UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: March 23, 2018

SUBJECT: Science Review of the AEATF II Brush/Roller Painting Human Exposure Monitoring Study (AEATF II Project ID AEA09; MRID 50521701).

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This memorandum presents the EPA/OPP Antimicrobials Division (AD) science review of the human exposure brush/roller painting 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) brush/roller painting study. The AEATF II designed the study to develop unit exposures for painting using a brush/roller. The results of the study are reported herein. 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 reviews are to be presented to the HSRB on April 25, 2018.

The study investigators monitored inhalation and dermal exposures to 18 different test subjects. BIT (1,2-benzisothiazoline-3-one) was the active ingredient in the paint used as the surrogate test compound by all test subjects. All of the test subjects were recruited from the general population (not professional painters); all painting activities were performed indoors; each subject painted roughly 2 gallons of paint; three concentrations of BIT were used in the study (~144, 375, and 619 ppm); and painting duration ranged from 48 to 172 minutes (average 113 minutes). Subjects opened the cans of paint (previously treated with BIT) and used paint brushes and rollers to paint the walls, ceilings, and trim of doors/windows in rooms that were purposely constructed in a warehouse for this study. Subjects were instructed to paint as they normally would do. EPA confirms that the data are considered the most reliable data for assessing handler exposures from antimicrobial-treated paints when using a brush/roller. 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 brush/roller dataset instead of the Pesticide Handlers Exposure Database (PHED) datasets to assess exposure for persons painting with an antimicrobial treated paint product. The exposure data in the AEATF II brush/roller scenario represent the painting with a brush and roller. The scenario does not cover the pouring of an antimicrobial product into the paint nor the airless spraying of the treated paint. Those scenarios are monitored in separate AEATF II studies.

Select summary statistics for the "unit exposures" (i.e., exposures normalized to pounds active ingredient handled) are presented in Table 1 for the dermal and inhalation routes of exposure. Each test subject 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). This WBD sectioning allows for estimating unit exposures for various clothing combinations of long/short pants and/or long/short sleeved shirts.

For comparison, results from the PHED paint brush study used in prior risk assessments is also presented in Table 1. The summary statistics from the new AEATF II study reported in Table 1 are estimated using the lognormal simple random sampling model while the PHED results are empirical estimates.

Table 1. Unit Exposures (UE) for the AEATF II Brush/Roller Scenario.				
Exposure Route	**Clothing**	**PHED ("best fit")[a]**	**AEATF II[b, c] (n= 18)**	
			Arithmetic Mean[d]	**95th Percentile[e]**
Dermal (mg/lb ai)	Long pants/long-sleeves, no gloves	180	115	351
	Long pants/short-sleeves, no gloves	NA	131	386
	Short pants/short-sleeves, no gloves	450	144	415
Inhalation[f] Inhalable OVS Total <100 µm	Breathing Zone (mg/lb ai)[g]	0.20	0.00777	0.0181
	Breathing Zone (8-hr TWA mg/m^3/lb ai)[h]	0.025	0.00097	0.00226

[a] Historically PHED data has been used to assess the paint brush exposures to antimicrobial products added to paint. The PHED "best fit" measure is the sum of the median and/or geometric mean for the various individual body parts. PHED inhalation dose estimates were calculated assuming a breathing rate of 1.7 m^3/hour. PHED inhalation UE represent inhalable (total) particulates. The PHED TWA estimate is based on the arithmetic mean. PHED dermal unit exposures are as reported in the USEPA/OPP/HED table for the commercial painters and HED SOPs for residential.

[b]Dermal and inhalation UEs are corrected for field recoveries.

[c] Statistics are estimated using a lognormal simple random sampling model. Dermal and inhalation UEs are estimated using substitution by ½ LOQ. Details are described in Appendix B.

[d] Arithmetic Mean (AM) = GM * exp{0.5*(lnGSD)^2}

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

[f] All measured inhalation residues were below the LOQ.

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

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

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

- The AEATF II brush/roller data and associated unit exposures are considered superior to the existing brush dataset for antimicrobial uses (i.e., 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 either the long-sleeved shirt, long pants, no gloves or the short pants, short-sleeved shirt, no gloves. Antimicrobials are typically used in paints as material preservatives and are considered treated articles and are sold with no pesticide labels, and therefore, it is not possible to provide for personal protective equipment, such as chemical resistant gloves. Typically, EPA/OPP assesses commercial painters using the long pants, long-sleeved shirts, no gloves scenario and residential painters using the short pants, short-sleeved shirt, no gloves scenario. The long pants, short-sleeved shirt, no gloves scenario is provided as an option for risk managers.
- The dermal unit exposures are based partially on study-derived clothing penetration factors because of unforeseen contaminated inner whole-body dosimeters. The impact of this substitution on the resulting dermal unit exposure is not substantial as most of the exposure is attributed to the hand exposure. Additional discussion is provided herein.
- Estimates of the geometric mean (GM), arithmetic mean (AM), and 95th percentile (P95) were shown to be accurate within 3-fold with 95% confidence for all scenarios. At this time, no additional monitoring for the brush/roller scenario is required.
- The statistical analysis (Section 2.4) provides evidence consistent with log-log-linearity with a slope of 1[1] between dermal exposure and pounds of active ingredient (ai) handled. An ideal result of the log-log-linearity test is an estimated slope between 0 and 1 with a confidence interval that includes 1 but not zero indicating that independence between exposure and pounds of active ingredient (a slope of zero) is rejected and that log-log-linearity with a slope of 1 is not rejected. The results of this analysis indicate the following:
    - The analyses of log-log-linearity in Section 2.4, Table 9, show that dermal exposure tends to increase with pounds of active ingredient handled (AaiH).
    - The confidence intervals for dermal exposure include 1 but not zero, indicating that independence is rejected and log-log-linearity with a slope of 1 is not rejected.
- The statistical analysis (Section 2.4) does not assess the log-log-linearity with a slope of 1 between inhalation exposure and pounds of active ingredient handled. All the measured inhalation residues were below the detection limit, leading to unreliable results for regression models.

To assess the risks resulting from painting with a brush/roller, EPA will combine appropriate unit exposure (UE) values with chemical-specific inputs (e.g., maximum labeled application rates, dermal absorption, toxicological endpoints of concern) and default inputs (high end 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 (% ai by weight) x Weight of treated product/article (pounds).

[1] The statistical analysis of log-log-linearity tests whether the slope of log exposure against log ai is 1, which supports the use of the data in the "unit exposure" formats. 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 B. We have therefore changed the terminology from "proportionality" to "log-log-linearity with a slope of 1."

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., paint brush/roller, airless paint sprayer, ready-to-use wipes, trigger pump sprayer, mop & bucket, pressure treatment of wood facilities, 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). Hand exposure as well as inhalation exposures are also being monitored. Prior to conducting intentional exposure studies in humans, the protocols are reviewed by the Human Studies Review Board (HSRB). The HSRB reviewed this brush/roller exposure study protocol in April 2014.

1.1 Brush/Roller Scenario Defined

The brush/roller scenario in this study is defined as opening the paint cans and painting a BIT-treated latex paint onto walls, ceilings, trim using both brushes and rollers as they normally would do. As indicated in the AEATF's protocol, *"The primary purpose of the paint application with brush and roller monitoring study is to develop more accurate information on potential consumer and worker exposures to antimicrobials. These data will consist of dermal and inhalation exposure estimates derived from monitoring subjects under conditions constructed to broadly represent those expected for the future application of arbitrary antimicrobial pesticides."* Subjects wore whole body dosimeters (WBD) underneath long-sleeved shirts, and long pants (plus a personal air sampler). The test subjects wore no gloves. The conditions under which the study participants handle the pesticide as they are monitored are referred to as the scenario. Both inner and outer dosimeters were worn by the monitored study participants, and both inner and outer dosimeters were analyzed for residues.

1.2 Study Objective

The AEATF II's study objective is to monitor inhalation and dermal exposures to be used as inputs in exposure algorithms to predict future exposures to persons painting with a brush/roller when using a paint treated with an antimicrobial product (e.g., material preservative). Dermal and inhalation exposure monitoring was conducted while study participants painted using various painting equipment (brush types and sizes, roller, extension pole, rags, ladder, paint cup, etc). These exposures will be used in pesticide exposure assessments as "unit exposures".

"Unit exposure" (UE) is defined as the expected external chemical exposure an individual may receive (i.e., "to-the-skin" or "in the breathing zone") per weight-unit of chemical handled and is the default data format used in pesticide handler exposure assessments. Mathematically, unit exposures are expressed as "handler" exposure normalized by the amount of active ingredient (ai) handled by participants in scenario-specific exposure studies (e.g., mg ai 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 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 of the geometric mean, arithmetic mean, and 95th percentile unit exposures. To meet this objective, AEATF II proposed an experimental design with 18 monitoring events (MEs) for consumer subjects painting surfaces with a brush and roller.

A secondary objective for EPA is for meeting 80% power for detecting log-log-linearity with a slope of 1. This objective is approximately met if the widths of the confidence intervals for the slope based on the lognormal model are at most 1.4.

1.3 Protocol Modifications, Amendments, and Deviations

1.3.1 Protocol Modifications Based on EPA and HSRB Reviews

EPA and the HSRB provided science-based changes to the brush/roller protocol during the review (EPA 2014 and HSRB 2014). The review comments and AEATF II responses are summarized in Table 2.

Table 2. EPA/HSRB Review and AEATF II Responses.

Issue Raised (Agency)	Proposed Response	Options/Comments
Researchers should offer a paint edger and paint cup to subjects and allow them to decide if they want to use these items. **(EPA)**	The protocol will be modified to offer these items to subjects.	--
A separate color of paint should be used for walls and trim. **(EPA)**	The protocol will be modified to specify different colors for walls and trim.	*[EPA notes that two colors of paint were alternatingly used the MEs, each ME only using a single color, and a different color was used between repainting the same room]*
Researchers should provide additional details about airflow in the painting rooms. **(EPA)**	A diagram of the rooms including planned location of entry door and exhaust fan will be added to the protocol.	A complete description including measured air changes per hour will be included in the final report.
The middle concentration of BIT in paint should be changed to halfway between low and high concentrations (360 ppm instead of 400 ppm) to improve regression data. **(HSRB)**	The protocol will be modified to change the target concentration to be 360 ppm.	If the native paint is different from 120 ppm then 360 ppm may not be exact middle.
The study design uses 3 concentrations of BIT in paint. Suggest using more concentrations of BIT with less subjects per concentration. **(HSRB)**	We plan to continue with current set of three concentrations with modified midpoint discussed above.	Although 6 concentrations are possible it adds considerable cost and complexity, plus raises the risks of errors. The increase in data quality is not enough to justify the issues created.

Consider including additional factors such as varied types of painting equipment and wall texture to capture more diversity of exposure. **(HSRB)**	We plan to continue with a single type of equipment (best selling) as this approach was determined with EPA during earlier reviews.	Our initial protocol included three types of equipment, but to keep n at 6 the study was limited to a single concentration of active in paint.
The protocol should define volatility of BIT and limit use of this data to actives with similar volatility. **(HSRB)**	We do not think this should be included in protocol, but left to EPA to consider how they will use the data.	*[EPA notes as part of this study review that the vapor pressure of BIT is 4.4E-7 mmHg at 20 C and will not result in substantial off gassing concerns]*
A painter's hat may be less representative of actual head shape than a sock/hood. **(HSRB)**	We plan to continue with a painter's hat as it is more comfortable for subjects, and easier to work with when dressing / undressing subjects.	We intend to add a dosimeter cloth under the hat to allow determination of possible protective effect of the hat.
The test room should be ventilated with an exhaust fan to provide fresh air throughout the monitoring event. **(HSRB)**	We will update the protocol to have the exhaust fan on during the ME and specify the fan size.	Issue arose from a conflict between initial reviews by EPA and CDPR.
Background wall wipes may not be necessary or useful. **(HSRB)**	We propose to leave collection of these background wipes in the protocol but make analysis optional at the discretion of the study director if helpful to interpret data.	Purpose was to demonstrate minimal transfer from dry paint to cloth. This will be to ensure that BIT residues on subjects clothing are predominantly from wet paint exposure.
The protocol should specify that the paint will be used as received without dilution, as well as specify the paint sheen. **(HSRB)**	No changes planned.	The protocol specifies that BIT in a minimal volume of diethylene glycol will be added to mid and high levels. No other dilution of paint is allowed in current protocol. Complete paint information including sheen is contained in the paint label attached to the protocol.
Multiple wording change suggestions and typo corrections.	Protocol will be updated with corrections as appropriate.	--

1.3.2 Protocol Amendments

The study report (page 75-76) lists 2 protocol amendments. The amendments included edits to the reference method (correcting a typo and providing more detail) and clarification to the guidelines for transporting samples from the field to the laboratory.

1.3.3 Protocol, Method, and SOP Deviations

Eight protocol, 1 method, and 7 SOP deviations were noted in the study (study report page 76). Of the reported deviations, the use of a penetration factor due to the use of BIT-treated inner WBDs has an impact on the outcome of this exposure study as discussed in Section 2.1 below.

The other reported deviations include inability to advertise in local newspaper, switching solvents, device malfunctions, some samples being stored greater than 6 months, incorrect reference, and SOP lapses (e.g., not recording weekly temperatures, not generating an audit report, etc.). For a detailed description of each of the protocol and SOP deviations the reader is referred to the study report. EPA accepts the study author's conclusion that these deviations, except the WBD contamination issue, did not adversely affect the outcome of the study. EPA in conjunction with Health Canada's Pest Management Regulatory Agency (PMRA) has reviewed the contaminated WBD and provided a path forward (see Section 2.1).

1.4 Material & Methods

The following is a summary of the key field aspects of the study.

- ***Study Location:*** The paint brush/roller study was conducted indoors in a warehouse with purposely built rooms specifically for this study. The warehouse was located in Fresno, CA. Photos and schematics of the rooms are in Appendix G starting on page 351 of the study report.
- ***Substance Tested:*** The test substance monitored was 1,2-Benzisothiazolin-3-one (BIT) as the active ingredient; CAS number 2634-33-5.
- ***Test System:*** The study was designed to monitor exposures to subjects painting with brush/rollers while varying concentrations of BIT in paint and thus the amount of active ingredient handled (AaiH). Surfaces within the 10ft x 12ft rooms with 8ft ceilings that were painted included walls, ceilings, and trim/baseboards. Painting equipment available to each subject included paint cup, edger, ladder, paint roller extension pole, and painters rag; the use of such equipment was left up to the discretion of the subjects as they were allowed to paint as they normally would do. Figure 1 below illustrates the surfaces built into the test rooms, including the trim around baseboards, doors, and simulated windows. The color of the trim is different than the color of the walls in Figure 1 because the color of the paint used between each ME to re-paint the same room was a different color.

Figure 1. Test Room Built for Brush/Roller Study (Door, Window Trim & Baseboards).

- ***Sample Size:*** The study consisted of 18 monitoring events (ME). Each ME is a different subject (i.e., different person/individual).

- ***Duration:*** The sampling times ranged from 48 to 172 minutes (average 113 minutes). Individual ME air sampling pump flow rates and start/stop sampling times are reported on page 153 of the AEATF II study report.

- ***AaiH:*** The AaiH ranged from 0.00272 to 0.0141 lb BIT. The specific AaiH for each individual ME is reported on pages 88 and 89 of the AEATF II study report.

- **Surface Area Painted & Paint Handled:** While the target amount of paint handled was 2 gallons per ME and this amount was roughly achieved (range 8.52 to 9.94 kg paint handled), the surface area painted had a larger range. The surface area ranged from 267 ft^2 (8.52 kg paint) to 888 ft^2 (9.53 kg paint). The surface area painted per gallon of paint ranged from 172 to 511 ft^2. Each ME painted 1 to 2 rooms.

- ***Painting Procedures***: The subjects were provided closed 1-gallon cans of BIT-treated paint. Subjects open the paint cans and painted walls, ceilings, baseboards, and door/window trims. Subjects were told to paint as they would normally would do and use the equipment as described above (e.g., rags, paint cups, etc). Subjects were assigned 2 gallons of paint and were told to paint as many of the rooms as needed to paint 2 gallons.

Each subject had their own single color of paint and the color of paint was different in the room from the last subject. Study investigator's observational notes are in Appendix H of the AEATF II study report.

- ***Environmental Conditions*:** Environmental conditions (humidity and indoor temperatures) are reported for each individual ME on page 86 of the AEATF II study report. Indoor temperatures ranged from 67.9 to 84.8 ° F. The humidity indoors ranged from 32.2 to 63.3%. "*The air changes per hour (ACH) of two of the test rooms was measured before the start of the study using a tracer gas decay method. The ventilation fan was turned on during the measurement as it was during study use. The room air exchange was measured as 11-12 ACH with the door open, and 7 ACH with the door closed. The portable and window air conditioner units used to cool the rooms were designed to recirculate room air and not expected to change the ACH.*" (V1:28)

2.0 Results

2.1 QA/QC

2.1 Contamination of Inner WBDs

BIT was used as the surrogate compound in the brush/roller study. As happenstance, 10 of the 18 Inner WBDs were treated during the manufacturing process using BIT as the material preservative. The 10 BIT-treated WBDs were from two vendor lot numbers. Thus, 10 MEs had their dermal inner WBDs "contaminated" (i.e., the textile was purposely treated with a labeled formulated product containing BIT and used as a material preservative). The amount of contamination in the WBD was higher than the amount of BIT collected on the WBDs from the treated paint in the study (WBD pre-treated BIT > WBD exposed paint BIT). The subjects wearing the affected inner WBDs included MEs: 1, 2, 4, 6, 7, 10, 12, 13, 16, and 17. The following is a discussion on EPA and Health Canada's Pest Management Regulatory Agency (PMRA) thought process and alternative methods in determining our decision on how best to use the submitted data.

<u>Options Considered for Contaminated WBDs:</u>
EPA and PMRA considered four options to deal with the contamination of the WBDs:

(1) Repeat the study;
(2) Use a mean study-derived clothing penetration factor to replace the residues for the contaminated inner WBDs
(3) Use the default clothing penetration factor of 50% to replace the residues for the contaminated inner WBDs; or
(4) Use the upper bound of 100% clothing penetration factor to replace the residues for the contaminated inner WBDs.

In reviewing these options, multiple methods are used to determine the mean clothing penetration factors (PFs) in Option 2 above. See Appendix A for specific algorithms, etc. In summary, a single PF is calculated for all of the individual body parts (n=48). Additionally,

individual PFs are calculated for each of the body parts (i.e., front torso, lower arm, lower leg, rear torso, upper arm, and upper leg). The arithmetic means in Option 2 above are calculated as empirical arithmetic means and as arithmetic means from the lognormal model (i.e., exp(mu + V/2), where mu and V are the mean and variance of the logarithms of the ratios). Confidence intervals are also provided. Geometric means are also calculated for Option 2.

To determine the best option to move forward, the dermal unit exposures were calculated for options 2 through 4. The PF was calculated as the ratios of inner dosimeters of BIT residues divided by the outer dosimeters of BIT residues for the same ME and body part using the MEs that did not have "contaminated" inner dosimeters (i.e., ME numbers 3, 5, 8, 9, 11, 14, 15, and 18). For the single arithmetic empirical mean, arithmetic lognormal mean, and geometric mean PFs (95%CI) are 12.3% (7.1, 22), 12.5% (7.5, 22), and 5.1% (3.5, 7.6), respectively. The table of PFs is provided in Appendix A (Table 1 of the October 2018 memorandum by Jonathan Cohen).

Table 3 provides the dermal unit exposures developed solely for this WBD contamination PF comparison exercise (the final study's brush/roller unit exposures are reported in the above Table 1) using the single PFs of 5.1% (geometric mean), 12.3% and 12.5% (arithmetic empirically and lognormally derived means), 50% (default), and 100% (upper bound). The values in Table 3 use the interim data provided by AEATF II and so the dermal unit exposure estimates differ slightly to the final values presented in Table 1 above. Table 1 also provides the previous dermal unit exposures from PHED for comparison. Finally, the percentage of the exposure contributed by the hands is provided. The calculation of this percentage in Table 3 uses the estimated arithmetic mean unit exposure for hands only divided by the estimated arithmetic mean unit exposure for each clothing scenario. An alternative approach is to use the arithmetic mean of the ratios of the hand exposure to total exposure, which gives hand contributions of 84% for commercial painters, 65% for homeowner painters, and 49% of total dermal including all the inner and outer dosimeters (for a hypothetical naked painter), using the Mean-empirical option.

Table 3. Dermal Unit Exposures from AEATF Brush/Roller Paint Study Using Single PF.

Option	Dermal Unit Exposure (mg/lb ai)	% Hand Contribution for AEATF Study*
Commercial Painters (long pants, long-sleeved shirt, no gloves)		
5.1% (Geo)	115	95
12.3% (Mean-empirical)	117	94
12.5% (Mean-lognormal)	117	94
50% (Default)	127	86
100% (Max)	141	78
Residential Painters (short pants, short-sleeved shirts, no gloves)		
5.1% (Geo)	143	77
12.3% (Mean)	145	76
12.5% (Mean-lognormal)	145	76
50% (Default)	155	71
100% (Max)	169	65

* Percentage from hands = Arithmetic Mean Unit Exposure for Hands Only / Arithmetic Mean Unit Exposure for Clothing

The dermal unit exposures have also been calculated using the PFs for individual body parts. The results of the individual body part PFs yield nearly identical dermal unit exposures as the single PF method. The results for the individual body part PFs dermal unit exposures are provided in the Appendix A (Appendix A's October 2017 memorandum, Table 2).

Discussion of Options for Contaminated WBDs:

- Option 1: Repeat the study.

Most of the samples (i.e., all of the inhalation, all of the hands, 8 of the inner WBDs, and all of the outer WBDs) were not affected by the BIT-contaminated WBDs. Additionally, the majority of the dermal exposures are to the subject's hands. Therefore, EPA and PMRA do not believe it is warranted for the AEATF to repeat this intentional human study.

- Option 2: Use a mean study-derived penetration factor to replace contaminated WBDs.

The PFs for the individual body parts were calculated separately because it was thought that there could be physical rationales for them to differ (e.g., billowing effects of sleeves, V-necks around chest, etc). However, the results of the overall dermal unit exposures are nearly identical when using the single PF versus individual body part PFs. Since these PFs are being solely used for the determination of the dermal unit exposures in this study, the simplicity of the single PF is selected. Next, as it reasonably captures the potential day-to-day variability of clothing penetration, the arithmetic mean protection factor across all participants is utilized. Both a simple arithmetic mean and one assuming clothing penetration is lognormally distributed were calculated; no difference in the final dermal unit exposures was observed when rounded to 3 significant figures. Therefore, for simplicity purposes, EPA and PMRA selected Option 2 using the simple arithmetic mean (i.e., 12.3%).

- Option 3: Use the default penetration factor of 50% to replace the contaminated WBDs.

Although the dermal unit exposures do not differ substantially using the data derived versus default PFs, we are data-driven, and have decided not to use the 50% default PF for a specific study.

- Option 4: Use the upper bound of 100% penetration factor to replace the contaminated WBDs.

Although the dermal unit exposures do not differ substantially using the data derived versus maximum of 100% penetration (this is attributed to the fact that the majority of the exposure is to the hands), single layer of clothing does offer some protection, and we have decided not to use the outer dosimeters with no protection afforded by clothing.

Conclusion/Selection of Path Forward for Handling Contaminated WBDs:

EPA and PMRA selected Option 2 from above which is to use the simple arithmetic mean (i.e., 12.3%) penetration factor, and recommended to the AEATF II to complete the brush/roller study and submit the final report for review. After our determination, the

AEATF II used the 12.3% PF, completed the study, and submitted it for this review. We further recommend when using surrogate compounds that are also registered as material preservatives in textiles, soaps, etc., that pre-study background samples are analyzed for all vendor lots of sampling devices.

2.2 QA/QC Recovery Results

Controls. The non-fortified field and laboratory control samples (blanks) were as follows: The lab and field hand wash and face/neck were all less than the limit of quantification (LOQ); the lab (see "field" controls below) outer dosimeters were all less than the LOQ; all the lab and field inhalation samplers were less than the LOQ; and all the lab and field painter's hat control samples were less than the LOQ. All but one of the lab inner dosimeters were less than the LOQ, the one lab inner dosimeter laboratory control had measured BIT of 395 ug. There were contamination issues with the field controls for the outer and inner dosimeters (see pages 70, 71, and individual recovery values on pages 119-121, and 125-127 of AEATF II study report). The study report provides the following:

- "The outer dosimeter garments had been previously observed to contain background levels of BIT which were addressed by pre-washing outer dosimeter garments prior to use in the study. This washing was not completely effective in eliminating BIT from outer dosimeters used in the field. The field control samples for outer dosimeters showed measurable residues above the LOQ in 10 of 18 samples ranging from 3.78 μg to 22.5 μg per sample. Although residues were found in the field control outer dosimeter samples these were low compared to the total BIT found in the subject samples, and are not expected to impact the conclusions of the study. Any background BIT found in subject garments would tend to overestimate the reported subject exposure."
- For the inner dosimeters..."*Background BIT contamination in the various test system pieces used to prepare field fort samples affected recoveries in low and high field fortified samples.*" (V1:71). Page 61 of the study report further explains... "*Field fortification pieces were cut from randomly selected inner dosimeters, and although no record of dosimeter lot is available, it is likely that high field fortification recoveries are associated with use of one or more lots containing high background residues."*

The LOQs for the various matrices were: air sampling fiber filters and tubes 10 ng/each sample, neck/face wipe 0.1 μg/sample, WBD sections 3 μg/section, painter's hat 3 μg/sample, painter's hat inner dosimeter square 3 μg/sample, and hand wash 1 ng/mL (hand wash samples were 500 mL per sample).

Method Validation. The pre-study method validation for each of the sampling matrices was based on 7 samples for each of three fortification levels. The results of the method validation (MRID 50549401) are as follows: hand wash & neck/face wipes 99.9±3.23%; hand wash solution 96.8±3.04%; inner dosimeters 91.5±5.05%; outer dosimeters 96.6±5.50%; hats 96.7±7.22%; OVS tubes 93.4±5.46%; and RespiCon filters 95.5±4.02%.

Laboratory Recoveries. The concurrent laboratory recovery values for all of the matrices (averages from the hand wash, outer dosimeters, etc.) ranged from 86.1±8.95 to 96.0±16.3

percent. The number of laboratory recovery samples ranged from 18 for hand wash and painter's hats, 20 for inhalation samples, face/neck wipes, outer WBDs, and 24 for inner WBDs. Actual field samples (i.e., subject's dosimeters) were not corrected for concurrent laboratory results.

Field Recoveries. The field recovery values for the matrices are as follows:

Sampling Matrix	Fortification Levels (ug/sample)	% recovery
Air sampling tubes	0.1 and 2.0	81.3±7.24
Fiberglass tubes	0.1 and 2.0	87.5±7.75
Hand wash	2.0 and 200	92.4±8.50
Face/neck wipes	0.5 and 10	87.0±8.13
Outer dosimeters	12 and 1000	103±23.9
Inner dosimeters	12	1645±1940 (1)
	1000	104±20.3
Painters hat	12 and 1000	88.7±9.11

N = 27 per fortification level

[1]*"Field fortification pieces were cut from randomly selected inner dosimeters, and although no record of dosimeter lot is available, it is likely that high field fortification recoveries are associated with use of one or more lots containing high background residues."* (V1:61)

The field samples (i.e., dosimeter samples) were adjusted for the field recovery samples fortified on the same day that the samples were collected; no corrections were made if the average field recovery results were greater than 100% (page 57 of study report). The field recovery samples were transported, stored, and analyzed with the corresponding field (dosimeter) samples. Results of each individual field recovery are provided on pages 107 to 127 of the AEATF II study report.

2.2 Calculating Unit Exposures

Dermal Unit Exposure. Dermal exposure was 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, face/neck wipes, and painter's hats. The inner and outer WBDs were sectioned and analyzed by body part (i.e., upper and lower arms, front and rear torso, and upper and lower legs). Samples were adjusted, as appropriate, according to recovery results from field fortification samples (i.e., field recovery results were used to correct field samples where field recoveries were <100%).

A hand wash removal efficiency study was conducted separately with human subjects for BIT in paint. Hand washes were collected in this study as follows: *"Dermal hand exposure was assessed by washing and scrubbing the subjects' hands with 500 mL of water/IPA (50:50, v/v) solution and one package of gauze wipes (two per package). Over a sample collection bowl, a small amount (~50 mL) of the premeasured 500 mL of isopropyl alcohol/water (50:50, v/v) sample was poured over one of the gauze wipes (BAND-AID® Johnson & Johnson Large Mirasorb® Gauze Sponges, 4 in. x 4 in.) and the subject's hands to moisten the paint. With the*

wet gauze wipe, study personnel scrubbed one hand, loosening and removing the paint. The second gauze wipe was wet with some fresh isopropyl alcohol/water (50:50, v/v) and used to scrub the second hand, loosening and removing the paint. The two gauze wipes were added to the collection bowl. Study personnel then poured more of the isopropyl alcohol/water (50:50, v/v) over the subject's hands while they rubbed and washed their hands together like one would when washing under a faucet. Subjects were instructed to rub and scrub their hands together. The remainder of the premeasured 500 mL of isopropyl alcohol/water (50:50, v/v) was slowly poured over the subject's hands while they were directed to rub and rinse their hands for a final clean rinse. The solution and wipes were collected as a sample." (V1:37)

The hand wash samples in this study were corrected using the results from the hand wash removal efficiency study which indicated a removal efficiency of 60.3% for low level fortification of 154 ppm of BIT in paint and 73.3% for high level fortification of 547 ppm of BIT in paint (USEPA 2018). An average removal efficiency (66.8%) was calculated for the mid-point. Although not part of the protocol's objective for the hand wash removal efficiency study, the face/neck wipe samples were also corrected using these same correction factors. The following correction factors from the removal efficiency study were used:

- Low Level (concentrations in brush and roller study from 141 to 147 ppm BIT) 73.3% correction factor = MEs 1, 2, 4, 11, 13, 18
- Mid Level (concentrations in brush and roller study from 368 to 382 ppm BIT) 66.8% correction factor = MEs 5, 8, 10, 12, 14, 15
- High Level (concentrations in brush and roller study from 595 to 649 ppm BIT) 60.3% correction factor = MEs 3, 6, 7, 9, 16, 17

One final adjustment factor was used for the face/neck samples to correct for the area of the face covered by the safety glasses. A correction factor of 1.11 was used to correct the face/neck residue values (page 59 of the AEATF II study report).

The various analyses of residues on the dosimeters worn by each individual subject allow for the estimation of exposure for the following 3 clothing configurations:

(1) "Long-Long" or "Long Long Dermal" or "Long Dermal" = long pants, long-sleeved shirt, and no gloves for commercial painters;
(2) "Long-Short" or "Long Short Dermal" = long pants, short-sleeved shirt, and no gloves for commercial and/or residential/consumer painters; and
(3) "Short-Short" or "Short Dermal" = short pants, short-sleeved shirt, no gloves for residential/consumer painters.

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, painter's hat, inner dosimeter painter's hat, 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, painter's hat, inner dosimeter painter's hat, and hand wash:

- outer and inner lower arms,
- 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 short pants, short-sleeved shirts (Short-Short) plus face/neck wash, painter's hat, inner dosimeter painter's hat, and hand wash:

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

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 two personal air sampling pumps. The subjects wore a… "*personal air sampling pump and OVS air sampling tube with glass filter and XAD2 sorbent was placed in the subjects' breathing zones to determine subjects' inhalation exposure to BIT. The OVS air sampling tube was used to determine the total concentration of BIT in the air. The air flow of the pump was calibrated to a targeted rate of 2.0 liters per minute prior to use. A second low-volume, personal air-sampling pump attached to a three stage RespiCon™ Particle Sampler was placed in the subjects' breathing zones using a chest harness to determine the size distribution of any particles containing BIT in the air. The air flow of the pump was calibrated to a targeted rate of 3.1 liters per minute prior to use.*"

The results from the OVS tubes are reported herein as the "total" or "inhalable" air concentration monitored from the glass fiber filter (<100 µm) and XAD2 sorbent backing. The RespiCon™ Particle Sampler samples the "respirable" portion of the inhalation sample and was capable of sizing particles of 2.5, 10, and 100 µm. Note: All inhalation samples were <LOQ.

Inhalation unit exposures for the OVS sampling tubes are provided using the two following methods:

(1) 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) * sampling duration (hours/day) / 8 (hours / day).

(2) Inhalation exposure (mg/lb ai) or dose is calculated as the air concentration ((mg/m^3) / lb ai) * breathing rate (1 m^3/hour) * sampling (hours/day).

Inhalation unit exposures were not calculated for the RespiCon samplers because all the samples were below the LOQ. If needed, the unit exposures could be calculated using the following formulas from the RespiCon Operation and Service Manual (TSI, 2007) for the respirable, thoracic and inhalable aerosol size fractions:

Respirable Fraction: $Cresp = \frac{(M_1) * 1000}{(Q_1) * Ts}$

Thoracic Fraction: $Cthor = \frac{(M_1 + M_2) * 1000}{(Q_1 + Q_2) * Ts}$

Inhalable Fraction: $Cinh = \frac{(M_1 + M_2 + M_3) * 1000}{(Q_1 + Q_2 + Q_3) * Ts}$

Where:

Cresp	=	Respirable fraction (mg/m^3)
Cthor	=	Thoracic fraction (mg/m^3)
Cinh	=	Inhalable fraction (mg/m^3)
M_1	=	Mass (mg) deposited on filter #1 (2.5 micron cut point)
M_2	=	Mass (mg) deposited on filter #2 (10 micron cut point)
M_3	=	Mass (mg) deposited on filter #3 (100 micron cut point)
Q_1	=	Flow rate through filter #1 (2.66 Lpm)
Q_2	=	Flow rate through filter #2 (0.33 Lpm)
Q_3	=	Flow rate through filter #3 (0.11 Lpm)
Ts	=	Sample duration (minutes)

Given that the LOQ is 10 ng per filter used in the RespiCon sampler, the LOQ per sample is 10 ng for the respirable fraction, which is based on one filter, 20 ng for the thoracic fraction, which is based on two filters and 30 ng for the inhalable fraction which is based on three filters. The corresponding air flow rate is 2.66 liters per minute (lpm) for the respirable fraction, 2.99 lpm for the thoracic fraction, and 3.11 lpm for the inhalable fraction.

2.3 Dermal and Inhalation Exposure Results

Results. A summary of the individual and mean dermal and inhalation results of the brush/roller are presented in Table 4. Both empirical means and the results of the lognormal simple random sample means are provided for comparison; the latter being the recommended values summarized in Table 1. The clothing configuration of long pants, long sleeved shirts (Long-Long) as well as short pants, short-sleeved shirts (Short-Short), and no gloves are provided. The clothing configurations of long pants, short sleeved-shirts (Long-Short), and no gloves are also provided. Also shown for comparison to the total dermal exposure are the dermal results for the hand exposures only. These tables report the results for each individual worker along with empirical and lognormal simple random sampling method statistical summaries.

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

- Empirical simple random sampling model (see Appendix B, Tables 1 through 10 for detailed summaries);
- Lognormal simple random sampling model (see Appendix B, Tables 12 and 16, and for more details, Tables 17 through 26).

The results of the lognormal simple random sampling 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). The estimates using substitution of half the LOQ for non-detected values are recommended. For a detailed discussion of the lognormal simple random sampling model calculations and results the reader is referred to Appendix B (along with a discussion of the HSRB-suggested quadratic models on pages 58 and 59 of Appendix B).

Study Observations. The paint brush/roller study includes the recorded individual participant activities by observers. Detailed observations recorded during each ME capturing the events that occurred during the painting activities can be viewed in the study report's Appendix H (pages 359 to 414). Although a review of these observations indicates some instances where the subjects touched painted surfaces, these types of exposures are expected based on the task and are not considered outliers in the data. There is also an instance (in ME15) where the study observer instructed the subject in painting to avoid a behavior that affected exposure. EPA initially was concerned that the observer interfered with the subject's behavior that most likely reduced the exposures of the subject. EPA asked the AEATF II what was the rationale behind instructing ME15 to paint differently. The study director's response was as follows: *"The subject in ME15 was painting in a manner that seemed to researchers to be unreasonable--trying to hurry and transfer as much paint as rather than painting as he would at home. The protocol contained language anticipating this "If the Principal Investigator determines that a subject's painting technique is outside reasonable consumer practice (e.g. gross over application, under application, or sloppiness) the subject will be reinstructed and then allowed to continue." (protocol, page 18)."* The study director also included a picture of the painting practice prior to the instruction by the observer to illustrate why the instruction was given (see Figure 2). Based on the picture in Figure 2, the instruction is considered by EPA to be reasonable and prudent.


Figure 2. Subject ME's Painting Prior to Observer's Instruction on How to Dab Brush in Pan.

There is also an instance (in ME01) where the observer instructed the subject not to pick the paint off their hands (thus preserving the residues). The following observations are highlighted:

- **ME01:** Subject was observed to have paint on knuckles from rubbing against wall; also picked at paint on hands and was asked to stop.
- **ME02:** Painted the least amount of surface area (267 ft^2); observer noted that subject had a lot of visible paint on hands (but this ME had the 3rd lowest hand residues); at 10:23 am indicated she felt dizzy, rubs hand and face while sitting in chair, resumes painting. Requested to end the study at 10:38 am (monitoring had started at 9:00 am). She stated that she felt fine.
- **ME03:** Notes lots of extra paint on brush but does not mention any paint observed on hands; subject has the 2nd highest hand residue value.
- **ME04:** Subject used hand to push roller back onto the roller frame; subject had the second lowest hand residue value.
- **ME05:** Noted a lot of paint on hands; subject had the 4th highest hand residue value; requests to stop because of neck pain from painting ceiling, leaves ceiling 80% done, continues painting window trim, wall 3 minutes later.
- **ME08:** Subject pushed the roller cover back onto roller frame several times; 3rd highest hand residue value.
- **ME11:** Air sampling pump off ~10 seconds.
- **ME15:** Subject was overloading brush causing thick drips; observer recommended dabbing brush on ribbed tray to prevent this (ME started at 10:41 am and instruction was given at 10:46 am); it was noted that the very heavy drips from overloading brush was corrected. Paint visible (heavy) on hands. This subject's hands had the highest hand residue value by 2-fold (i.e., uncorrected hands 2424 ug).

- **ME16:** Subject had the lowest hand residue value (uncorrected hands 37.7 ug); used both the brush and roller, cup and both cans of paint; painted for 59 minutes.

Impact of Non-detects. All the hand samples were above the limit of quantification (LOQ). Four of the 18 face/neck samples were less than the LOQ (i.e., all the multiple wipe samples <LOQ). All the painter's inner hat samples were above the LOQ and 5 of the hat samples were <LOQ. For the five hat samples below the LOQ, the inner hat sample was not analyzed, but for consistency was treated for these statistical analyses as being <LOQ. The head exposure is calculated as the sum of the inner and outer hat measurements, and has been included in the dermal exposure estimates. Two of the outer dermal dosimeters were <LOQ. For the inner dermal dosimeters 49 of the 108 were below the LOQ (including the estimated values for the contaminated samples). The impact of the non-detects is reviewed in Appendix B (pages 22 to 25), including the statistical methods of substituting NDs with ½ LOQ, full LOQ, zero, and censored data maximum likelihood (MLE). The dermal arithmetic mean unit exposures for the Long Dermal clothing scenario using the four substitution methods described above are 116, 116, 115, and 113 mg/lb ai, respectively. The dermal arithmetic mean unit exposures for the Short Dermal clothing scenario using the four substitution methods described above are 144, 145, 143, and 141 mg/lb ai, respectively. The inhalation exposure measurements were all <LOQ. The inhalation 8-hour time weighted average arithmetic mean unit exposures for the OVS tubes using the three substitution methods ½ LOQ, full LOQ, and censored data maximum likelihood (MLE) for handling non-detects (zero substitution is unavailable for the log-normal models) are: OVS sampler 0.00097, 0.00194, 0.00063 (mg/m^3)/lb ai. See Appendix B, pages 22 to 25 for details.

The unit exposures provided in the summary Tables 1 and 4 are based on substituting ½ LOQ for non-detects.

Table 4. Summary of dermal and inhalation (OVS tubes) unit exposure estimates

Monitoring Event (ME)	AaiH (lb)	Unit exposure (mg/lb AaiH)				Unit exposure ((mg/m^3)/lb AaiH)
		Hands	Long-Long	Short-Short	Long- Short	Inhalation TWA
1	0.00308	192.2	205.1	229.7	227.4	0.00171
2	0.00272	43.4	49.6	73.4	63.6	0.00188
3	0.01410	143.5	155.4	207.2	187.0	0.00038
4	0.00305	36.7	54.3	77.3	71.4	0.00186
5	0.00808	157.3	178.4	220.5	204.4	0.00065
6	0.01280	23.7	28.7	39.1	30.6	0.00040
7	0.01300	64.1	71.4	96.3	87.5	0.00042
8	0.00766	205.4	207.6	227.0	212.3	0.00067
9	0.01200	17.2	19.5	26.7	26.1	0.00043
10	0.00787	26.8	32.8	42.0	37.2	0.00066
11	0.00308	61.7	73.6	95.5	86.2	0.00167
12	0.00753	96.8	121.9	153.9	137.5	0.00072
13	0.00287	48.4	64.4	84.3	76.1	0.00180
14	0.00712	52.5	63.4	117.4	89.3	0.00072
15	0.00777	520.6	526.3	549.6	541.5	0.00066
16	0.01240	5.2	9.7	13.7	11.7	0.00043
17	0.01320	69.7	80.6	99.0	87.5	0.00039
18	0.00276	57.2	63.8	105.9	75.9	0.00189
Empirical Mean	0.00784	101.2	111.5	136.6	125.2	0.00096
Empirical SD	0.00422	120.4	120.4	124.1	123.2	0.00062
Lognormal Simple Random Sample Mean	0.00809	107.6	115.5	143.8	130.8	0.00097
Lognormal Simple Random Sample SD	0.00570	154.2	139.7	155.4	148.3	0.00069

Let X_i be the i^{th} AaiH or unit exposure value and let $Y_i = \ln(X_i)$.

Empirical Mean = $\overline{X} = \sum_{i=1}^{18} X_i / 18$

Empirical SD = $S_X = \sqrt{\sum_{i=1}^{18} \left(X_i - \overline{X}\right)^2 / 17}$. Suppose X is lognormally distributed, so that Y = ln(X) is normally distributed with a population mean μ and a population variance σ^2.

Lognormal Simple Random Sample Mean = Estimated population mean of X = Estimate of $\exp(\mu + \frac{1}{2} \sigma^2) = \exp(\overline{Y} + \frac{1}{2} S_Y{}^2)$ where $\overline{Y} = \sum_{i=1}^{18} Y_i / 18$ and $S_Y = \sqrt{\sum_{i=1}^{18} \left(Y_i - \overline{Y}\right)^2 / 17}$.

Lognormal Simple Random Sample SD = Estimated population standard deviation of X = Estimate of $\exp(\mu + \frac{1}{2} \sigma^2) \sqrt{\exp(\sigma^2) - 1} = \exp(\overline{Y} + \frac{1}{2} S_Y{}^2) \sqrt{\exp(S_Y{}^2) - 1}$.

2.4 Evaluation of Scenario Benchmark Objective

Benchmark Objective. The data from the study has been analyzed to see if the brush/roller scenario meets the AEATF II objective of a relative 3-fold accuracy (i.e., K = 3). These analyses used 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 the Antimicrobial Division (AD)). Appendix B (pages 26 to 29 and pages 41 to 43) provides the detailed 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" also expressed as "K-factor"). 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"), normal and lognormal probability plots of dermal and inhalation UEs are provided in Appendix B (pages 31 to 40, Figures 2 to 21) to illustrate that the lognormal distribution is a better fit than the normal distribution for the normalized exposure. These plots support the assumed lognormal distributions for the normalized exposure. Note: all logarithms defined in this review are natural logarithms.

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

- Empirical estimates; and
- Assuming a lognormal distribution and a simple random sample (SRS).

The 95% confidence limits for each of these estimates were obtained by generating 10,000 parametric bootstrap samples from the fitted lognormal distribution. 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. EPA has determined that the brush/roller study results meet the 3-fold relative accuracy objective except sometimes for the empirical 95th percentile (see Tables 5 and 6). Appendix B also presents fRA values calculated using a non-parametric bootstrap approach, with generally similar results.

Table 5: Results of Primary Benchmark Analysis for Dermal Exposure						
	Long Dermal Exposure			Short Dermal Exposure		
Statistic	**Unit Exposure Estimate (mg/lb ai)**	**95% CI**	**fRA**	**Unit Exposure Estimate (mg/lb ai)**	**95% CI**	**fRA**
GM_S	74	48 − 116	1.6	87	57 − 133	1.5
GSD_S	2.6	1.9 – 3.6	1.4	2.5	1.8 – 3.4	1.4
GM_S = geometric mean assuming SRS = "exp(average of 18 ln(UE)) values" GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 18 ln(UE)) values"						
AM_S	111	67 − 197	1.8	125	78 − 217	1.7
AM_U	116	69 − 201	1.7	131	80 − 221	1.7
AM_S = average of 18 unit exposures AM_U = arithmetic mean based on $GM_S = GM_S * \exp\{0.5*(\ln(GSD_S)^2\}$						
$P95_S$	526	175 − 1252	3.0	541	198 − 1306	2.7
$P95_U$	351	176 − 692	2.0	386	200 − 740	1.9
$P95_S$ = 95th percentile (i.e., estimated as the maximum unit exposure from the 18 unit exposures) $P95_U$ = 95th percentile based on $GM_S = GM_S * GSD_S^{1.645}$						

Table 6: Results of Primary Benchmark Analysis for Inhalation (Inhalable TWA)).						
	OVS Total			< 2.5 µm		
Statistic	**Unit Exposure Estimate (8-hr TWA mg/m³/lb ai)**	**95% CI**	**fRA**	**Unit Exposure Estimate (8-hr TWA mg/m³/lb ai)**	**95% CI**	**fRA**
GM_S	0.00079	0.00059 – 0.00107	1.4	0.00051	0.00038 – 0.00069	1.4
GSD_S	1.89	1.53 – 2.35	1.2	1.89	1.53 – 2.35	1.2
GM_S = geometric mean assuming SRS = "exp(average of 18 ln(UE)) values" GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 18 ln(UE)) values"						
AM_S	0.00096	0.00070 – 0.00135	1.4	0.00062	0.00045 – 0.00086	1.4
AM_U	0.00097	0.00071 – 0.00136	1.4	0.00062	0.00045 – 0.00087	1.4
AM_S = average of 18 unit exposures AM_U = arithmetic mean based on $GM_S = GM_S * \exp\{0.5*(\ln(GSD_S)^2\}$						
$P95_S$	0.00189	0.00142 – 0.00531	2.8	0.00127	0.00091 – 0.00342	2.7
$P95_U$	0.00226	0.00143 – 0.00356	1.6	0.00145	0.00091 – 0.00229	1.6
$P95_S$ = 95th percentile (i.e., estimated as the maximum unit exposure from the 18 unit exposures) $P95_U$ = 95th percentile based on $GM_S = GM_S * GSD_S^{1.645}$						

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 or ai). In the Governing Document and in statistical reviews of some 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. This analysis was not done for inhalation exposures because all the measurements were non-detects.

To evaluate the relationship for this scenario EPA performed **regression analysis of log(exposure) against log(AaiH)** to determine if the slope of this log-log-linear model is not significantly different than 1 – providing support for a "proportional" (an abbreviation for " log-log-linear with slope 1") relationship – or if the slope is not significantly different than 0 – providing support for an independent relationship. If the slope is positive, not zero and not 1, then the arithmetic mean 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 for the dermal exposure measures the change in log mg dermal exposure for each unit change in log lb ai. A slope of 1 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.**

The resulting regression slopes and confidence intervals are summarized in Table 7. A more detailed table of the slopes (including calculations for alternative treatments of non-detects) is presented in Appendix B (page 43, Table 27).

For the dermal exposures, the slopes ranged from 0.75 to 0.78 and the confidence intervals for the slope included one but did not include zero. Thus, the analyses rejected independence (a slope of zero) and supported (more precisely, did not reject) proportionality (a slope of one).

A secondary objective for EPA is for meeting 80% power for detecting log-log-linearity with a slope of 1. This objective is approximately met if the widths of the confidence intervals for the slopes are at most 1.4. This secondary objective was not met and so the statistical (post-hoc) power was less than 80%.

Figures 3 to 5 show the data and corresponding fitted regression models for the dermal exposure routes. The data points marked with the symbols "L", "M" and "R" are the measured values in the "2. Low" "3. Mid" and "4. High" BIT concentration groups. Appendix B (pages 44 to 47, Figures 22 to 25) also presents probability plots of the residuals from these fitted regression models; these probability plots show that this simple log-log-linear regression model fits reasonably well.

Table 7. 95 Percent Confidence Intervals for the Slope of Log Exposure (mg) versus Log Pounds of Active Ingredient for Dermal Exposures.

Clothing	Slope	Confidence Interval	Confidence Interval Width
Long pants, long sleeved-shirt	0.78	0.00 – 1.57	1.57
Short pants, short sleeved-shirt	0.75	0.03 – 1.47	1.45
Long pants, short sleeved-shirt	0.76	0.01 – 1.51	1.50

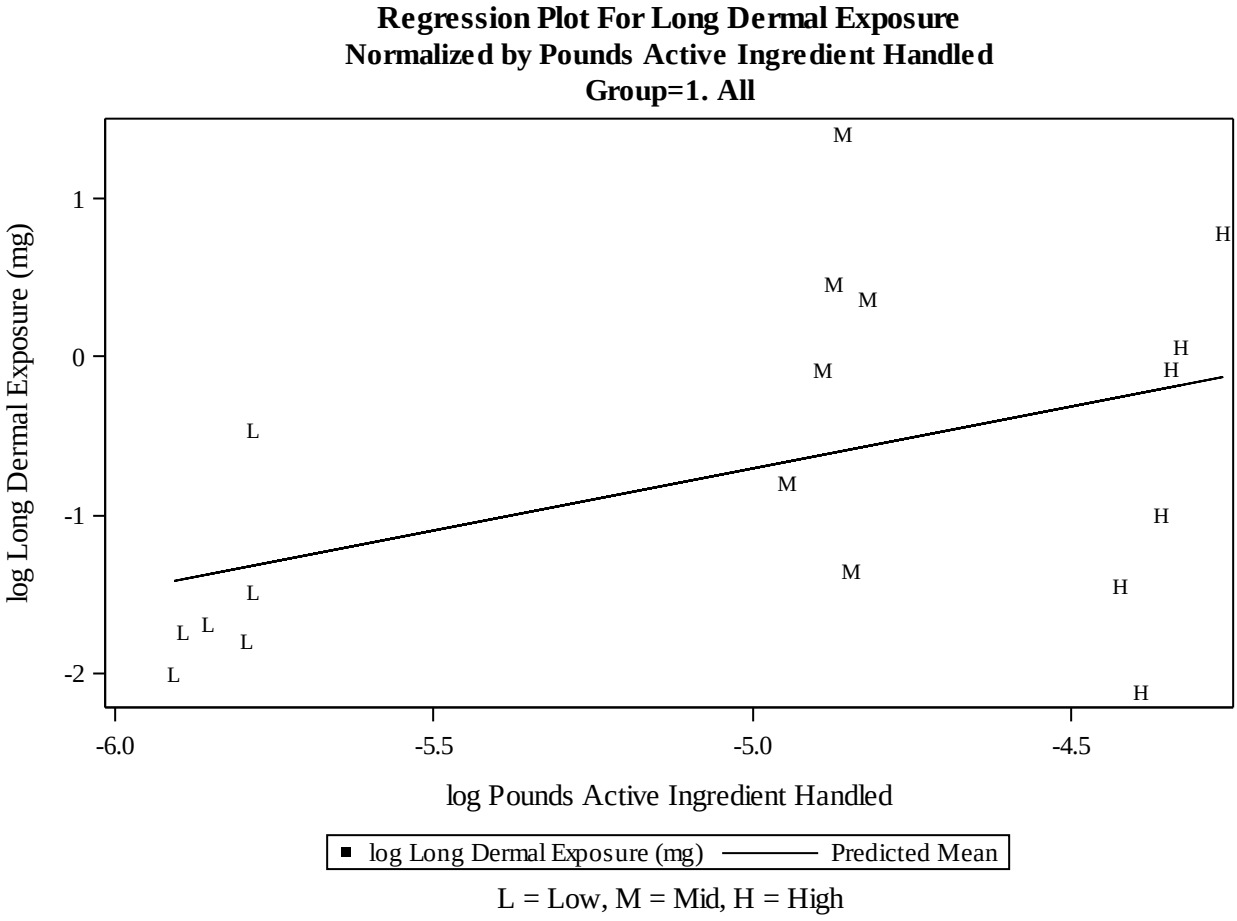

Figure 3. Regression plot for Long Dermal

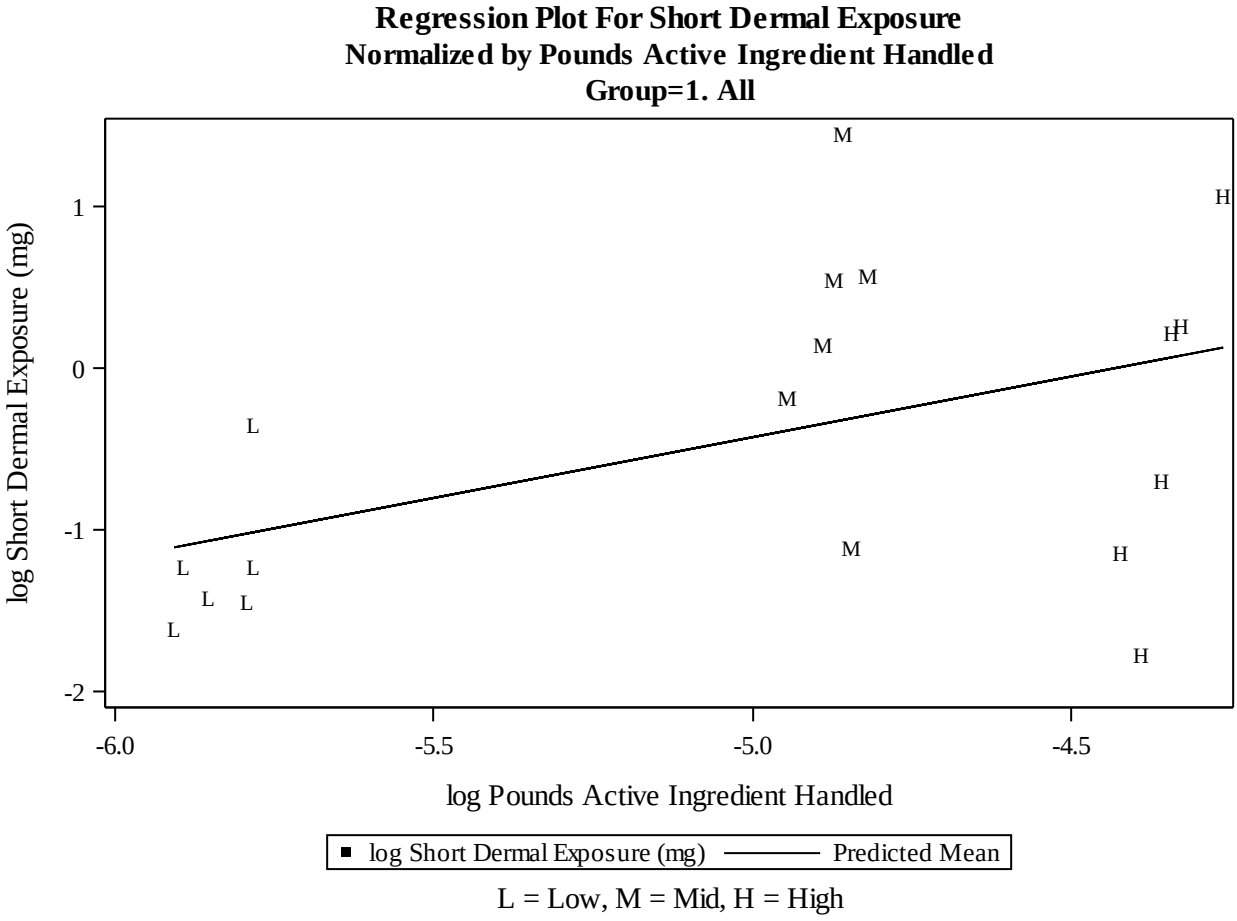

Figure 4. Regression plot for Short Dermal

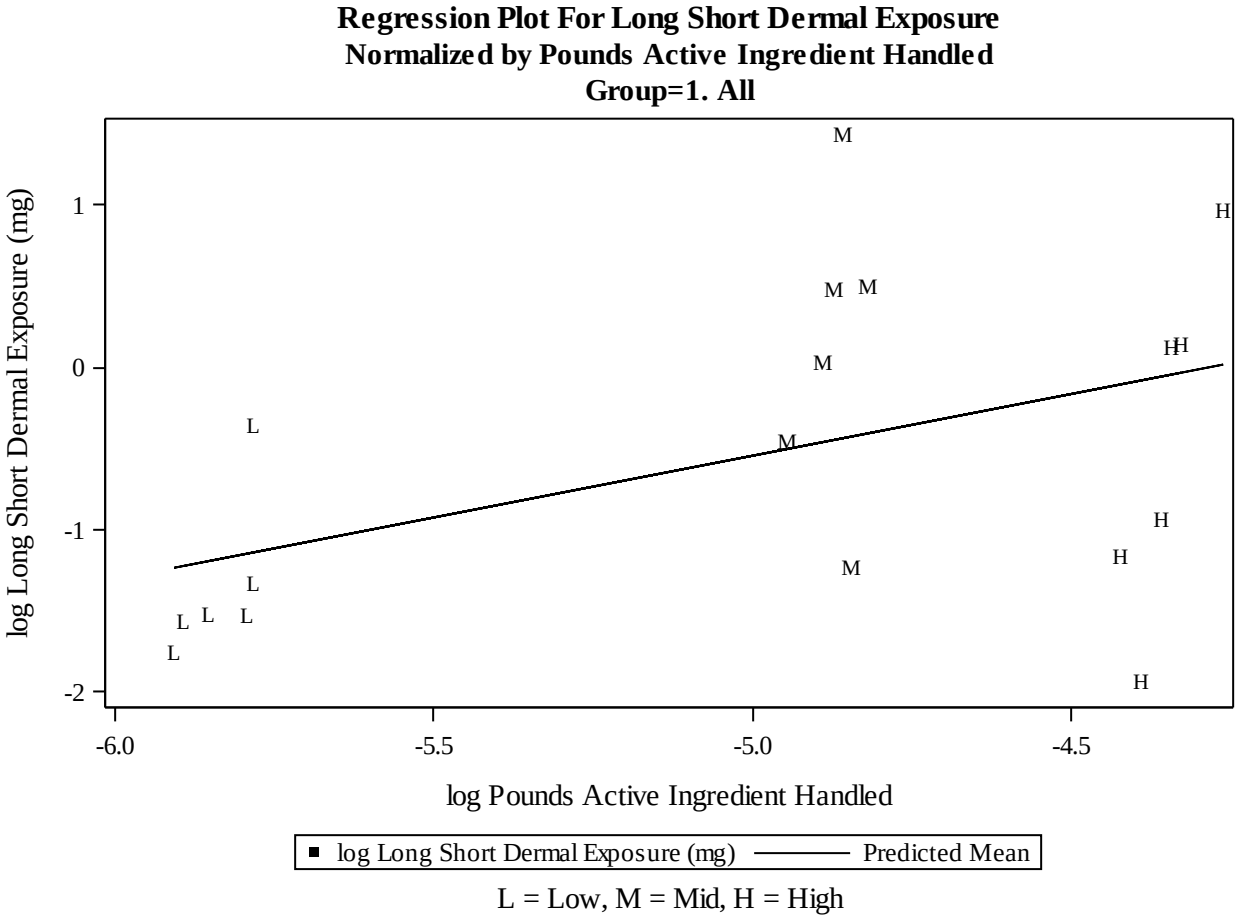

Figure 5. Regression plot for Long Short Dermal

Threshold of AaiH for Over- or Under-Predicting Exposure – The log-log-linear regression model regresses the log exposure against the log lb ai. The normalized (unit) exposure model is the log-log-linear regression model where the slope of log exposure against log lb ai is assumed to be equal to 1. The analysis is based on comparing the two model predictions of the conditional means, i.e., the estimated arithmetic means for a given amount of active ingredient. It is shown in Appendix B (pages 59 to 60) that if the regression formulation is correct and the estimated regression slope is less than one, then the conditional arithmetic mean exposure for a given amount of ai will be over-predicted if the normalized exposure model is extrapolated to high levels of the amount of active ingredient and the conditional arithmetic mean exposure will be under-predicted at low levels of the amount of active ingredient. This applies to all the dermal exposure cases.

For the three dermal exposure cases, Table 8 gives the threshold amounts of active ingredient handled which are the minimum amounts 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). Also tabulated are the corresponding exposure values at the threshold levels of active ingredient.

Table 8. Threshold values for the minimum amount of active ingredient handled for which the normalized exposure model will over- or under-estimate dermal exposure.

Clothing	Slope (log mg / log lb ai)	Threshold (lb ai)	Exposure at threshold (mg)
Long pants, long sleeved-shirt	0.78	0.00719	0.831
Short pants, short sleeved-shirt	0.75	0.00691	0.994
Long pants, short sleeved-shirt	0.76	0.00700	0.798

Figures 6 through 8 show the statistical models and thresholds for the dermal exposure routes. These figures display the measured values together with the predicted conditional arithmetic mean exposure calculated using the normalized exposure model (where the slope of log exposure against log ai is assumed to be one) and using the more general regression model (where the slope of log exposure against log ai is estimated). The threshold is the amount of ai for which the two predicted conditional means are the same. The data points marked with the symbols “L”, “M” and “R” are the measured values in the “2. Low” “3. Mid” and “4. High” BIT concentration groups. The normalized exposure model calculation is plotted as a green line; this calculation uses unit exposures to estimate the conditional mean exposure for a given amount of active ingredient. The log-log-linear regression model calculation is plotted as a brown curve, since both axes are linear; this calculation uses the log-log-linear regression model to estimate the conditional mean exposure for a given amount of active ingredient.

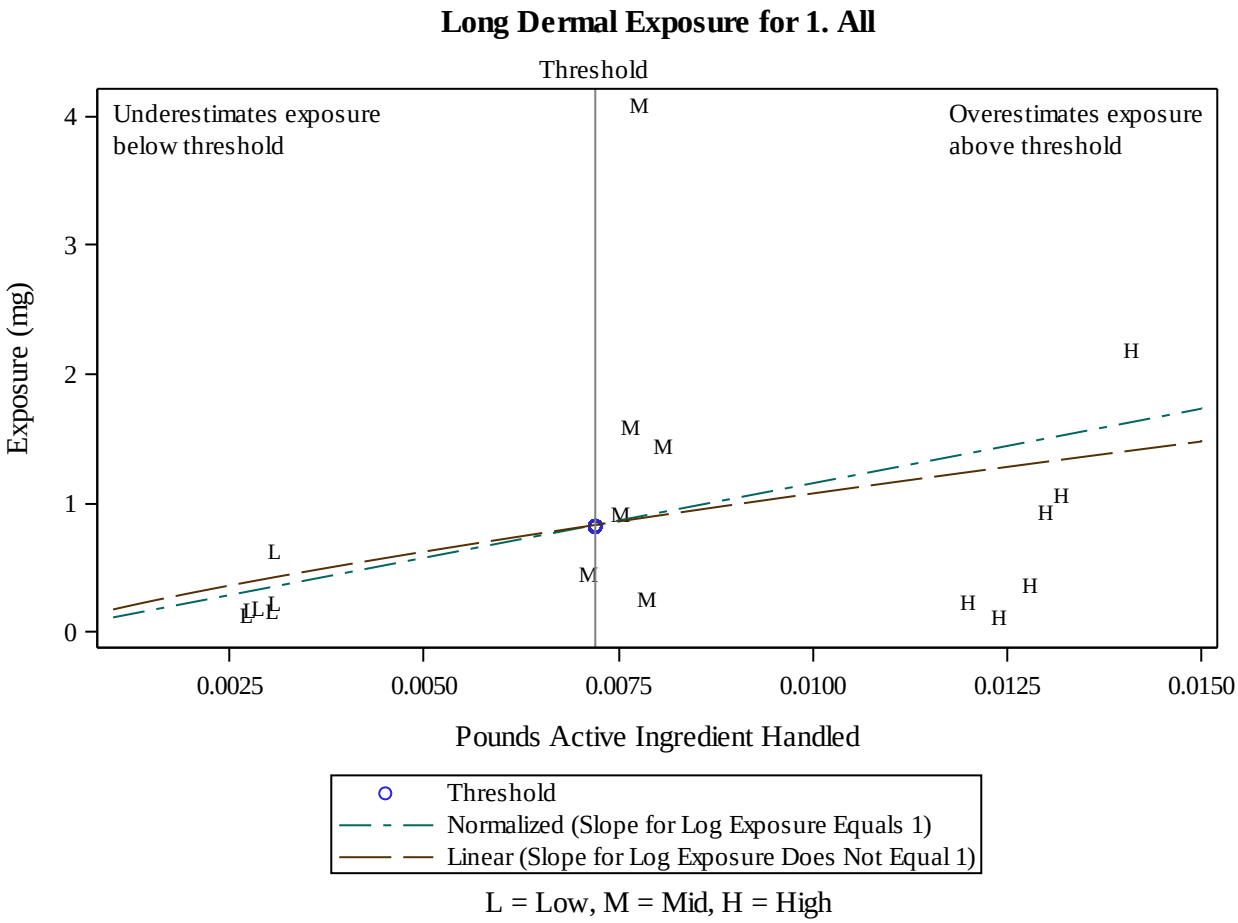

Figure 6. Conditional means for long dermal exposure predicted using the normalized exposure model and the general log-log-linear model; threshold value.

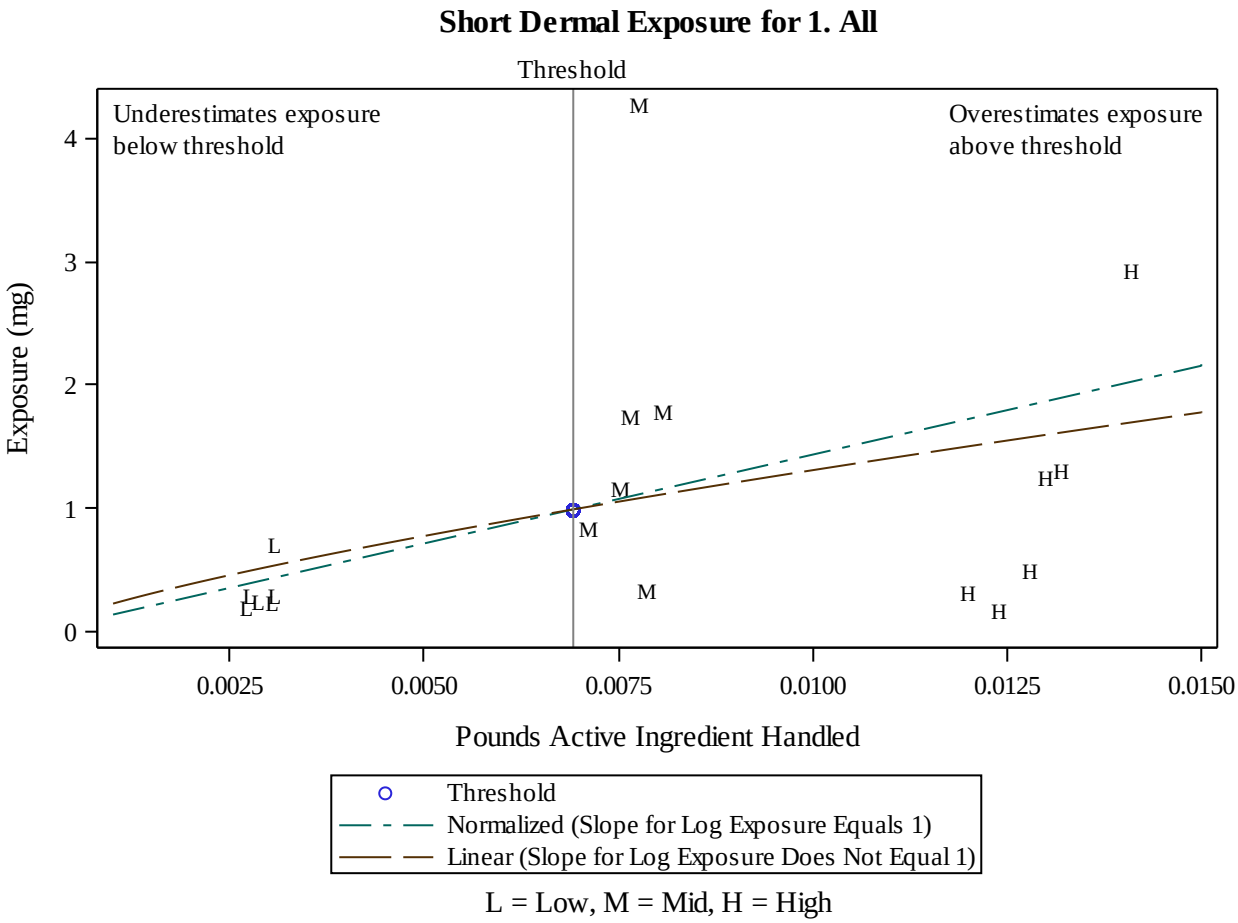

Figure 7. Conditional means for short dermal exposure predicted using the normalized exposure model and the general log-log-linear model; threshold value.

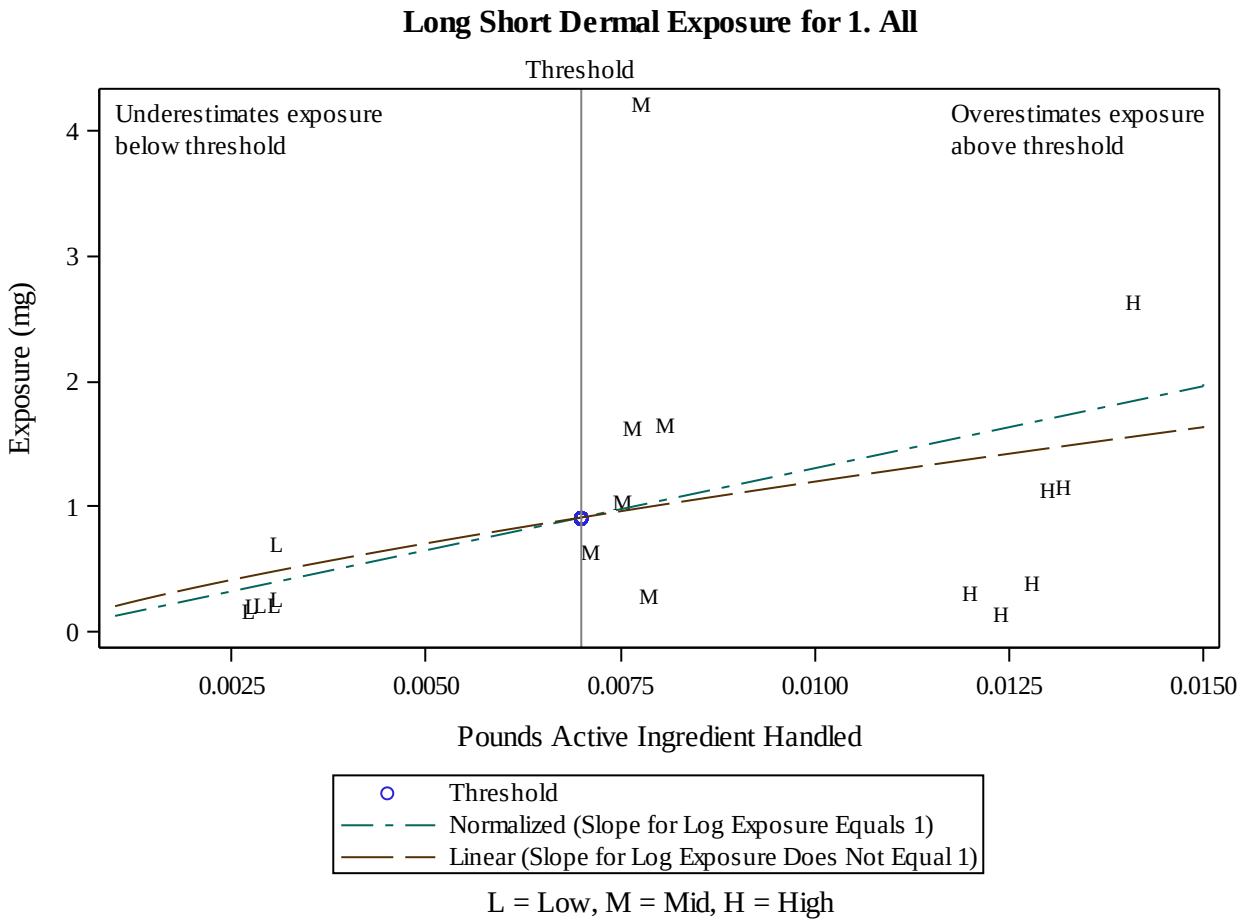

Figure 8. Conditional means for long short dermal exposure predicted using the normalized exposure model and the general log-log-linear model; threshold value.

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

walls/ceilings/trim indoors in Fresno are not substantially different than painting with a brush and roller inside other buildings throughout the country. The indoor site is also deemed a worse-case scenario compared to outdoors. Given a limited set of resources for the overall AEATF II monitoring program, the assumption that painting does not vary geographically was sufficiently reasonable to forgo the random site selection (of all buildings throughout the country) in favor of spending the limited resources to monitor additional distinctly different scenarios (e.g., trigger pump spray, airless paint sprayers, etc).

(2) 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.

(3) 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 (meeting better than the 3-fold relative accuracy goal).

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 CA painters (e.g., those that paint but did not volunteer), buildings (e.g., a warehouse with purposely built rooms was selected for this study), and time periods (e.g., summer versus winter, day versus night, 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).

(4) EPA will continue using exposures normalized by AaiH as a default condition. In this review we evaluated the presumption of "proportionality" that the mean exposure is a positive multiple of the AaiH (i.e., the mean exposure is proportional to the AaiH and the exposure tends to increase with increasing AaiH). Proportionality is evaluated by testing if the log-log-linear model has a slope of 1. The analyses of log-log-linearity show that dermal exposure tends to increase with pounds of active ingredient handled (AaiH). Data will continue to be collected by the AEATF II to add to the knowledge base of normalized exposures.

(5) The dermal unit exposures are based partially on study-derived penetration factors because of unforeseen contaminated inner whole-body dosimeters. The surrogate chemical used in the study, BIT, is also a material preservative used to treat textiles during the manufacturing process. As happenstance, 10 of the 18 inner WBDs were treated during the manufacturing process using BIT as the material preservative. Thus, 10 MEs had their dermal inner WBDs "contaminated". The amount of contamination in the WBD was higher than the amount of BIT collected on the WBDs from the treated paint in the study; and therefore, these inner WBDs were not used. The subjects wearing the affected inner WBDs included MEs: 1, 2, 4, 6, 7, 10, 12, 13, 16, and 17. These inner WBDs were replaced using a 12.3% penetration factor applied to the outer WBD to estimate the inner WBD residues as described in this

review. The impact of this substitution on the resulting dermal unit exposure is not substantial as most of the exposure is attributed to the hand exposure. As illustrated in Table 3, for the long pants, long sleeved, shirt, no glove clothing scenario, 94% of the dermal exposure is attributed to the hands.

(6) The correction factors developed from hand wash removal efficiency study were also used to correct the face/neck wipe residues. The hand wash procedure is different than the face/neck wipe procedure because there is no rinse step. Nonetheless, using the correction factor is more conservative (protective of worker exposure) than making no correction for potential losses during sampling.

(7) The field control and fortified inner dosimeters samples showed contamination. The study report explained the contamination as... "*Background BIT contamination in the various test system pieces used to prepare field fort samples affected recoveries in low and high field fortified samples.*" The study report further explains... "*Field fortification pieces were cut from randomly selected inner dosimeters, and although no record of dosimeter lot is available, it is likely that high field fortification recoveries are associated with use of one or more lots containing high background residues."* More care will need to be taken in future studies when the surrogate compound being tested is also registered as a material preservative in textiles and/or solutions that might be used as sampling media/solvents.

(8) All the measured inhalation residues were below the limit of quantification. Similarly, the existing PHED inhalation exposure for the paint brush study had all non-detect values but at a much higher detection limit of 2 ug per sample. This AEATF II brush/roller study used two inhalation samplers (i.e., OVS tubes and RespiCon), with LOQs of 10 ng/sample. The fact that the inhalation exposures were not detected while using what can be considered a low LOQ, shows that inhalation exposure is negligible for BIT concentrations like those use in this study. The low inhalation exposure during painting with a brush/roller was not unexpected. EPA's assessment of material preservatives in paint includes both brush/roller and airless sprayer painting scenarios. As indicated in the existing PHED painting data, the airless paint spraying scenario is the risk driver for inhalation exposure to paint.

4.0 Conclusions

EPA has reviewed the AEATF II brush/roller 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 with some issues that have been rectified. The two issues of note are the background contamination of the inner WBD and the interference with the normal work practice of one of the MEs. The background contamination was rectified using clothing penetration factors as described within the review and are not believed to have had a substantial impact on the dermal unit exposures since most of the dermal exposure is to the hands. The change in the one MEs work practice may have reduced the highest exposure value for the ME with the maximum exposure. 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 brush/roller 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 paint treated with antimicrobial products with a brush/roller. The AEATF II

unit exposures summarized in Table 1 are recommended to be used for regulatory purposes.

- Estimates of the GM, AM, and P95 were shown to be accurate within 3-fold with 95% confidence. At this time, no additional monitoring for the brush/roller scenarios is required.

5.0 References

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Hackathorn, D.R. and D.C. Eberhart. 1985. Data Base Proposal for Use in Predicting Mixer-loader-applicator Exposure. American Chemical Society Symposium Series 273, pp. 341-355.

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MRID 50549401. Validation of Method GPL-MTH-081 and Freezer Storage Stability: Analytical Method for the Determination of Benzisothiazolinone (BIT) in Paint, Dressing Sponges, Hand Washes, Cotton Inner and Outer Dosimeters, Painter's Hats, Air Sampling Tubes and Fiberglass Filters. GPL Study No.: 130478. Study Completion: March 1, 2017.

SAP. 2007. Memorandum: Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held January 9 – 12, 2007 on the Review of Worker Exposure Assessment Methods. U.S. Environmental Protection Agency.

TSI. 2007. Model 8522 RespiCon Particle Sampler Operation and Service Manual, P/N1980320, Revision E, TSI Incorporated, August 2007.

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Appendix A

Analyses of the Brush and Roller Study Using Alternative Clothing Penetration Factors

(To be included as a separate electronic file)

Appendix B

Statistical Review of the AEATF II Brush and Roller Study

(To be included as a separate electronic file)