UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: March 11, 2011

SUBJECT: Review of Agricultural Handler Exposure Task Force (AHETF) Monograph: Open Cab Airblast Application of Liquid Sprays

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This memorandum presents the Health Effects Division review of the occupational handler exposure scenario monograph "Open Cab Airblast Application of Liquid Sprays" submitted by the Agricultural Handler Exposure Task Force (AHETF, 2010). Scientific review of the five exposure studies comprising this scenario can be found in a separate data evaluation review (DER) memorandum (Crowley, 2011; D387287). The AHETF satisfactorily followed the study protocols and satisfied data analysis objectives. EPA considers the open cab airblast scenario complete and its results are recommended for use in routine assessment of exposure and risk for open cab airblast applicators.

1.0 Executive Summary

This document represents the Health Effects Division (HED) review of the Agricultural Handler Exposure Task Force (AHETF) Monograph: Open Cab Airblast Application of Liquid Sprays (AHETF, 2010). HED confirms that the data meets the study design objectives outlined in the AHETF Governing Document (AHETF, 2008) and is considered the most reliable data for assessing exposure and risk to individuals applying liquid spray pesticides[1] with open cab airblast equipment while wearing the following personal protective equipment (PPE): long-sleeved shirts, long pants, shoes, socks, chemical-resistant gloves, with or without chemical-resistant hats, and no respirator[2]. The AHETF data and associated "unit exposures" are considered superior to the existing open cab airblast applicator dataset.[3] AHETF efforts represented a well-designed, concerted process to collect reliable, internally-consistent, and contemporary 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 primary objective for dermal exposure results (normalized to the amount of active ingredient handled) to be accurate within 3-fold at the geometric mean, arithmetic mean and 95th percentile was met. The secondary objective to evaluate proportionality between dermal and inhalation exposure and the amount of active ingredient handled with 80% statistical power – a key assumption in the use of exposure data as "unit exposures" – was not met. Despite having less-than-expected statistical power, regression analysis does not reject proportionality between exposure and the amount of active ingredient handled for either the dermal and inhalation routes of exposure. Thus, for this scenario, HED will continue to use the exposure data normalized by the amount of active ingredient as a default condition for exposure assessment purposes.

Select summary statistics for the open cab airblast applicator scenario "unit exposures" are presented in Table 1 below, as well as the previous value used (from the Pesticide Handler Exposure Database, PHED) for comparison.

[1] The data is not applicable to volatile chemicals (e.g., fumigants).

[2] Adjustments to this dataset would be required to represent alternative personal protective equipment (e.g., applying a protection factor to represent exposure when using a respirator or additional protective clothing). These types of adjustments would be used in risk assessments as appropriate, given the availability of reliable factors, and are not addressed in this review.

[3] Pesticide Handlers Exposure Database (PHED) Scenario 11: Airblast Application, Open Cab (APPL)

Table 1. Unit Exposures (ug/lb ai handled): Open Cab Airblast Applicators					
Exposure Route	**PPE**	**PHED**	**AHETF[b]**		
		"Best Fit"	**Geometric Mean**	**Arithmetic Mean[d]**	**95th Percentile[e]**
Dermal[a]	single-layer, CR gloves, CR hat[c]	unavailable	66.4	215	826
	single-layer, CR gloves	240	387	1590	6148
Inhalation	no respirator	4.5	0.781	4.71	17.6

[a] CR = chemical-resistant; single-layer = long-sleeve shirt, pants, shoes/socks
[b] Statistics are estimated using a variance component model accounting for correlation between measurements conducted within the same field study (i.e., measurements collected during the same time and at the same location). Additional model estimates (e.g., empirical and simple random sample assumptions) are described in Section 3.0.
[c] Per current EPA policy, dermal unit exposures reflect 50% adjustment of hand and face/neck measurements, since the average percent contribution to total dermal exposure by the hands, face, and neck is approximately 50%.
[d] Arithmetic Mean (AM) = GM * exp{0.5*((lnGSD)^2)}
[e] 95th percentile = GM * GSD^1.645

2.0 Background

The following provides background on the AHETF objectives for this research and also discusses previous reviews of the open cab airblast scenario by the Human Studies Review Board (HSRB).

2.1 AHETF Objectives

The AHETF is developing a database (Agricultural Handlers Exposure Database or AHED) which can be used to define worker exposures associated with major agricultural and non-agricultural handler scenarios. A scenario can be defined as a pesticide handling task based on activity such as mixing/loading or application. Other factors such as formulation (e.g., liquids, granules), tractor type (e.g., open or closed cab), and/or application equipment type (e.g., airblast, aircraft or boom sprayers) are also key criteria for defining scenarios. AHETF-sponsored studies are typically designed to represent individuals wearing long-sleeved shirts, long pants, shoes, socks, chemical-resistant gloves as appropriate, and no respirators. In some cases, such as the scenario addressed by this monograph, additional personal protective equipment/clothing may also be a key element of the scenario (e.g., certain types of headgear to reduce overhead exposures).

AHETF studies use dosimetry methods intended to define pesticide handler dermal and inhalation exposures, which represent the chemical exposure "to-the-skin" (i.e., "deposited on") and "in the breathing zone." For the purposes of pesticide handler exposure assessment, dermal and inhalation exposures are expressed as "unit exposures" – expressed as exposure per weight-unit chemical handled. Mathematically, unit exposures are expressed as exposure normalized by the amount active ingredient handled (AaiH) by participants in scenario-specific exposure studies (e.g., mg exposure/lb ai handled). Unit exposures are then used generically to predict exposure for other chemicals having the same or different application rates.

Two major assumptions underlie the use of exposure data in this fashion. First, the expected external exposure is unrelated to the identity of the specific active ingredient in the pesticide formulation. That is, the physical characteristics of a scenario such as the pesticide formulation (e.g., formulation type – wettable powder, liquid concentrate, dry flowable, etc.), packaging (e.g., bottle or water-soluble packet), or the equipment type used to apply the pesticide influence exposure more than the specific pesticide active ingredient (Hackathorn and Eberhart, 1985). Thus, for example, exposure data for spraying one chemical using open cab airblast equipment can be used to estimate exposure while spraying another chemical proposed for use with open cab airblast equipment. Second, dermal and inhalation exposure are assumed proportional to the amount of active ingredient handled. In other words, if one doubles the amount of pesticide handled, one doubles the exposure.

The AHETF approach for monitoring occupational handler exposure was based on criteria reviewed by HED and presented to the Human Studies Review Board (HSRB) for determining when a scenario is considered complete and operative. Outlined in the AHETF Governing Document (AHETF, 2008), the criteria can be briefly summarized as follows:

- The primary objective of the study design is to be 95% confident that key statistics of dermal exposure (normalized to the amount of active ingredient handled, i.e., dermal "unit exposures") are accurate within 3-fold. Specifically, the upper and lower 95% confidence limits should be no more than 3-fold higher or lower than the estimates for each the geometric mean, arithmetic mean, and 95th percentile dermal unit exposures. To meet this primary objective AHETF proposed an experimental design that provides a sufficient number of field trials and a sufficient number of monitored individuals. Note that this "fold relative accuracy" (*f*RA) objective does not apply to normalized inhalation exposure, though estimates are provided for reference (see Table 4).

- The secondary objective is to evaluate the assumption of proportionality between exposure and amount of active ingredient handled (AaiH) in order to be able to use the AHETF data generically across application rates. To meet this objective, the AHETF proposed a log-log regression test to distinguish complete proportionality (slope = 1) from complete independence (slope = 0), with 80% statistical power, achieved when the width of the 95th confidence interval of the regression slope is 1.4 or less. Note, again, that this objective does not apply to normalized inhalation exposure; however the tests are performed for informational purposes.

To simultaneously achieve both the primary and secondary objectives described above and contain costs, the AHETF developed a study design employing a 'cluster' strategy. Each cluster is defined by a region. Typically, these regions are defined by a few contiguous counties in a given state(s) within a US EPA growing region. For most handler scenarios a configuration of 5 regional clusters each consisting of 5 participants is used to meet the objectives from a statistical sample size perspective. In some cases, the presence of existing data incorporated into the scenario requires alterations to the study design. For the open cab airblast applicator scenario, 15 monitored workers from a study conducted in 2004 (Smith, L., 2004; EPA Review: Dawson, J., 2006, D316628) were available to include in the open cab airblast exposure scenario. Thus, new data collected was proposed for 3 new clusters with 5 workers per cluster. The participants together with the conditions under which the worker handles the active ingredient are sometimes referred to as monitoring units (MUs). Within each cluster, the AHETF partitions the practical AaiH range handled by the participants in each cluster appropriate to a given scenario. In general, the strata of AaiH for any given scenario is commensurate with typical commercial production agriculture and HED handler risk assessments considerations with respect to amount of area that could be treated in a single work day.

In this case, the scenario is application of liquid spray pesticides using airblast sprayers hauled by trucks or tractors with open cabs while wearing the following personal protective equipment (PPE): long-sleeved shirts, long pants, shoes, socks, chemical-resistant gloves, with and without chemical-resistant hats, and no respirator. Dermal and inhalation exposure monitoring was conducted for 28 workers[4] (referred to as "monitoring units", or MUs) applying liquid spray pesticides using open cab airblast equipment[5]. Three new monitoring studies were conducted, each monitoring different workers while spraying tree or trellis crops in 3 different states in the U.S. where airblast equipment would typically be used – pecans in Oklahoma, and grapes in each California and New York. The monitoring conducted in these studies would be combined with previously conducted monitoring on peaches in Georgia, apples and pears in Idaho, and oranges in Florida. References for the studies are in Table 2 below.

Table 2. AHETF Open Cab Airblast Applicator Studies

Study ID		Study Title
AHE#	EPA MRID	
AHE07	46448201	Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of a Liquid Pesticide Product by Open Cab Airblast Application to Orchard Crops
AHE62	48289611	Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Open Cab Equipment in California Trellis Crops
AHE63	48289612	Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Open Cab Equipment in New York Trellis Crops
AHE64	48289613	Determination of Dermal and Inhalation Exposure to Workers During Airblast Applications of Liquid Sprays Using Open Cab Equipment in Oklahoma Tree Nuts

The figures below (from AHETF, 2010) depict examples of this activity for which the exposure data are applicable.

[4] Only 3 workers out of a planned 5 were monitored in AHE62. Thus, the total of 28 instead of 30 monitored workers (when combined with the 15 from AHE07). See Section 3.1 and 3.2.

[5] Some open cab vehicles had a canopy or roof. Potential effects on dermal exposure are discussion in Section 3.1.

Figure 1: Open Cab airblast application in GA peaches

Figure 2: Open Cab airblast application in ID apples

Figure 3: Open cab airblast application (with canopy) in FL oranges

2.2 HSRB Review and Comments

The ability of the EPA to use the open cab airblast applicator exposure monitoring studies to develop regulatory decisions is contingent upon compliance with the final regulation establishing requirements for the protection of subjects in human research (40 CFR Part 26), including review by the Human Studies Review Board[6]. The following is a timeline of HSRB reviews related to this scenario:

Table 3. Open Cab Airblast Application Scenario – HSRB Review Timeline

Date	HSRB Review
June 2006	AHE62 (CA-grapes) Protocol (at that time titled "AHE36")
	AHE63 (NY-grape) Protocol (at that time titled "AHE37")
October 2008	Open Cab Airblast Application Scenario Design
	AHE62 (CA-grapes) Protocol (revised)
	AHE63 (NY-grape) Protocol (revised)
	AHE64 (OK-pecans) Protocol

Execution of the field studies followed favorable reviews by the HSRB; however, throughout the review process, numerous comments and suggestions were noted and incorporated when possible. Appendix D of the AHETF scenario monograph (AHETF, 2010) outlines both scientific and ethical issues related to the open cab airblast scenario that were addressed. The following summarizes the more substantive scientific HSRB review comments related to this process and how the AHETF responded.

2.2.1 Characterization of non-respondents and responders who declined to participate (11/14/08 and 12/30/08 HSRB Meeting Reports)

[6] http://www.epa.gov/osa/hsrb/; HSRB review required only for protocols for AHE62, 63, and 64 – AHE07 was conducted in 2003 and not subject to HSRB review.

The HSRB was concerned with the inability to evaluate study participants against the universe of open cab airblast applicators, considering the AHETF indicated they would experience a very low response rate. Continued AHETF attempts to contact non-responders was unsuccessful; thus, comparison with those eligible for participation was not possible. However, AHETF did attempt to address the HSRB comment by comparing study participants with those eligible non-participants via an informal survey of local agricultural experts.

The surveyed experts were asked to evaluate how the selected employers and equipment compares to the local population of airblast applicators, using the following characteristics to determine whether they were typical of other growers/applicators in the area where the monitoring was conducted:

- Whether the participant was the grower, employed by a grower or was a commercial applicator;
- The total acres of target crop (for grower MUs only)
- # of employed experienced airblast applicators
- Equipment type

It appears based on this informal survey/poll of local experts that the participants in these studies were not atypical of the population of open cab airblast applicators. EPA believes that this methodology, however, could be improved for future AHETF studies, perhaps via a more systematic database compilation of the information obtained during the recruitment phase. A summary of the findings is provided in Table 44 below.

Table 4. Synopsis of Experts Used to Evaluate the Representativeness of Monitored Workers

Study ID	Recruited	Responded	Response
AHE62 (CA-grape)	5 USDA agricultural extension agents	5	• 4 of 5 agreed that the study participants were typical in the counties monitored. • 1 thought acreage was unrepresentative of some counties monitored
AHE63 (NY-grape)	3 USDA agricultural extension agents (Cornell University) 1 pesticide application technology specialist 1 USDA agricultural extension agent (Pennsylvania State University)	4	• 3 of 4 agreed that the study participants were typical in the counties monitored. • 1 of 4 did not agree due to the absence of the "Kinkelder" airblast sprayer – an older model prone to spray drift.
AHE64 (OK-pecans)	1 professor of Entomology and Plant Physiology (OK State University) 1 professor of Horticulture and Landscape Architecture (OK State University) 10 USDA agricultural extension agents	7	• 4 of 7 agreed that the study participants were typical in the counties monitored. • 3 of 7 did not agree o 1 said acreage should be larger than that monitored o 2 said enclosed cabs were more representative

2.2.2 Documented Survey Implementation Expertise (11/14/08 and 12/30/08 HSRB Meeting Reports)

Given the admittedly difficult attempts at recruitment for occupational pesticide exposure monitoring studies, the HSRB advised the AHETF to employ individuals with expertise in survey implementation. As a result, the AHETF abandoned use of so-called Local Site Coordinators for recruitment purposes and employed individuals familiar with survey methodology.

2.2.3 No more than 1 worker from the same employer (11/14/08 and 12/30/08 HSRB Meeting Reports)

The HSRB noted that to accurately represent the assumptions of the statistical model and "nested" sample design, the AHETF could utilize no more than 1 worker per employer due to potential exposure correlations for workers of the same employer (e.g., training similarities, etc.). The AHETF responded by indicating that, for the airblast studies, no more than 1 employee of a grower or commercial applicator would be monitored. This was accurately reflected in the executed exposure monitoring.

2.2.4 Better Characterization of the Recruitment Process (11/14/08 HSRB Meeting Report)

The HSRB recommended that the AHETF better define the recruitment process so as to identify the individuals or organizations contacted. Specifically, this arose from concerns that the recruitment will focus on growers with multiple workers at the expense of those who employ only 1 pesticide operator or growers who treat their own farm. The AHETF responded by producing a full set of recruitment-related standard operating procedures (SOPs). Among other issues, for the purposes of contacting growers on the "call" list, no distinction is made between a single grower working his own farm, a grower with a single employee, and a grower with multiple employees.

2.2.5 Capturing Applicator Behavior (11/14/08 and 12/30/08 HSRB Meeting Reports)

The HSRB was concerned that the scripted nature of the exposure monitoring would not capture the extent of exposures typical of open cab airblast applicator behavior under normal circumstances. Per protocol, the AHETF employed observers who recorded applicator behavior throughout the workday. All manner of behaviors were captured, from specifics of the application procedures (i.e., sequence of row treatments) to observations of spray drift and contact with treated foliage.

2.2.6 Exclusion of Monitoring Exposure During Applications to Dormant Crops and Hops (11/14/08 HSRB Meeting Report)

The HSRB expressed concern with the exclusion of monitoring exposure for both dormant crops as well as hops, despite pesticide applications made to both using open cab airblast applications. The AHETF noted that with consultation with EPA, that the monitoring conducted for the array of non-dormant crops would be considered sufficiently adequate for assessment of open cab airblast exposures to dormant crops and hops – as well as other crops not specifically monitored.

Given the logistical considerations of the sampling design (i.e., the increased chances of finding willing participants for more common pesticide applications), HED agrees that for the purposes of the generic database, the proposed studies are adequate for assessment of open cab airblast exposure.

2.2.7 Effect of Product and Packaging (11/4/08 HSRB Meeting Report)

The HSRB noted that a rationale was not provided for the statement that neither the product nor packaging would have any influence on exposure, citing the potential for increased exposure due to cleaning spray nozzles clogged from use of solid formulations diluted in water. The AHETF recognized that formulation could potentially affect exposure during applications of liquid sprays if a solid formulation were to clog nozzles and require cleaning by the applicator. In these studies, it is apparent that workers did interact with the spray nozzles; however, since all formulations used in these studies were liquid concentrates, attribution of these interactions to use of solid formulations cannot be made.

2.2.8 Consideration of Alternative Study Design (11/4/08 HSRB Meeting Report)

Due to statistical concerns with the AHETF sampling design expressed by the HSRB during earlier review meetings, including selection of workers and sample representativeness, the HSRB outlined an alternative sampling approach, which included a more robust approach at identifying and recruiting potential participants. With respect to recruitment procedures such as developing the universe of potential participants, writing recruitment letters, employing experienced interviewers, and comparing participant characteristics with those of the applicator population, the AHETF believes, and EPA agrees that, they have followed the fundamental principles of the HSRB recommendations. The changes in recruitment procedures also satisfied the EPA requirement to incorporate "random elements" whenever feasible in the sampling process.

2.2.9 Evaluation of Combining AHE07 with new monitoring in AHE62-64 [12/30/08 HSRB Meeting Report]

The HSRB recommended an evaluation of the AHE07 dataset against new exposure monitoring in AHE62-64, in the event obvious or significant differences are apparent which could complicate utilizing a combined dataset. The Agency agrees that the datasets should not be combined without adequate review. Results are presented in Section 3.1 for the entire combined dataset as well as a comparison showing relatively insignificant differences between the datasets. The Agency has no concerns with combining the datasets and feels the mixed-model approach for statistical analysis properly accounts for potential data clustering for both the existing data and new monitoring.

3.0 Results

Exposure results were reported in reports for each study and reviewed in Crowley, 2011 (D387287). The following sections summarize the exposure monitoring results and the scenario benchmark statistical analyses presented in the AHETF scenario monograph (AHETF, 2010).

3.1 Exposure Monitoring and Calculations

Monitored on actual days of work, participants handled between 5 to 90 lbs of active ingredient (carbaryl or malathion), spraying 3 to 30 acres in 1.4 to 10.6 hours. Dermal exposure was measured using hand washes, face/neck wipes, whole body dosimeters (100% cotton union suits) for the remainder of the body (torso, arms, and legs), and gauze patches on the inside and outside of chemical-resistant (CR) hats for exposure to the head. Inhalation exposure was measured using personal air sampling pumps and OSHA Versatile Samplers (OVS) mounted on the shirt collar. Results represent dermal exposure with and without chemical-resistant hats while wearing a long-sleeved shirt, pants, shoes/socks, and chemical-resistant gloves, and inhalation exposure without respiratory protection.

Additionally, as presented at a June 2007 HSRB meeting, in order to account for potential residue collection method inefficiencies[7], the AHETF has made adjustments to hand and face/neck field study measurements according to EPA directions as follows:

- if measured exposures from hands, face and neck contribute less than 20% as an average across all workers, no action is required;
- if measured exposure contribution from hands and face/neck represents between 20% and 60% of total, the measurements shall be adjusted upward by 50%, or submission of a validation study to support the residue collection method;
- if measured exposure contribution from hands and face/neck represents is greater than 60%, a validation study demonstrating the efficiency of the residue collection methods is required.

For these studies, measurements for dermal exposure with chemical-resistant hats fell in the second category and hand rinse and face/neck wipe measurements have been adjusted upward by 50% (i.e., multiplied by 2). Measurements for dermal exposure without chemical-resistant hats fell in the first category and were not adjusted.

Inhalation exposure is measured using a personal air sampling pump and an OSHA Versatile Sampler (OVS) tube with a glass fiber filter and Chromosorb 102 solvent. The tube is attached to the worker's shirt collar to continuously sample air from the breathing zone. All samples are adjusted as appropriate according to recovery results from field fortification samples.

Total dermal exposure was calculated by summing exposure across all body parts for each individual monitored. Total inhalation exposures were calculated by adjusting the measured air concentration (i.e., ug/L) using a breathing rate of 8.3 liters per minutes (LPM; converted from 1.0 m^3/hr), representing light activities such as mixing/loading light packages (NAFTA, 1998), and total work/monitoring time.[8] Dermal unit exposures (i.e., ug/lb ai handled) are then calculated by dividing the summed total exposure by the amount of active ingredient handled.

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[7] The terminology used to describe this is "method efficiency adjusted" (MEA) or "method efficiency corrected" (MEC).

[8] Inhalation Exposure (ug) = collected air residue (ug) x [breathing rate (L/min) ÷ average pump flow rate (L/min)]

Results represent dermal exposure while wearing a long-sleeved shirt, pants, shoes/socks, chemical-resistant gloves, with and without chemical-resistant hats and inhalation exposure without respiratory protection. Though some open cab vehicles were equipped with canopies, this did not offer any additional protection as no difference was observed in the dermal exposure results. This was initially addressed in the data review for AHE07 (D316628), but also included in the reviews for AHE62-64 (Crowley, 2011; D387287).

A summary of the 28 open cab airblast applicator MUs is provided in Table 3 below. Additional evaluation of exposure data are presented in Sections 3.2-3.4 and more detailed exposure data are provided in Appendix A, Table 1.

Table 3. Open Cab Airblast Application MU Summary

Study ID	MU ID	State	Crop	Work/ Monitoring Time (hours)	Area Treated (acres)	AaiH (lbs)	Unit Exposure (ug/lb ai)		
							Dermal		Inhalation
							without CR hats[a]	with CR hats	
AHE07	1	GA	peach	5.5	25	75	128	17.4	0.205
	3	GA	peach	6.6	15	45	1075	138	1.20
	4	GA	peach	5.8	25	75	51.9	11.7	0.249
	6	GA	peach	8.1	20	60	327	24.0	0.803
	8	GA	peach	8.3	17	52	1673	246	5.68
	10	ID	apple	7.7	16	32	566	149	1.07
	12	ID	apple	7.9	16	33	228	23.5	1.28
	13	ID	apple	6.5	18	36	1464	45.0	1.09
	15	ID	apple	7.2	12	24	1363	158	1.47
	16	ID	apple	6.7	20	40	499	51.8	0.800
	17	ID	apple & pear	6.2	17	34	116	6.4	0.548
	22	FL	orange	4.8	20	60	406	103	0.851
	23	FL	orange	7.0	30	90	335	78.9	0.392
	26	FL	orange	4.8	30	90	148	59.2	0.337
	27	FL	orange	7.4	30	90	1211	286	5.88
AHE62	A1	CA	grape	5.1	20	34.3	134	26.0	0.889
	A2	CA	grape	2.9	12	5.0	287	89.2	7.13
	A3	CA	grape	4.6	9.5	10.4	290	43.5	4.26
AHE63	A1	NY	grape	10.6	24	48.4	1531	146	2.42
	A2	NY	grape	6.9	17.5	35.6	1098	206	0.612
	A3	NY	grape	6.2	12	24.4	2073	46.9	2.77
	A4	NY	grape	4.2	7.5	15.2	17.8	4.0	0.214
	A5	NY	grape	1.4	3	6.1	302	54.9	4.97
AHE64	A1	OK	pecan	7.8	15	63.1	317	67.7	0.677
	A2	OK	pecan	2.7	5	10.1	9355	2524	1.44
	A3	OK	pecan	3.0	7	35.3	95.0	49.1	0.380
	A4	OK	pecan	3.3	5	25.2	9250	3202	0.264
	A5	OK	pecan	2.5	9	18.2	3.8	6.5	0.00026

[a] Dermal exposure with CR hats reflects hand rinse and face/neck wipe method efficiency adjusted (MEA) data.

Figures 4 through 6 below present the data in graphical form. The full range of both dermal and inhalation unit exposures is visible, as well as a side-by-side study comparison. Section 3.5 combines and treats the data statistically as one distribution, so there is value in comparing them in this way. Additionally, inhalation monitoring for MU A5 in AHE64 (OK-pecan) is shown to be significantly lower in magnitude than the rest of the dataset in Figure 6. Additional treatment of this monitoring is considered in Section 3.2.3.

Figure 4: Dermal Unit Exposures with CR hats (ug/lb ai)

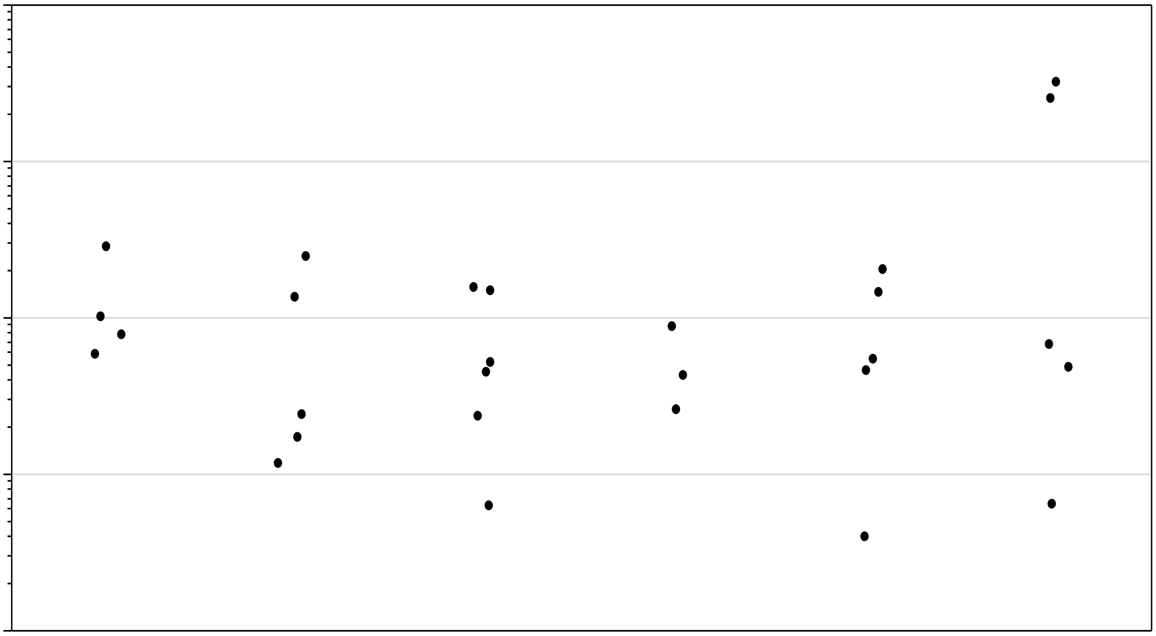


Figure 5: Dermal Unit Exposures w/o CR hats (ug/lb ai)

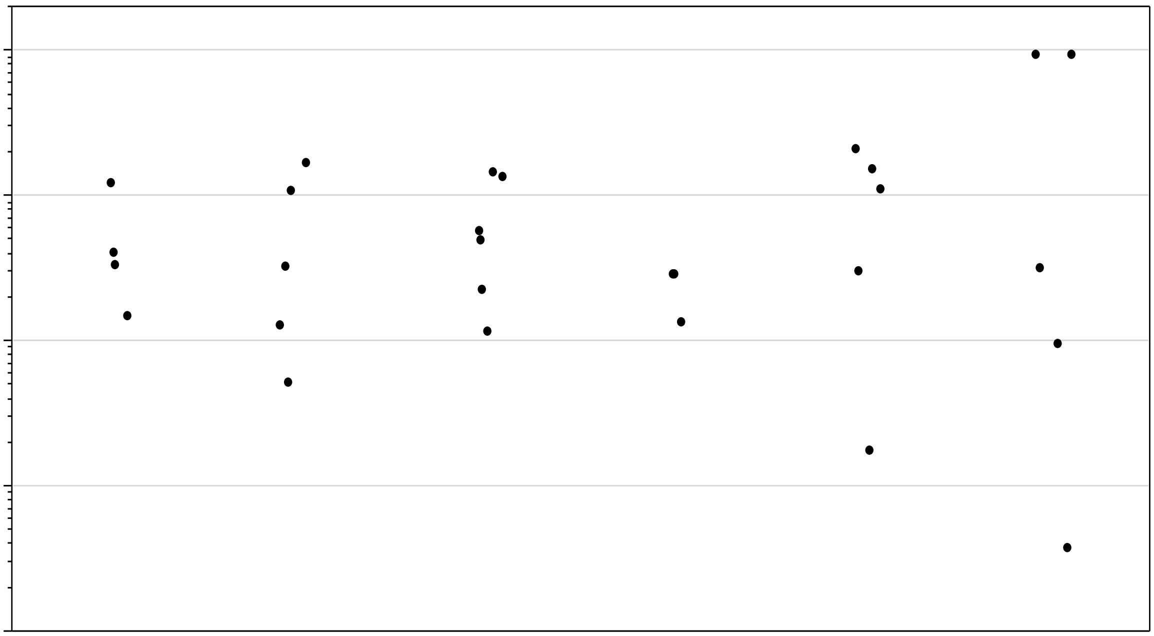
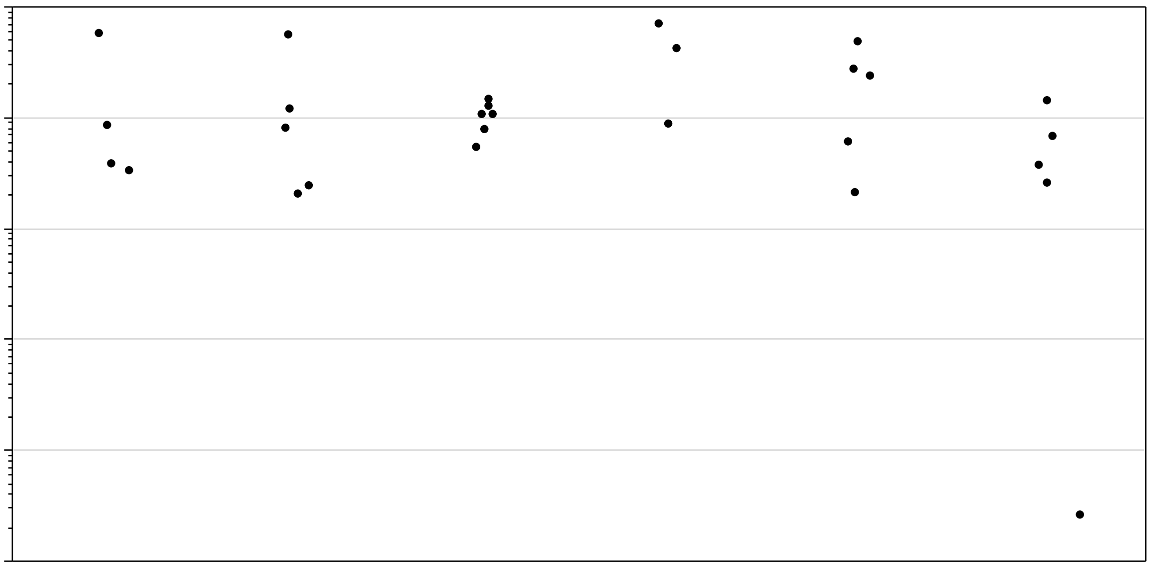


Figure 6: Inhalation Unit Exposures (ug/lb ai)



3.2 Evaluation of Scenario Benchmark Objectives

The AHETF monograph details the extent to which the open cab airblast applicator scenario meets objectives described in Section 2.1. The monograph states that while the primary objective was met, the secondary objective was not. As for reviews of previous AHETF scenario monographs (Sarkar, B., 2010), EPA (OPP/HED/CEB) has independently confirmed these results.

3.2.1 Primary Objective: fold Relative Accuracy (fRA)

The primary benchmark objective for AHETF 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"). The AHETF analyzed the data using various statistical techniques to evaluate this benchmark. First, both dermal and inhalation unit exposures were shown to fit lognormal distributions reasonably well. Lognormal probability plots are provided as Appendix B.

Next, the AHETF calculated estimates of the GM, AM and P95 based on three variations of the data:

- Non-parametric empirical (i.e., ranked) estimates;
- Assuming a lognormal distribution and a simple random sample (SRS); and,
- Hierarchical variance component modeling to account for potential MU correlations.

As presented in Appendix C of the AHETF Governing Document (AHETF, 2008), the 95% confidence limits for each of these estimates were obtained by generating 10,000 parametric bootstrap samples. Then, the fRA for each statistic was determined as the maximum of the two ratios of the statistical point estimates with their respective upper and lower 95% confidence limits. The primary benchmark of 3-fold accuracy for select statistics was met for dermal exposure data with and without chemical-resistant hats, including when adjusting dermal exposure with chemical-resistant hats using MEA hand rinse and face/neck wipe results. Note, though not applicable to the benchmark, the fRA values for inhalation are also presented and are below 3-fold at geometric mean but above 3-fold at the arithmetic mean and 95th percentile.

Table 4. Open Cab Airblast Application Scenario – Results of Primary Benchmark Analysis

Statistic	Dermal Unit Exposure (ug/lb ai)						Inhalation Unit Exposure (ug/lb ai)		
	With CR hats[a]			Without CR hats					
	Estimate	95% CI	fRA	Estimate	95% CI	fRA	Estimate	95% CI	fRA
GM_S	66.4	37.3 – 117	1.8	387	206 – 720	1.9	0.764	0.335 – 1.81	2.4
GSD_S	4.63	3.08 – 6.99	1.5	5.37	3.43 – 8.42	1.6	6.56	3.95 – 10.9	1.7
GM_M	66.4	37.3 – 117	1.8	387	206 – 719	1.9	0.781	0.335 – 1.82	2.3
GSD_M	4.63	3.08 – 7.06	1.5	5.37	3.44 – 8.52	1.6	6.65	3.98 – 11.3	1.7
ICC	0.00	0.00 – 0.32	--	0.00	0.00 – 0.32	--	0.10	0.00 – 0.46	--
GM_S = geometric mean assuming SRS = "exp(average of 28 ln(UE)) values". GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 28 ln(UE)) values" GM_M = variance component model-based geometric mean GSD_M = variance component model-based geometric standard deviation ICC = intra-class correlation									
AM_S	281	85.9 – 524	3.3	1227	546 – 4379	3.6	1.71	1.13 – 15.1	8.8
AM_U	215	94.7 – 529	2.5	1590	619 – 4523	2.8	4.48	1.36 – 17.6	3.9
AM_M	215	94.9 – 536	2.5	1590	625 – 4623	2.9	4.71	1.39 – 19.1	4.1
AM_S = average of 28 unit exposures AM_U = arithmetic mean based on GM_S = GM_S*exp{0.5*((lnGSD_S)^2)} AM_M = variance component model-based arithmetic mean = GM_M* exp{0.5*((lnGSD_M)^2)}									
$P95_S$	2524	256 – 2527	9.9	9250	1701 – 20929	5.4	5.88	3.82 – 73.0	12.4
$P95_U$	826	336 – 1995	2.5	6148	2290 – 16154	2.7	16.8	5.17 – 55.1	3.3
$P95_M$	826	338 – 2016	2.4	6148	2304 – 16340	2.7	17.6	5.26 – 57.7	3.4
$P95_S$ = 95th percentile (i.e., the 27th unit exposure out of 28 ranked in ascending order) $P95_U$ = 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									
[a] Dermal exposure values reflect 2X default adjustment for hands and face/neck measurements.									

3.2.2 Secondary Objective: Testing Proportionality

The secondary objective of AHETF studies is to be able to distinguish, with 80% statistical power, complete proportionality from complete independence between dermal exposure and amount of active ingredient handled. Based on the AHETF analysis, in which the relationship between exposure and amount of active ingredient handled is tested using a mixed-effect log-log regression, this benchmark was not met.

3.2.2.1 AHETF Analysis

To evaluate the relationship for this scenario the AHETF performed regression analysis of ln(exposure) and ln(AaiH) to determine if the slope is not significantly different than 1 – providing support for a proportional relationship – or if the slope is not significantly different than 0 – providing support for an independent relationship. Both simple linear regression and mixed-effect regression were performed to evaluate the relationship between dermal exposure and AaiH. A confidence interval width of 1.4 (or less) indicates at least 80% statistical power. The resulting regression slopes and confidence intervals are summarized in Table 5.

Table 5. Summary Results of log-log Regression Slopes

Model	Dermal Exposure						Inhalation Exposure		
	With CR hats[a]			Without CR hats[b]					
	Est.	95% CI	CI Width	Est.	95% CI	CI Width	Est.	95% CI	CI Width
Simple Linear	no AHETF analysis			0.99	0.12 – 1.85	1.74	0.57	-0.09 – 1.22	1.30
Mixed-Effects	0.87	0.08 – 1.67	1.59	0.99	0.12 – 1.85	1.74	0.53	-0.25 – 1.31	1.57

[a] Reflects use of MEA hand and face/neck wipe data.
[b] Note because the correlation estimate (i.e., the "intra-class correlation", or ICC) is 0, the slope estimates for the simple linear regression and the mixed model are identical.

For dermal exposure with and without chemical-resistant hats, the slopes of the mixed-effects regressions are 0.87 and 0.99, respectively with both sets of 95% confidence intervals excluding 0 while including 1, suggesting that a proportional relationship is consistent with the data. For inhalation exposure the mixed-effects regression slope is 0.53, with 95% confidence intervals including both 0 and 1, suggesting that either an independent or a proportional relationship is consistent with the data. In terms of the secondary objective, in no case was the width of the mixed effect regression 95% confidence interval less than 1.4, indicating the power to detect complete independence from complete proportionality was less than 80%.[9] The AHETF suggests, and EPA concurs, that this may be the result of the range of AaiH being small relative to the range in exposure observed.

3.2.2.2 Additional ICC Considerations (EPA Analysis)

Considering discussions from a meeting of the HSRB in October 2010 and a similar analysis presented in a review of the AHETF Closed Cab Airblast Application Scenario Monograph discussed at the January 2011 HSRB meeting, EPA conducted additional analysis with respect to statistical procedures and the intra-class correlation coefficient (ICC) for the open cab airblast applicator dataset. The AHETF statistical analysis for proportionality used the Kenward-Rogers denominator degrees of freedom (DDF) method to calculate confidence intervals for the log-log regression slope[10]. However the Kenward-Rogers method in PROC MIXED in SAS 9.2 ignores covariance parameters with zero variances, suggesting that other methods should be used when the ICC is zero – such as the case for the dermal exposure (ICC estimate for inhalation exposure is non-zero). Under contract with EPA/OPP, ICF, Inc. investigated the alternate approaches to calculate the DDF for a similar set of exposure monitoring studies conducted by the

[9] Despite this being valuable with respect to post-hoc evaluation of the study design criteria, this may not be relevant for dermal exposure since the test did not rule out proportionality.

[10] Note that the choice of denominator degrees of freedom method does not affect the estimated slope and its standard error, but it can affect the confidence interval. Since a bootstrap method was used to compute confidence intervals and fold relative accuracy for the normalized exposure summary statistics (arithmetic mean, 95th percentile, etc.), this issue does not impact those calculations.

Antimicrobial Exposure Assessment Task Force II (AEATF-II)[11]. The ICF memo reviewed the different methods for calculating the DDF for fixed effects in a mixed model using the SAS MIXED procedure based on an article by Schaalje, et al[12] and concluded that the "containment" method is most appropriate for calculating mixed-effect model confidence intervals when the ICC=0. Table 6 below summarizes the five available methods outlined in the ICF memo.

Table 6. Summary of SAS Methods for Computing Fixed-Effects DDF in PROC MIXED[a]

DDF Method	SAS Abbreviation	Comments
Residual	residual	Uses residual degrees of freedom. Ignores covariance structure as defined by the RANDOM and REPEATED statements. This method is not recommended.
Containment	contain	Default method when RANDOM statements are present. Accounts for the minimum contribution of the random effects that syntactically contain the fixed effects of interest.
Between-Within	bw	Default method when REPEATED statements are present and RANDOM statements are not present. Only exact when the data are balanced and the design is a repeated measures design with compound symmetry, and where the levels of the within-subjects effects are not replicated within any of the subjects. Otherwise the method is at best approximate and can be unpredictable.
Satterthwaite / Fai-Cornelius	satterth	Designed to approximate the denominator degrees of freedom for split-plot designs with complicated covariance structures and/or unbalanced data sets.
Kenward-Rogers	kr	Designed to approximate the denominator degrees of freedom for designs with complicated covariance structures and/or unbalanced data sets. Results from simulations suggest better performance than the Satterthwaite method. If a covariance parameter has zero variance then this method ignores that covariance.

[a] RANDOM statement used to define the cluster effect.

For dermal exposure with and without chemical-resistant hats the ICC estimate is zero for which the "containment" method is recommended. Using this method, however, does not alter the overall conclusions with respect to the secondary study objective. That is, the 95% confidence intervals for dermal exposure with and without chemical-resistant hats still include 1 and excludes 0 (0.072 – 1.68 and 0.11 – 1.86, respectively). The confidence interval widths are still greater than 1.4 as well. Additional details for this analysis are provided in Appendix C. The SAS code is provided in Appendix D.

3.2.2.3 Evaluation of Regression Diagnostics for Normality and Constant Variance of Residuals

Following discussions at the January 2011 HSRB meeting for the AHETF Closed Cab Airblast Application Scenario Monograph, EPA conducted standard linear regression diagnostic analyses for the open cab airblast applicator dataset. For both normalized dermal and inhalation exposures, residuals were demonstrated to be normally distributed and no pattern was observed

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[11] "Additional statistical issues for the AEATF Mop Study Statistical Review for HSRB". Contract No.: EP-W-06-091.

[12] Schaalje, G. B., J. B. McBride, G. W. Fellingham. "Approximations to Distributions of Test Statistics in Complex Mixed Linear Models Using SAS® Proc MIXED" *Proceedings of the Twenty Sixth Annual SAS Users Group International Conference*. April 2001. Long Beach, CA. ISBN 1-58025-864-6. SAS Institute, Cary, NC 27513.

that would violate the constant variance assumption. Additional details for this analysis are provided in Appendix C. The SAS code is provided in Appendix D.

3.2.3 Consideration of AHE64 (OK-pecan) MU A5 for Inhalation Exposure

The AHETF described the influence of the inhalation exposure MU A5 in AHE64 (OK-pecan) in the monograph report saying, "Much of the difficulty with the inhalation data was the result of a single MU with an exceptionally small exposure value (about 3 orders of magnitude lower than the next highest value) – the separation of this observation from the dataset is clear in Figure 6. The AHETF demonstrated that the widths of the 95% confidence interval of the statistics of the inhalation unit exposure distributions are decreased when AHE64-A5 is excluded (shown in Table-9 below). Also shown in Table 9 is additional AHETF analysis demonstrating that both the mixed effect regression slope and its confidence interval width decrease when MU A5 in AHE64 is excluded.

Table 9. Statistical Results when Excluding Inhalation Observation AHE64 MUA5

Exposure Route		Inhalation Unit Exposure (ug/lb ai) Statistics (95% CI)[a]			Mixed-Effect Regression Analysis		
		Geometric Mean	Arithmetic Mean[b]	95th Percentile[c]	Est. slope	95% CI	CI Width
Inhalation (no respirator)	All 28 observations	0.781 (0.335 – 1.82)	4.71 (1.39 – 19.1)	17.6 (5.26 – 57.7)	0.53	-0.25 – 1.31	1.57
	Excluding AHE64-A5	1.03 (0.683 – 1.53)	1.81 (1.11 – 3.06)	5.90 (3.16 – 10.9)	0.40	-0.10-0.90	1.00

[a] Statistics are estimated using a variance component model accounting for correlation between measurements conducted within the same field study (i.e., measurements collected during the same time and at the same location). Additional model estimates (e.g., empirical and simple random sample assumptions) are described in Section 3.0.
[b] Arithmetic Mean (AM) = GM * exp{0.5*((lnGSD)^2)}
[c] 95th percentile = GM * GSD^1.645

EPA conducted additional analysis (more fully presented in Appendix C with corresponding SAS code in Appendix D) confirming the significant influence of this observation on both the magnitude and precision of parameter estimates of the "ln(inhalation exposure) vs. ln(AaiH)" regression model. It can be seen from the additional analysis that MU A5 (AHE64) exerts influence primarily on the estimates of the fixed effects and their precision.

Interestingly, while the geometric mean unit exposure is slightly increased by excluding AHE64-A5, modeled estimates of both the arithmetic mean and 95th percentile values are decreased[13]. Though perhaps statistically anomalous, in additional correspondence with the Agency (provided as Appendix E), the AHETF did not think that this observation resulted from faulty equipment or other measurement error. Thus, EPA will continue to include it in the full dataset, which also results in higher estimates at the upper-end of the distribution, a reasonable outcome for regulatory assessment.

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[13] Though perhaps counterintuitive – excluding a low value might lead one to believe that the dataset is shifted upward – the exclusion of this value decreases the geometric standard deviation (GSD) of the lognormal distribution. As a result, low-end percentiles will increase, but high-end percentiles (i.e., arithmetic mean, 95th percentile) will decrease. Additionally, because the magnitude of the excluded value is so much lower than the rest of the observations, its exclusion has hardly any effect on non-parametric estimates.

3.3 Data Generalizations and Limitations

The need for an upgraded generic pesticide handler exposure database has been publicly discussed and established (Christian, 2007). The data will be used generically to assess exposure for applicators applying any conventional chemical applied as a spray using airblast equipment hauled by trucks or tractors with an open cab. However, certain limitations need to be recognized with respect to collection, use, and interpretation of the exposure data.

3.3.1 Generic Use in Exposure Assessment

The data comprising this scenario are acceptable for use in assessing exposure for applicators applying pesticides to any crop using any type of open cab airblast equipment, while wearing a long-sleeve shirt, pants, shoes/socks, chemical resistant gloves, with or without chemical-resistant hats, and no respirator. This does not preclude additional consideration or use of acceptable available chemical-specific studies, biomonitoring studies, or other circumstances in which exposure data can be acceptably used in lieu of these data.

3.3.2 Applicability of AHETF Data for Volatile Chemicals

The data generated in this study are acceptable to use as surrogate data for assessing applicator exposure to other conventional pesticides used in open cab airblast equipment, which are generally chemicals of low volatility. Since they are not typically used in airblast sprayers, the Agency does not expect for it to be used to support regulatory decisions for high volatility pesticides (e.g., fumigants).

3.3.3 Use of "Unit Exposures"

As previously shown, statistical analyses provide support for use of the exposure data normalized by the amount of active ingredient handled, though with less-than-expected statistical power. HED will continue to recommend use of the exposure data normalized by the amount of active ingredient handled as a default condition for the foreseeable future.

3.3.4 Representativeness and Extrapolation to Exposed Population

Targeting and selecting specific monitoring characteristics (i.e., "purposive sampling") as well as certain restrictions necessary for logistical purposes (e.g., selection of major crops that use open cab airblast application methods to ensure a large pool of potential applicators; requiring potential applicators to use certain pesticides due to ensure laboratory analysis of exposure monitoring matrices; and requiring selection of workers who normally wear the scenario-defined minimal PPE), made the studies comprising this scenario neither purely observational nor random to allow for characterization of the dataset as representative of the population of open cab airblast applicators. Thus, it is important to recognize these limitations in considering this dataset as representative of all open cab airblast applicators.

It appears however, that the dataset has captured routine behavior as well as limiting the likelihood of "low-end" exposures via certain scripting aspects (e.g., monitoring time requirements to avoid non-detect exposures), both of which are valuable for regulatory assessment purposes. Also, the random elements incorporated into the recruitment process likely mitigated selection bias on the part of participants or recruiters. Thus, with respect to costs, feasibility, and utility, the resulting dataset is considered a reasonable approximation of expected exposure for this population.

3.4 Conclusions

HED has reviewed the AHETF Open Cab Airblast Application scenario monograph and concurs with the technical analysis of the data as well as the evaluation of the statistical benchmarks objectives. Conclusions are as follows:

- Deficiencies in the existing open cab airblast application scenario dataset (i.e., PHED) have been recognized and the need for new data established.
- The AHETF data developed and outlined in the monograph and this review represent the most reliable data for assessing open cab airblast application exposure.
- Per stated objectives, estimates of the GM, AM, and P95 were shown to be accurate within 3-fold with 95% confidence;
- The assumption of proportionality between both dermal and inhalation exposure and the amount of active ingredient handled was not rejected. As a result, HED will continue using exposures normalized by AaiH as a default condition for exposure assessment purposes for the foreseeable future.

4.0 References

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Appendix A
Supplemental Table 1: AHETF Open Cab Airblast Applicator Dermal and Inhalation Exposure Data

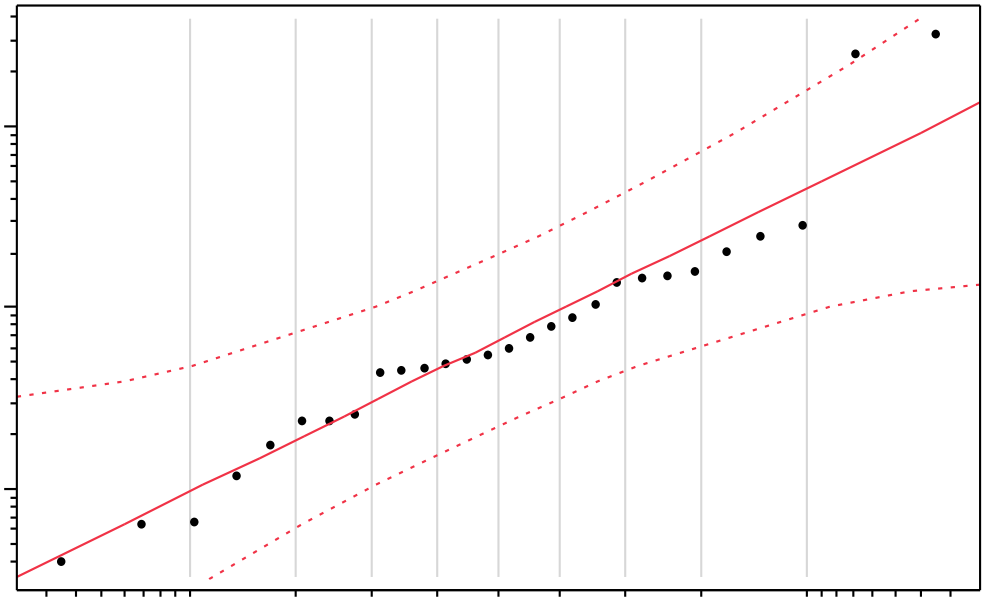
Table 1. Open Cab Airblast Application – Dermal and Inhalation Exposures

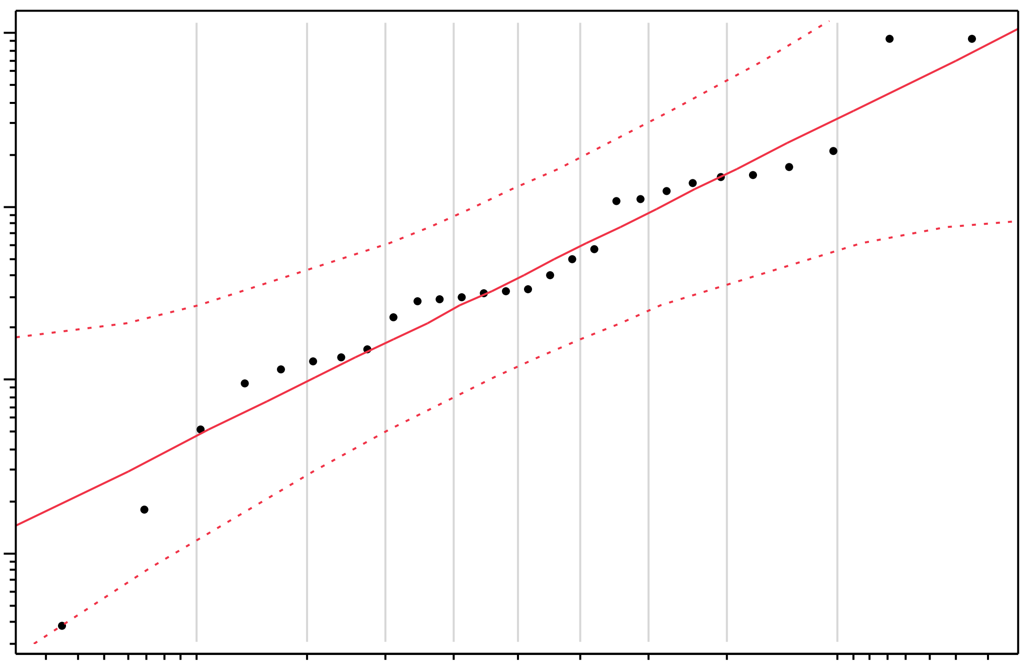
Study ID	MU ID	AaiH (lbs)	Dermal										Inhalation	
			Inner WBD[a] (µg)	Hand (µg)		Head (µg)		Feet[b] (µg)	Total Exposure (µg)		Unit Exposure (µg/lb ai)		Total (ug)	Unit Exposure (µg/lb ai)
				Non-MEA	MEA	with CR hat	w/o CR hat		with CR hat[c]	w/o CR hat	with CR hat[c]	w/o CR hat		
AHE07	1	1	285	424	848	170	8859	2.2	1305	9570	17.4	128	15.4	0.205
	3	3	2166	1851	3702	340	44348	1.7	6210	48367	138	1075	54.0	1.20
	4	4	454	179	358	67.1	3257	0.39	879	3890	11.7	51.9	18.7	0.249
	6	6	814	217	434	189	18569	0.85	1438	19601	24.0	327	48.2	0.803
	8	8	2507	4146	8292	1971	80298	23.3	12793	86974	246	1673	296	5.68
	10	10	4084	275	550	123	13755	0.92	4758	18115	149	566	34.4	1.07
	12	12	558	51.4	103	115	6923	0.79	777	7533	23.5	228	42.3	1.28
	13	13	1101	203	406	111	51416	0.59	1619	52721	45.0	1464	39.3	1.09
	15	15	2878	160	320	595	29664	6.6	3800	32709	158	1363	35.2	1.47
	16	16	1172	389	778	112	18390	8.4	2070	19959	51.8	499	32.0	0.800
	17	17	161	11.4	22.8	31.5	3754	0.97	216	3927	6.4	116	18.6	0.548
	22	22	2266	1614	3228	690	20476	1.2	6185	24357	103	406	51.0	0.851
	23	23	3960	877	1754	1380	25267	6.9	7101	30111	78.9	335	35.3	0.392
	26	26	2595	840	1680	1045	9856	7.2	5327	13298	59.2	148	30.4	0.337
	27	27	14852	2869	5738	5072	91118	108	25770	108947	286	1211	529	5.88
AHE62	A1	A1	288	271	542	61.3	4050	--	891	4609	26.0	134	30.5	0.889
	A2	A2	279	15.0	30.0	137	1139	--	446	1433	89.2	287	35.7	7.13
	A3	A3	239	13.8	27.6	185	2767	--	452	3020	43.5	290	44.3	4.26
AHE63	A1	A1	5362	242	484	1232	68487	--	7078	74091	146	1531	117	2.42
	A2	A2	6786	225	450	110	32086	--	7346	39097	206	1098	21.8	0.612
	A3	A3	750	58.9	118	277	49771	--	1145	50580	46.9	2073	67.6	2.77
	A4	A4	20.7	16.1	32.2	7.4	233	--	60.3	270	4.0	17.8	3.25	0.214
	A5	A5	191	29.9	59.8	84.0	1623	--	335	1844	54.9	302	30.3	4.97
AHE64	A1	A1	2773	486	972	529	16752	--	4274	20011	67.7	317	42.7	0.677
	A2	A2	16593	1029	2058	6842	76863	--	25493	94485	2524	9355	14.5	1.44
	A3	A3	781	416	832	119	2158	--	1732	3355	49.1	95.0	13.4	0.380
	A4	A4	72075	1380	2760	5867	159634	--	80702	233089	3202	9250	6.66	0.264
	A5	A5	4.5	0.5	1.0	112	64.8	--	118	69.8	6.5	3.8	0.294	0.00026

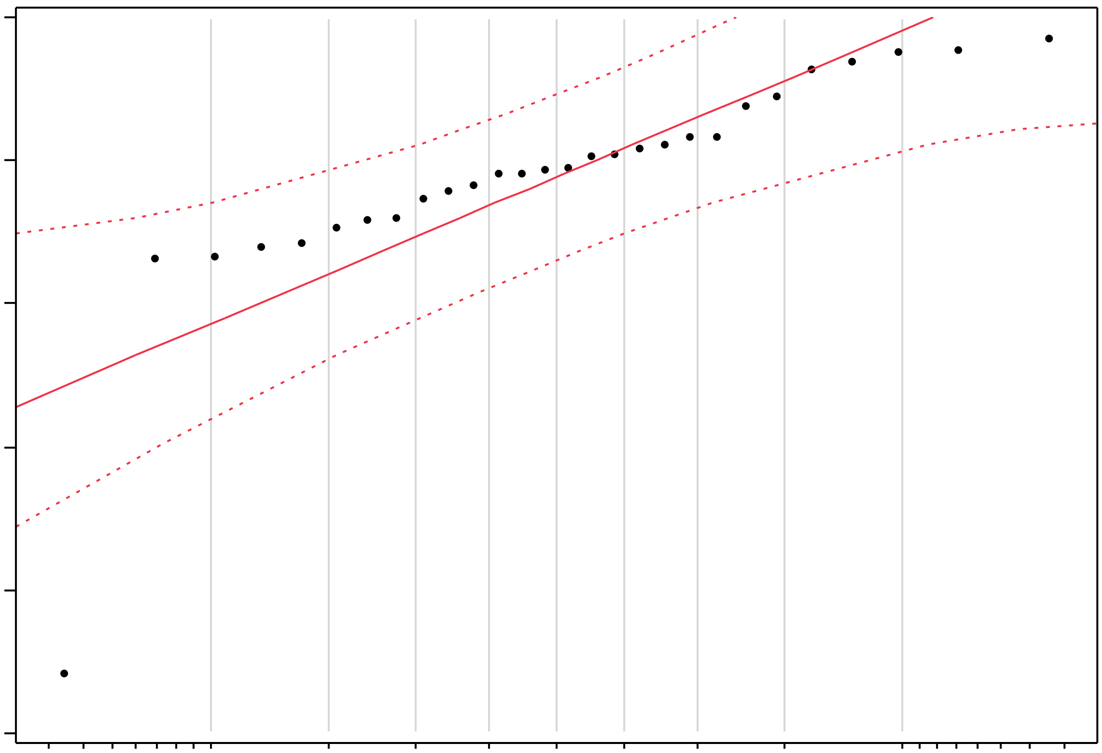
[a] Represents the sum of six body sections (upper and lower arms, front and back torso, upper and lower legs)
[b] AHE07 measured foot exposure. Its low contribution (< 1%) to total dermal exposure led to exclusion from monitoring workers' feet in AHE62-64.
[c] Dermal exposure with CR hats reflects use of MEA data.

Appendix B

Lognormal Probability Plots of Dermal and Inhalation Unit Exposures







Appendix C
Additional Analysis for Section 3.2.2.2, 3.2.2.3, and 3.2.3

I. Analysis for Section 3.2.2.2 (Additional ICC Considerations)

a. Dermal- no CR hat:

Solution for Fixed Effects								
Effect	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
lnAaiH	0.9850	0.4230	21	2.33	0.0300	0.05	0.1052	1.8647

Width of the 95% confidence interval of the slope =1.76

b. MEA corrected Dermal- with CR hat:

Solution for Fixed Effects								
Effect	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
lnAaiH	0.8743	0.3856	21	2.27	0.0340	0.05	0.07238	1.6763

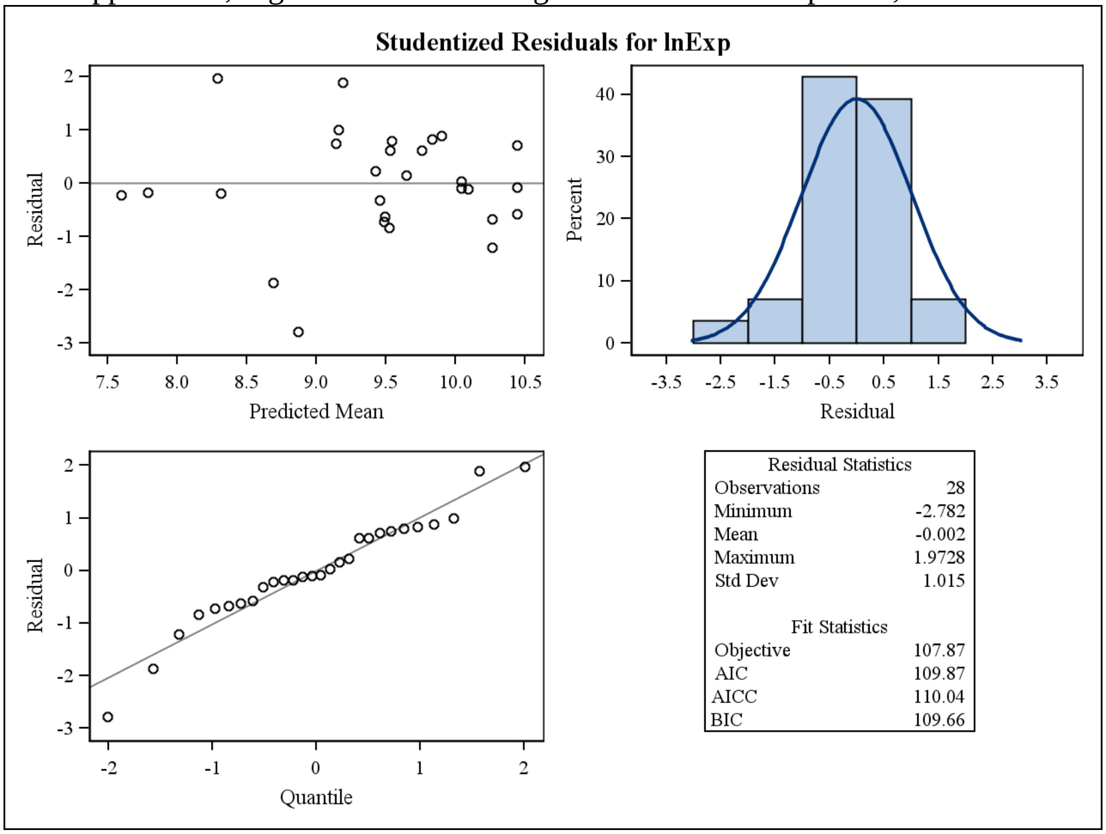
Width of the 95% confidence interval of the slope =1.60

II. Analysis for Section 3.2.2.3 (Regression Diagnostics)

a. Dermal with no CR hat

Because ICC is zero for the model "ln(dermal exposure, no CR hat) vs. ln(amt of ai handled)" EPA decided to use studentized residual instead of conditional studentized residual for diagnostics purposes. The difference between conditional residual and residual is that conditional residual takes account of the random effects. Figure 1 below shows a Q-Q plot of the studentized residuals from the mixed effect model fitted to the dermal data with no CR hat. The Q-Q plot comes close to a straight line; thus, we can accept that the studentized residuals are normally distributed. Also no specific pattern is observed in the "residual vs. predicted" plot; thus, there is no strong indication against assumption of constant variance.

Appendix C, Figure 1: Residual diagnostics of dermal exposure, no CR hat



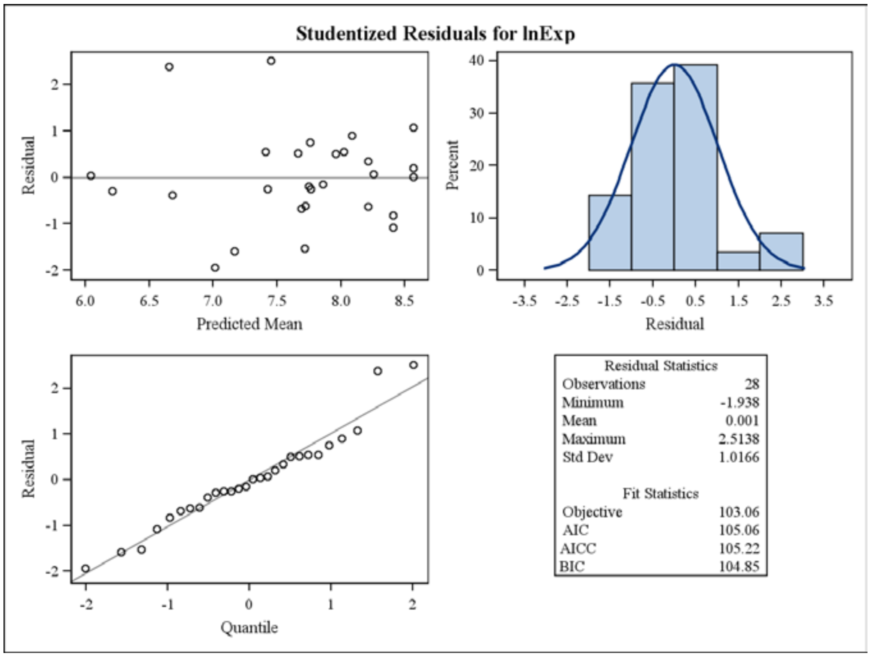
In addition to the above probability plot of the studentized residual, EPA also used formal statistical test to assess the normality of the residuals. All four tests shown below provide evidence that the studentized residuals are normally distributed ($p>0.05$).

```
                        Tests for Normality

Test                  --Statistic---    -----p Value------

Shapiro-Wilk          W     0.959419    Pr < W      0.3378
Kolmogorov-Smirnov    D     0.098612    Pr > D     >0.1500
Cramer-von Mises      W-Sq  0.062413    Pr > W-Sq  >0.2500
Anderson-Darling      A-Sq  0.426028    Pr > A-Sq  >0.2500
```

b. Dermal with CR hat (MEA corrected):

Because ICC is zero for the model “ln(MEA corrected dermal exposure, with CR hat) vs. ln(amt of ai handled)” EPA decided to use studentized residual instead of conditional studentized residual for diagnostics purposes. Figure 3 shows a Q-Q plot of the studentized residuals from the mixed effect model fitted to the dermal data (MEA corrected) with CR hat. The Q-Q plot comes close to a straight line; thus, we can accept that the studentized residuals are normally distributed. Also no specific pattern is observed in the “residual vs. predicted” plot; thus, there is no strong indication against assumption of constant variance.

Appendix C, Figure 3: Residual diagnostics of dermal exposure, with CR hat with MEA correction



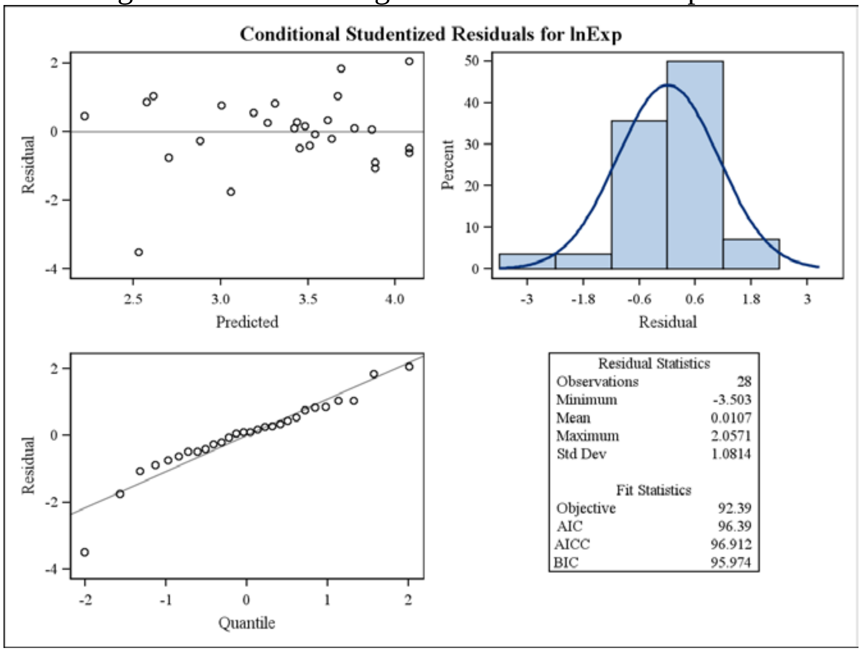
In addition to the above probability plot of the studentized residual, EPA also used formal statistical test to assess the normality of the residuals. All four tests shown below provide evidence that the studentized residuals are normally distributed (p>0.05).

```
                Tests for Normality

Test                  --Statistic---    -----p Value------

Shapiro-Wilk          W     0.953824    Pr < W      0.2468
Kolmogorov-Smirnov    D     0.115966    Pr > D     >0.1500
Cramer-von Mises      W-Sq  0.056386    Pr > W-Sq  >0.2500
Anderson-Darling      A-Sq   0.43476    Pr > A-Sq  >0.2500
```

c. Inhalation

Figure 4 below shows a Q-Q plot of the conditional studentized residuals from the mixed effect model fitted to the inhalation data. In the inhalation exposure model, ICC is not zero, so EPA used conditional residual instead of regular residual because it takes account of random effects due to clustering. The Q-Q plot comes close to a straight line; thus, we can accept that the conditional studentized residuals are normally distributed. Also no specific pattern is observed in the “residual vs. predicted” plot; thus, there is no strong indication against assumption of constant variance.

Figure 4: Residual diagnostics of inhalation exposure

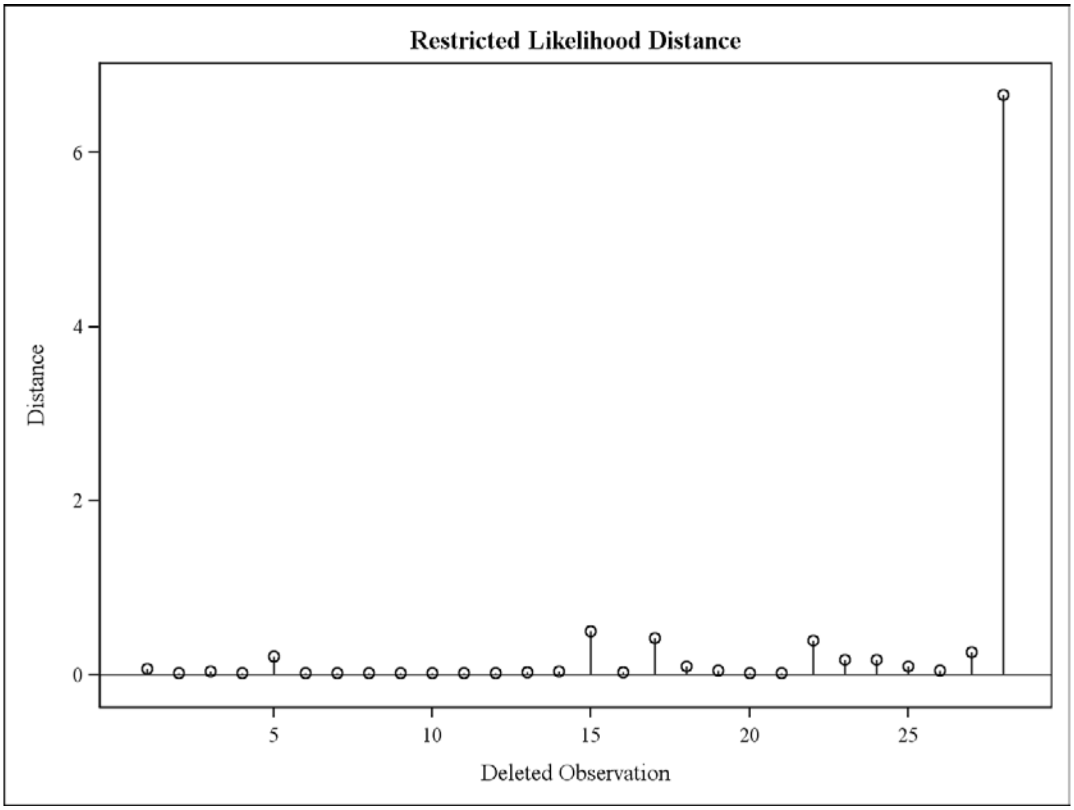


III. Analysis for Section 3.2.3 (Inhalation Exposure)

AHETF commented in their monograph that relationship between inhalation exposure and amount of active ingredient handled has the potential to be strongly influenced by the exposure for MU A5 in AHE64 (OK-pecan). From the residual plot shown in Figure 4 above, it was found that MU AHE64-A5 has conditional studentized residual > 3.0. EPA decided to conduct additional analysis to determine the influence of MU AHE64-A5.

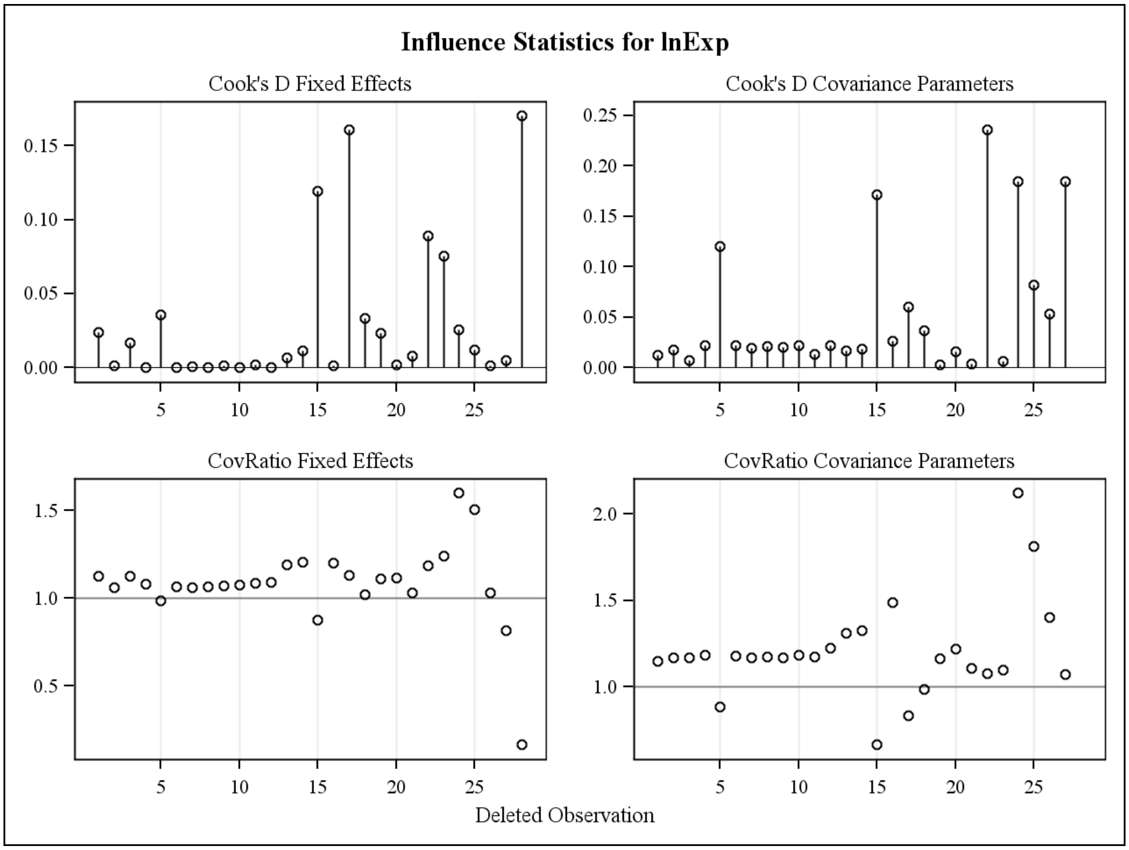
In linear mixed models fit by restricted maximum likelihood (REML), an overall influence measure is the restricted likelihood distance (Cook and Weisberg 1982). The likelihood distance gives the amount by which the restricted log-likelihood of the full data changes if one were to evaluate it at the reduced-data estimates (*Mixed Model Influence Diagnostics*, Oliver Schabenberger, SAS Institute). Figure 5 below shows restricted maximum likelihood distance for the inhalation exposure model.

Appendix C, Figure 5: Restricted likelihood distance of inhalation exposure model (log-log regression) using mixed effects



Clearly, observation 28 (MU AHE64-A5) stands out in terms of the summary statistic restricted likelihood distance (RLD). Because the RLD suggests that the MU AHE64-A5 is influential, the nature of that influence should be determined. Using Cook's D and CovRatio of inhalation exposure model (log-log regression), shown in Figure 6 below, the observation with the largest effect on the fixed effects estimates is 28 (Cook's D). The same observation has CovRATIO values of less than one. Deleting it from the analysis increases the estimated precision of the fixed effects estimates. MU AHE64-A5 exerts influence primarily on the estimates of the fixed effects and their precision, as can be seen from the Cook's D, and CovRATIO statistic for the fixed effects parameter.

Figure 5: Cook's D and CovRatio of inhalation exposure model (log-log regression) using mixed effects



References (specific to Appendix C)

Cook, R.D. and Weisberg, S. (1982), Residuals and Influence in Regression, New York: Chapman and Hall

Schabenberger, O. (2004), Mixed Model Influence Diagnostics, NC: SAS Institute Inc.

Appendix D
SAS Code for Analysis in Sections 3.2.2.2, 3.2.2.3, and 3.2.3

SAS Code for “Dermal Exposure without CR hats (No MEA)"

```
data  Derm_NOMEA_Nohats;
input cluster $ MU $ ai exp;
datalines;
AHE07_GA     1      75     9570
AHE07_GA     3      45     48367
AHE07_GA     4      75     3890
AHE07_GA     6      60     19601
AHE07_GA     8      52     86974
AHE07_ID     10     32     18115
AHE07_ID     12     33     7533
AHE07_ID     13     36     52721
AHE07_ID     15     24     32709
AHE07_ID     16     40     19959
AHE07_ID     17     34     3927
AHE07_FL     22     60     24357
AHE07_FL     23     90     30111
AHE07_FL     26     90     13298
AHE07_FL     27     90     108947
AHE62_CA     A1     34.3   4609
AHE62_CA     A2     5      1433
AHE62_CA     A3     10.4   3020
AHE63_NY     A1     48.4   74091
AHE63_NY     A2     35.6   39097
AHE63_NY     A3     24.4   50580
AHE63_NY     A4     15.2   270
AHE63_NY     A5     6.1    1844
AHE64_OK     A1     63.1   20011
AHE64_OK     A2     10.1   94485
AHE64_OK     A3     35.3   3355
AHE64_OK     A4     25.2   233089
AHE64_OK     A5     18.2   69.8

;
run;
data Derm_NOMEA_Nohats;
set Derm_NOMEA_Nohats;
lnAaiH=log(ai);
lnExp=log(Exp);
run;

ods graphics on;
ods rtf;
Proc Mixed Data=Derm_NOMEA_Nohats Method=REML cl covtest;
    Title3 "Mixed-Effects Regression of Ln Exposure on Ln Amt AI Handled";
    Class Cluster;
    Model LnExp = LnAaiH / solution alpha=0.05 DDFM = contain residual
outp=hsrb ;
    random cluster;

run;


ods rtf close;
proc print data=hsrb;
```

```
run;
proc univariate normal plot data=hsrb;
var studentresid;
run;
```

SAS Code for "Dermal Exposure with CR hats (MEA)"

```
data DermMEA;
input cluster $ MUID $  ai    exposure ;
datalines;
AHE07_GA     1      75     1305
AHE07_GA     3      45     6210
AHE07_GA     4      75     879
AHE07_GA     6      60     1438
AHE07_GA     8      52     12793
AHE07_ID     10     32     4758
AHE07_ID     12     33     777
AHE07_ID     13     36     1619
AHE07_ID     15     24     3800
AHE07_ID     16     40     2070
AHE07_ID     17     34     216
AHE07_FL     22     60     6185
AHE07_FL     23     90     7101
AHE07_FL     26     90     5327
AHE07_FL     27     90     25770
AHE62_CA     A1     34.3   891
AHE62_CA     A2     5      446
AHE62_CA     A3     10.4   452
AHE63_NY     A1     48.4   7078
AHE63_NY     A2     35.6   7346
AHE63_NY     A3     24.4   1145
AHE63_NY     A4     15.2   60.3
AHE63_NY     A5     6.1    335
AHE64_OK     A1     63.1   4274
AHE64_OK     A2     10.1   25493
AHE64_OK     A3     35.3   1732
AHE64_OK     A4     25.2   80702
AHE64_OK     A5     18.2   118
;

data DermMEA;
set DermMEA;
lnAaiH=log(ai);
lnExp=log(Exposure);
run;
ods graphics on;
ods rtf;

Proc Mixed Data=DermMEA Method=REML cl covtest;
    Title3 "Mixed-Effects Regression of Ln Exposure on Ln Amt AI Handled";
    Class Cluster;
    Model LnExp = LnAaiH /solution alpha=0.05 DDFM = contain residual
outp=hsrb1;
     random cluster;
```

```
  Run;
  ods rtf close;


proc univariate normal plot data=hsrb1;
var studentresid;
run;
```

SAS Code for “Inhalation Exposure"

```
data  inhalation;
input cluster $   MU_ID $     ai    inhalation_exposure ;
datalines;
AHE07_GA     1      75     15.4
AHE07_GA     3      45     54
AHE07_GA     4      75     18.7
AHE07_GA     6      60     48.2
AHE07_GA     8      52     296
AHE07_ID     10     32     34.4
AHE07_ID     12     33     42.3
AHE07_ID     13     36     39.3
AHE07_ID     15     24     35.2
AHE07_ID     16     40     32
AHE07_ID     17     34     18.6
AHE07_FL     22     60     51
AHE07_FL     23     90     35.3
AHE07_FL     26     90     30.4
AHE07_FL     27     90     529
AHE62_CA     A1     34.3   30.5
AHE62_CA     A2     5      35.7
AHE62_CA     A3     10.4   44.3
AHE63_NY     A1     48.4   117
AHE63_NY     A2     35.6   21.8
AHE63_NY     A3     24.4   67.6
AHE63_NY     A4     15.2   3.25
AHE63_NY     A5     6.1    30.3
AHE64_OK     A1     63.1   42.7
AHE64_OK     A2     10.1   14.5
AHE64_OK     A3     35.3   13.4
AHE64_OK     A4     25.2   6.66
AHE64_OK     A5     18.2   0.294
;
run;
data inhalation;
set inhalation;
lnAaiH=log(ai);
lnExp=log(inhalation_exposure);
run;

ods graphics on;
ods rtf;
Proc Mixed Data=inhalation Method=REML cl covtest;
    Title3 "Mixed-Effects Regression of Ln Exposure on Ln Amt AI Handled";
```

```
    Class Cluster;
    Model LnExp = LnAaiH /influence (iter=5) solution alpha=0.05 DDFM =
KenRog residual  ;
    random  cluster;
Run;
 ods rtf close;


proc print data=hsrb;

run;
```

Appendix E
AHETF Correspondence to EPA Regarding AHE64 MUA5

*T*oxicology & *E*xposure *A*ssessment *S*ervices, Inc.

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Raleigh, NC 27613
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To: Matt Crowley
Date: March 7, 2011
Re: MU A5 in AHE64 of the Open Cab Airblast Scenario
CC: Dave Johnson, Victor Canez, and Dave Barnekow
From: Larry Smith and Dennis Klonne

There appears to be a question regarding the exposure data (primarily the inhalation exposure data) for worker MU A5 in the AHE64 study of the Open Cab Airblast Scenario. In summary, there were no measurement or analytical problems or errors for the exposure matrices for this worker. There was no discussion in the Monograph regarding the low exposure values for inhalation and dermal exposures (either absolute values or normalized values) because no obvious reason was found for the results (see below). Only the effects of these data on the statistical objectives were discussed in the monograph.

The AHETF did observe the exceptionally low inhalation and dermal exposure (both absolute and normalized) values for this worker. An evaluation was conducted and several observations described below were made.

The following observations can be made regarding MU A5 in study AHE64:

- He had the lowest unit exposure values for both the dermal and inhalation routes. It makes sense that both values would tend to move in tandem with this open cab airblast scenario.
- He had the most experience of the workers in this scenario – 40 years. However, another worker in the scenario, also tied with 40 years of experience, had a much higher unit exposure for both dermal and inhalation routes.
- He used the same tank size as many other workers – 500 gal.
- He applied the smallest spray volume used in the scenario – 300 gal. However, another worker (A5, AHE63), also tied with a 300 gal spray volume, had a much higher unit exposure for both dermal and inhalation routes.
- He did have the lowest gallon-per-acre spray rate (33 gal/A) but a MU with a similar, albeit it slightly higher spray rate of 38 gal/A, had a much higher unit exposure for both dermal and inhalation routes.
- Although he applied only 2 loads, several other MUs that also applied 2 loads had much higher unit exposures for both dermal and inhalation routes.

- MUs who treated fewer acres had higher unit exposures for both dermal and inhalation routes.
- He had the 2nd shortest monitoring time in the scenario – 2.5 hrs. However, the MU with the shortest monitoring time (1.4 hr) and another with a very similar monitoring time (2.7 hr) had much higher unit exposures for both dermal and inhalation routes.

The one value that seems to really stand out about this particular worker is the percentage of the total dermal exposure that was on the hands and face/neck (78%); whereas the next highest value in the scenario is 14%. However, remember that this is despite the lowest absolute dermal exposure (69.8 μg) in the scenario. It is apparent that this is due to a lack of exposure on all the other body parts under the work clothing. The explanation for that could be due to one factor, such as the exceptional work habits of this individual, or to a multitude of factors, such as work habits, direction and configuration of nozzles, operating pressure of nozzles, tractor speed, wind speed and direction, etc., etc.

The detailed observations of the worker indicated no obvious explanation for the findings. The raw field data for AHE64 MU A5 was reviewed for indications that the OVS sample may have been compromised. The monitoring was conducted on 8/29/2009, starting at 0811 and ending at 1040 when the pump was turned off. Pump flow was measured at the start and end of monitoring (start = 2.041 L/min, end = 1.996 L/min). Additionally, the pump operation was visually confirmed during the monitoring period at the following times; 0811, 0841, 0919, 0932, and 1036. These data indicate the pump was operating normally throughout the monitoring period. There were no pump failures noted.

The worker observer's notes indicate the worker was prudent in his application techniques. For example, he turned off the sprayer when he made his turns at the end of each row. The worker wore a half-face respirator, but this would not have covered the OVS tube cartridge.

The sample handling and storage records show no anomalies. There are no indications of analytical anomalies for the A5 OVS tube analysis or laboratory control recoveries during the analytical runs.

In summary, although it was apparent that this worker's exposure was exceptionally low, there were no obvious explanations for the result. Thus, further discussion in the monograph along these lines was not deemed to be necessary.

The discussion of this worker in the scenario was done with the intent of demonstrating the effects of the unit exposures on the primary and secondary statistical objectives. As with any apparent outlying value, be it an exceptionally high or exceptionally low value, it can have some dramatic effects on the statistics and attainment of the statistical objectives. This was the case for this scenario, in which the inclusion of the inhalation unit exposure value for MU A5 in AHE64 prevented attainment of the primary statistical objective (i.e., 3-fold accuracy), even though the inhalation data are not held to this standard. The conclusion from this exercise was that "This MU produced an atypically small normalized inhalation exposure value that some users may choose to eliminate from the dataset when describing 'typical' inhalation exposure." (page 76 of the monograph)

Just as we also do not eliminate exceptionally high values from consideration, we do evaluate the impact of some of these values on the statistical description of the scenario. In this case, we performed the same exercise with some values that were exceptionally low. As noted in the monograph, it is up to future users of the database to determine the most appropriate use of the data, as objectives and needs can differ between users.