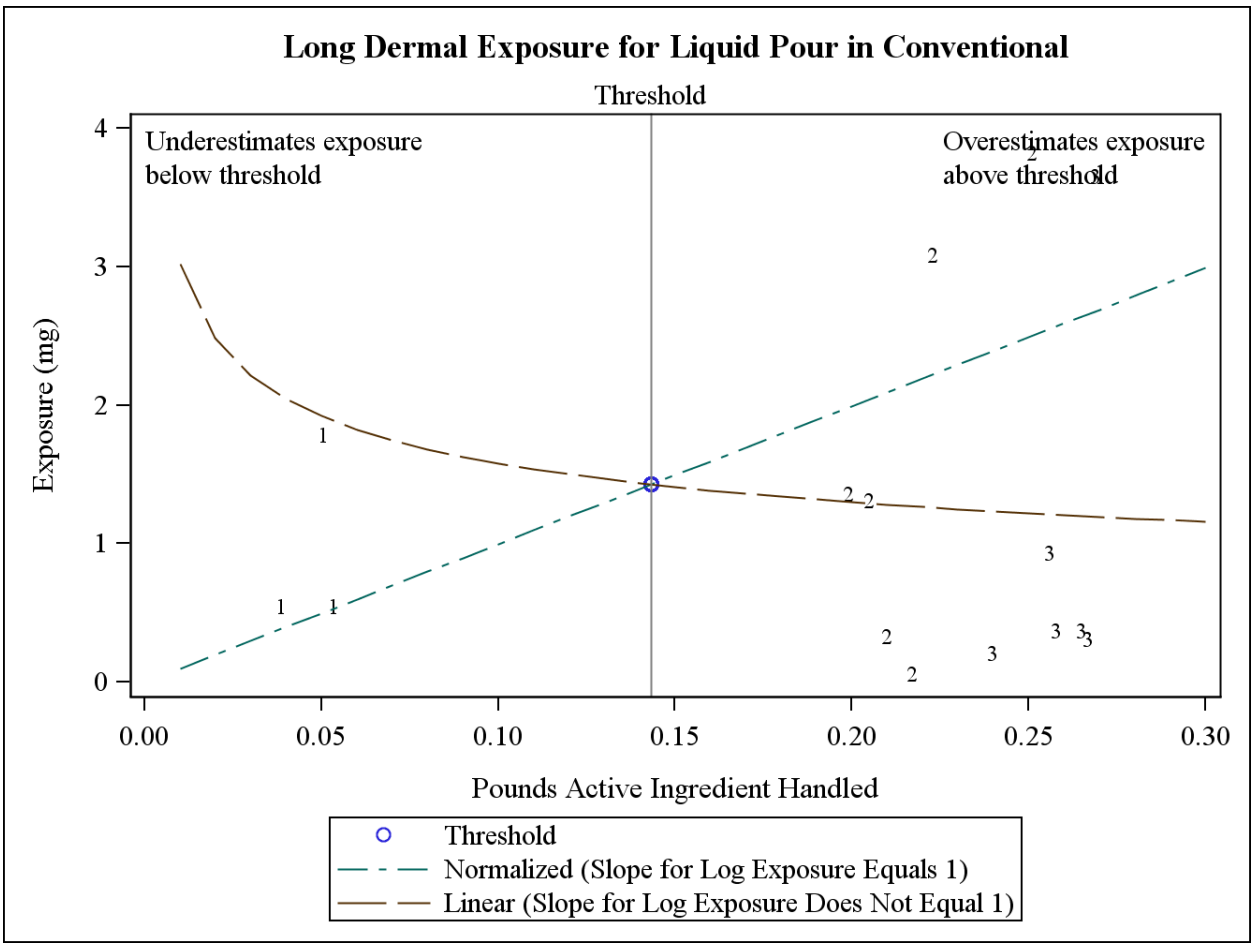

Figure 9. Predicted means for exposure from pouring from Conventional containers with long pants and long sleeves using the normalized exposure mixed model and general log-log-linear mixed model; threshold value.

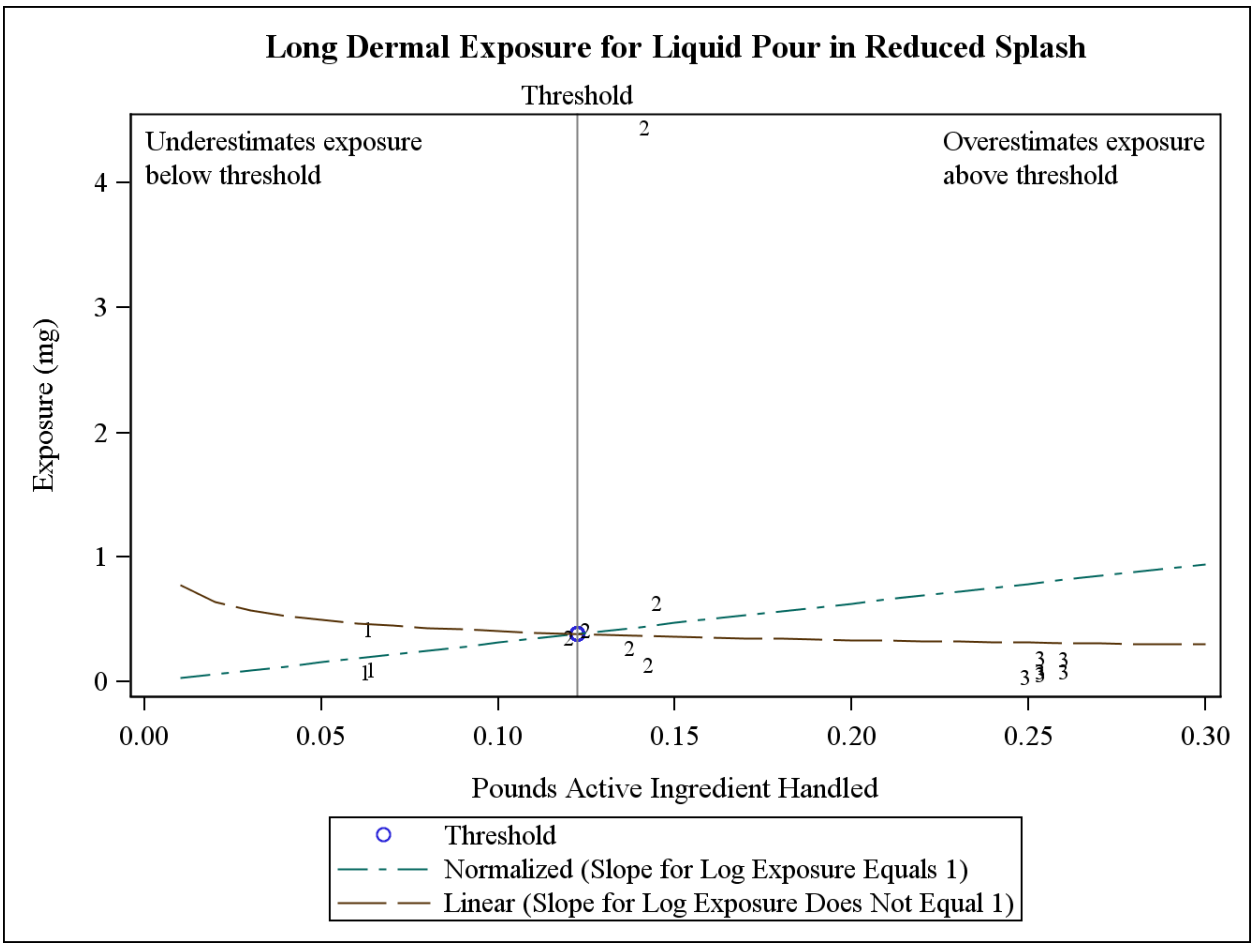

Figure 10. Predicted means for exposure from pouring from Reduced Splash containers with long pants and long sleeves using the normalized exposure mixed model and general log-log-linear mixed model; threshold value.

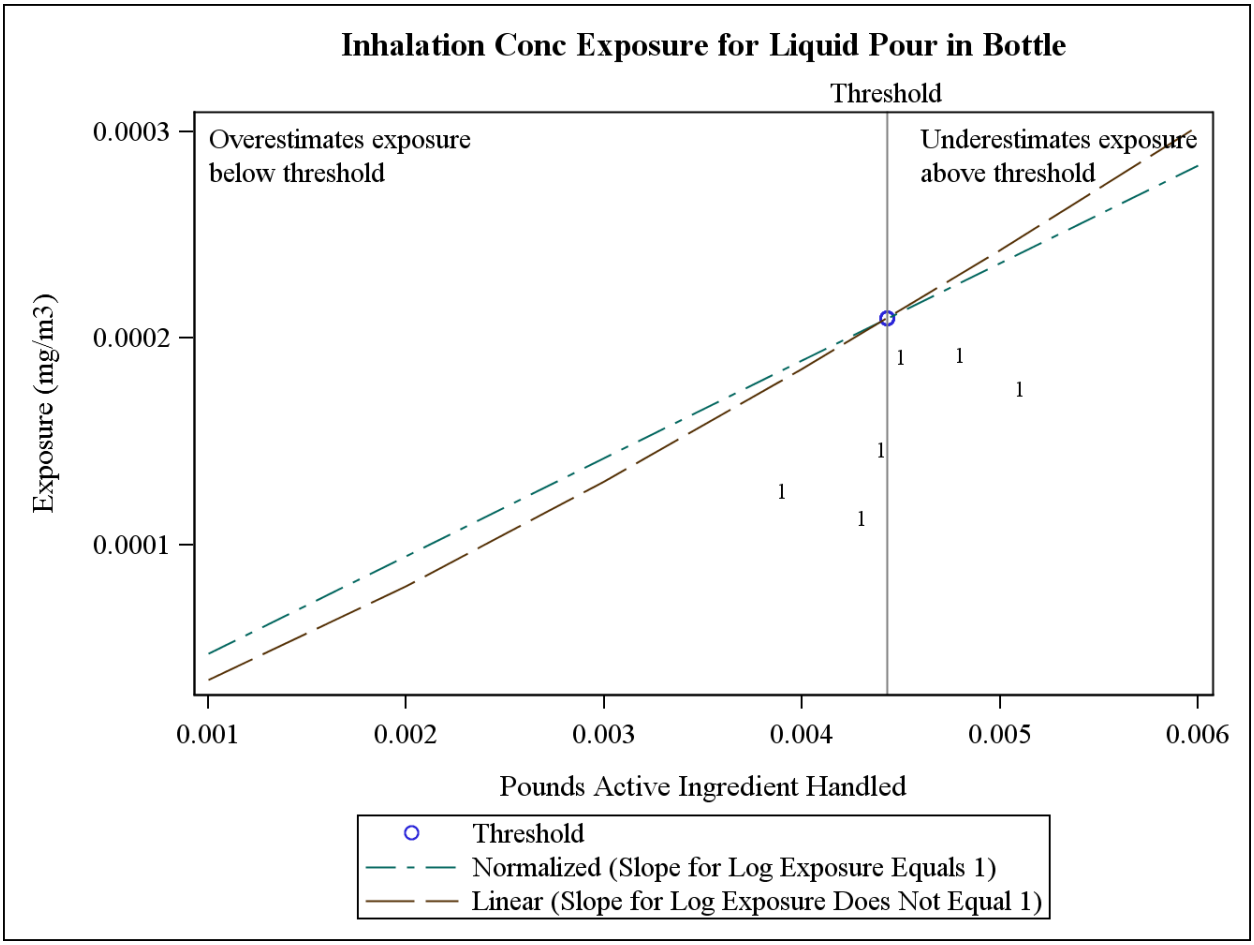

Figure 11. Predicted means for inhalation exposure from pouring into Bottles using the normalized exposure mixed model andgeneral log-log-linear mixed model; threshold value.

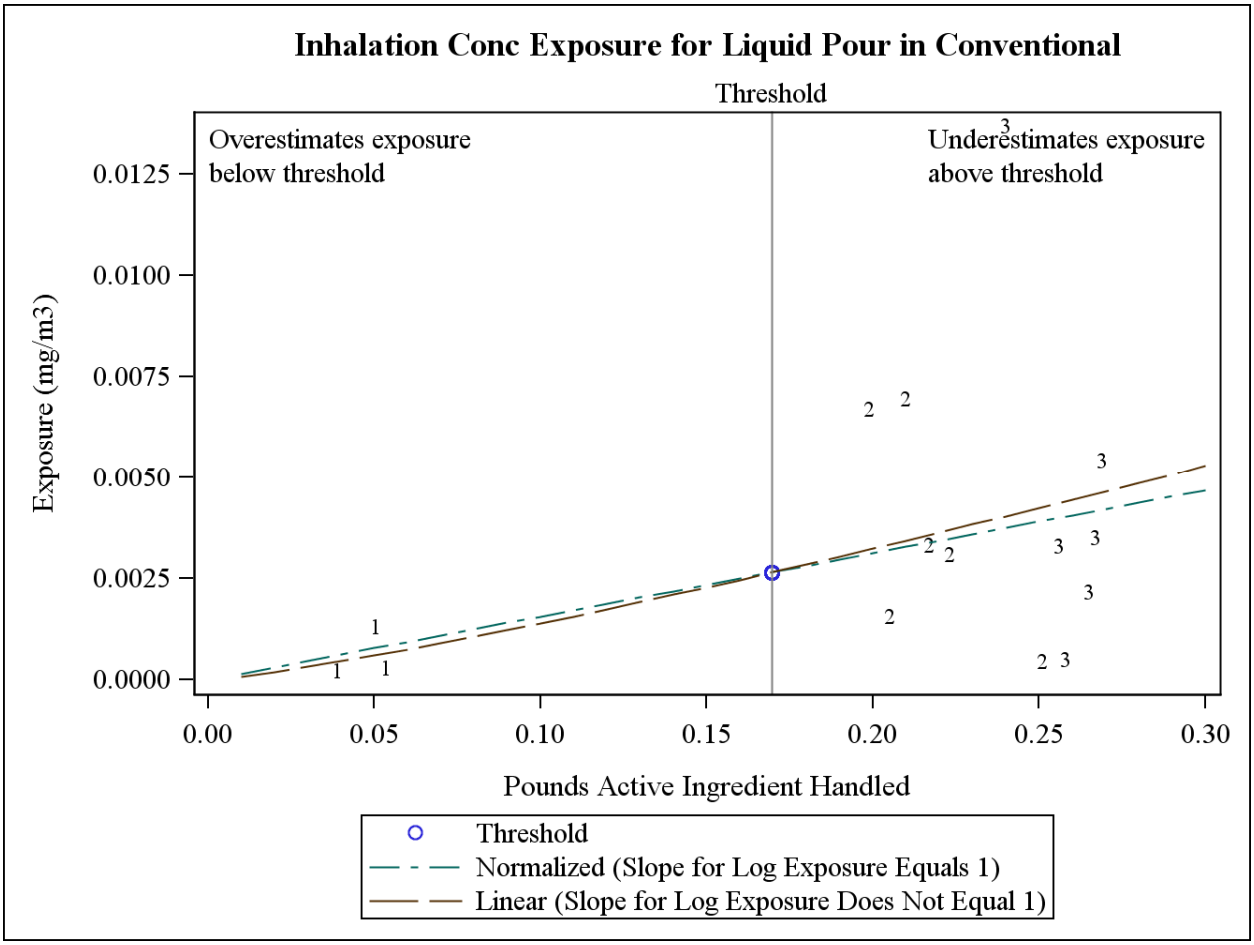

Figure 12. Predicted means for inhalation exposure from pouring from Convemtional containers using the normalized exposure mixed model and general log-log-linear mixed model; threshold value.

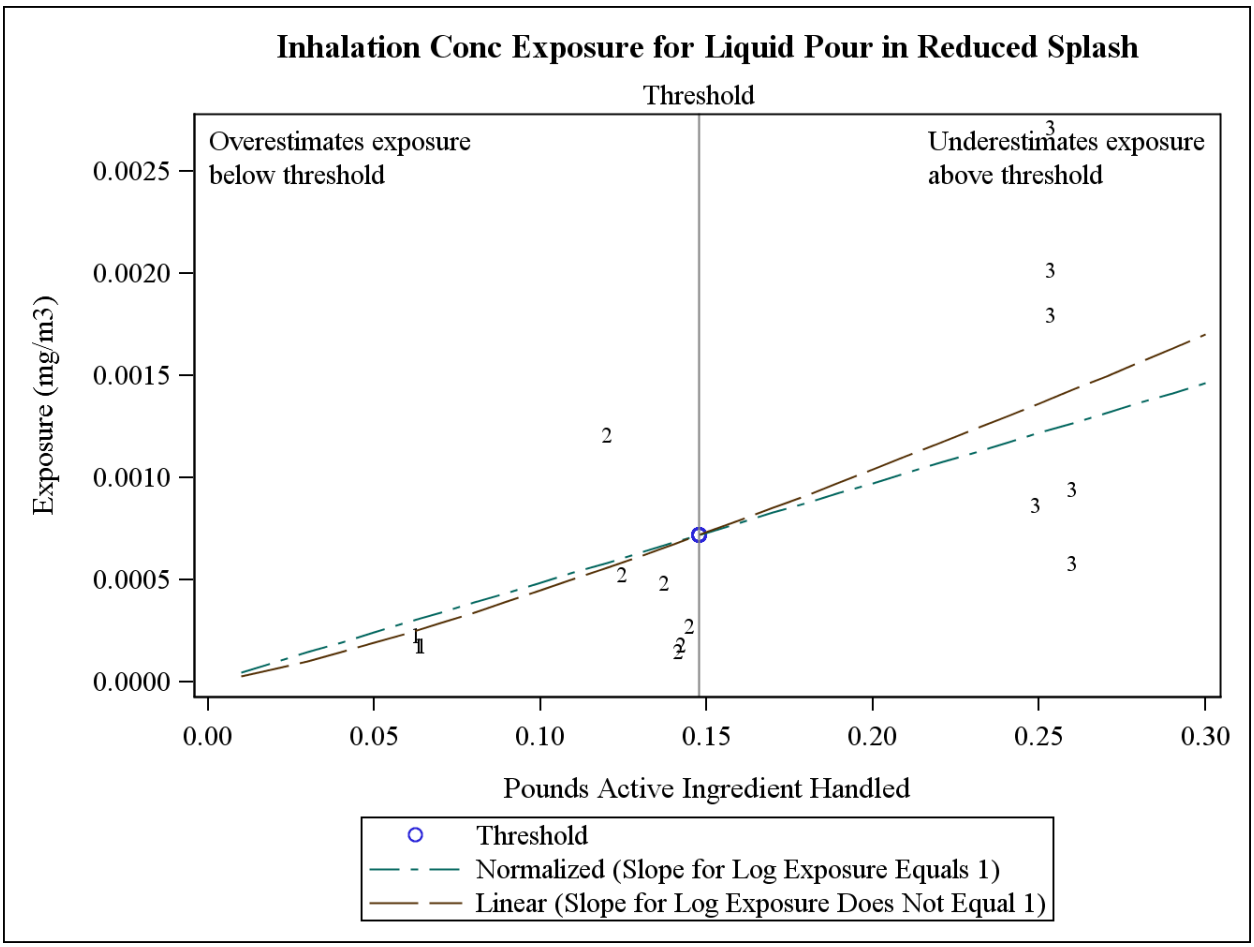

Figure 13. Predicted means for inhalation exposure from pouring from Reduced Splash containers using the normalized exposure mixed model and general log-log-linear mixed model; threshold value.

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 (SAP 2007). The study design 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 potential users of these data to characterize the results of this sampling effort:

(1) The study purposively selected Concord, Ohio, 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 pouring a liquid antimicrobial product in locations other than Concord, Ohio, 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 JRC. It is reasonable to assume that the mechanics of pouring a liquid product in two rooms in a laboratory located in Ohio are not substantially different than pouring a liquid inside other buildings throughout the country. It is also reasonable to assume that the pouring liquids in two rooms in a laboratory would also not be substantially different from pouring liquids 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 pouring of a liquid 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., painting, metal working fluids, pressure treatment of wood, etc.

(2) The test subjects used for in the study were limited to occupational workers (i.e., janitors). However, the resulting unit exposures will be used to assess exposures and risks for both occupational and residential users of antimicrobial products. This is a design limitation of the study. Without a robust side-by-side comparison of workers to consumers pouring liquids, the impact on exposures is unknown. The observational notes included with this study indicated that the test subjects did spill the product on hands when performing this task; indicating perhaps pouring liquids is not an experienced-based skill. Also part of the design limitation was the fact that the study was conducted indoors. While most antimicrobial applications occur indoors, outdoors uses also exist (e.g., outdoor swimming pools, agricultural uses, etc.). Indoors may provide less dilution of airborne residues and outdoors may provide opportunities for blow-back of residues if the mixer/loader is standing downwind while pouring.

(3) The removal efficiencies for the hand wash and face/neck wipes were both conducted using quaternary ammonium products from previously conducted studies. These removal efficiency studies were used in previously HSRB-reviewed AEATF II studies. See the EPA reviews to the HSRB for mop (DDAC) and aerosol (ADBAC) for prior discussion.

(4) 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 available inhalation toxicity data to see if the toxicity studies were performed as a gas or with an aerosol.

(5) The data generated in this study are acceptable to use as surrogate to assess pesticide labeled uses that require the open pouring of a liquid product.

(6) Except for the scenario of pouring into trigger spray bottles, the small sample size by itself does not create statistical limitations since the confidence intervals for the summary statistics based on the primary statistical model were reasonably narrow (in several cases meeting 2-fold relative accuracy or better). A notable exception is for the dermal exposure summary statistics for scenario 1a, pouring into spray bottles, which only met 3.6-fold relative accuracy for the variance component model.

More important is the fact that the original sets of subject participants, locations, and dates from which the subjects, and sampling dates were chosen were limited and hence might not be representative of all Ohio users that pour liquids (e.g., those that use liquid products but did not volunteer), buildings (e.g. a laboratory was selected 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 fully 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 liquid pour study scenario are not inconsistent with the assumption that inhalation exposure tends to increase proportionally with AaiH. However, the results for dermal exposure are inconsistent with the assumption that dermal exposure tends to increase proportionally with AaiH. Various alternative methods were used, unsuccessfully, to try to identify potential data points causing the negative slopes. The exposure driver appears to be the random drips and/or spills on the worker's hands rather than how much product was poured. The EPA will still normalize the liquid pour data by AaiH because logically each drip and/or spill on the hands is a given volume of liquid and the exposure is dependent upon the concentration of ai in that drip and/or spill. The study could not be designed to vary the concentration of ai to further investigate this assumption because higher concentrations of ai would require the use of chemical resistant gloves. The use of this inconsistent assumption 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 11 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.

(8) The measured air exchange rates in the laboratory rooms used for the pouring of the liquids ranged from ~7 to 11 air changes per hour (ACH). These ACH rates are higher then what is expected in a home residence. However, based on previous reviews of similarly low vapor pressure chemical and relatively low aerosol generating applications (e.g., mopping as opposed to aerosol can application), the ACH rate is not expected to have a substantial impact on the air concentrations monitored.

4.0 Conclusions

EPA has reviewed the AEATF II liquid pour 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 have not adversely impacted the reliability of these data. The EPA recommends that the inhalation and dermal UEs generated in this liquid pour 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 pouring of liquid products. The Long-Long dermal unit exposures summarized in Table 1 are recommended to be used for regulatory purposes regardless of the labeling for long-sleeved shirts and long-pants, short-sleeved shirts and long pants, or short-sleeved shirts and short pants (i.e., a label decision based on these dermal UEs will not need to require long sleeved shirts and long pants; the hand exposure is the risk driver).

- EPA developed a separate unit exposure for pouring into spray bottles. Although separating out the bottle scenario decreases the number of MEs in each scenario, EPA believes this to be the best use of these data. The estimated unit exposures for bottle can be used by EPA when assessing disinfectant labeled uses (i.e., trigger pump and spray for hard surfaces). If the bottle scenario was not separated out, the trigger pump and spray bottle exposures would be underestimated and exposures for the other types of pouring liquid scenarios would be overestimated.

- The statistical analysis for dermal exposure and pounds ai handled provides evidence against log-log-linearity with a slope of 1, and the estimated slopes are negative, although not statistically significant. The exposure driver appears to be the random drips and/or spills on the worker's hands rather than how much product was poured. The EPA will still normalize the liquid pour data by AaiH because logically each drip and/or spill on the hands is a given volume of liquid and the exposure is dependent upon the concentration of ai in that drip and/or spill. The study could not be designed to vary the concentration of ai to further investigate this assumption because higher concentrations of ai would require the use of chemical resistant gloves.

- Estimates of the GM, AM, and P95 were shown to be accurate within 3-fold with 95% confidence for pouring from conventional and reduced splash containers not into spray bottles for all the analyses of dermal and inhalation exposure.

- Estimates of the GM, AM, and P95 were shown to be accurate within 3.6-fold for the variance component model with 95% confidence for pouring into spray bottles for the analyses of the Long-Long dermal and inhalation exposure.

- Additionally, Table 11 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).

5.0 References

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Appendix A

Statistical Review of the AEATF II Liquid Pour Study

(To be included as a separate electronic file)