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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: [date placeholder], 2020

SUBJECT: **DRAFT** Review of Agricultural Handler Exposure Task Force (AHETF) Monograph: "Mechanical Transfer of Liquids" (AHE1022)

PC Code: --
Decision No.: --
Petition No.: --
Risk Assessment Type: --
TXR No.: --
MRID No.: 50940301

DP Barcode: D454706
Registration No.: --
Regulatory Action: --
Case No.: --
CAS No.: --
40 CFR: --

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This memorandum presents EPA's review of the occupational handler exposure scenario monograph "Mechanical Transfer of Liquids" (AHE1022) submitted by the Agricultural Handler Exposure Task Force (AHETF). It reflects comments and advice provided by the Human Studies Review Board following its review in January 2020[1]. The AHETF satisfactorily followed the study protocols, sampling design, and data analysis plan. EPA recommends use of the monograph and underlying data in routine regulatory assessment of human health exposure and risk as part of the federal pesticide registration process. Scientific review of the field and analytical reports (AHE500, AHE13, AH501) that outline the monitoring data collected to support this scenario are found in separate data evaluation review (DER) memoranda (Crowley, 2020; Arthur, 2007; EPA, 1998).

[1] [placeholder for reference]

1.0 Executive Summary

This document represents EPA's review of the Agricultural Handler Exposure Task Force (AHETF) Study AHE1022: Mechanical Transfer of Liquids (Bruce and Holden, 2019a). The submission compiles and statistically analyzes dermal and inhalation monitoring for workers who transfer liquid pesticides with mechanical systems (e.g., hoses and pumps) from their product containers into pre-mix and/or application equipment tanks. These systems preclude workers having to open pesticide containers and manually pour them into application equipment. Consistent with common industrial hygiene practice, they are considered engineering controls[2] and in the context of federal pesticide regulation, they are considered "closed systems"[3].

Study AHE500 was submitted in 2019 (Bruce, 2019) and augments existing data from studies AHE13 and AH501; all 3 study reports provide the underlying exposure monitoring field and analytical results, including laboratory analyses. They were reviewed separately by EPA and considered acceptable (Crowley, 2020; Arthur, 2007; EPA, 1998). The scenario monograph report (AHE1022) that is the subject of this review compiles the exposure monitoring results from those 3 studies into a formal generic exposure scenario which can be utilized by pesticide regulatory agencies for exposure assessment purposes.

Overall, the AHETF adequately followed the general study design outlined in the AHETF Governing Document (AHETF, 2008 and 2010) and scenario sampling and data analysis protocol (AHETF, 2011a and 2011b). 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 AHETF data and associated unit exposures are considered superior to the existing data in the Pesticide Handler Exposure Database (PHED) used to assess exposure and risk for this scenario.[4] The data are considered the most reliable data for assessing exposure and risk to individuals transferring liquid pesticide products[5] using mechanical systems to transfer liquid pesticides while wearing the following personal protective equipment (PPE): long-sleeved shirts, long pants, shoes, socks, chemical-resistant gloves, and no respirator[6]. Importantly, the dataset excludes monitoring of workers who, when using suction/extraction systems to transfer pesticides, removed the chemical extraction probes prior to rinsing them within the pesticide container – EPA agreed with AHETF's identification of this activity as inconsistent with use of closed systems.

The primary quantitative objective was for dermal exposure results (normalized to the amount of active ingredient handled) to be accurate within 3-fold at the geometric mean, arithmetic mean

[2] https://www.cdc.gov/niosh/engcontrols/

[3] At the time of the study, the applicable regulation was 40 CFR §170.240(d) where closed systems were those that "enclose the pesticide to prevent it from contacting handlers or other persons". Currently "closed systems" are covered under a revised Worker Protection Standard at 40 CFR §170.305 and §170.607.

[4] Pesticide Handlers Exposure Database (PHED) Scenario 6. All Liquid Formulations: Closed Mixing.

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

[6] Adjustments to this dataset would be required to represent alternative personal protective equipment (PPE) (e.g., applying a protection factor to represent exposure when using a respirator or additional protective clothing) and are not addressed in this review. Importantly, data users should note that additional PPE is not typically considered in the context of an engineering control like mechanical/closed loading systems.

and 95th percentile. This objective was not met: AHETF results showed accuracy of approximately 3.8-fold at the arithmetic mean and 3.3-fold at the 95th percentile. As a result, EPA incorporated the uncertainty beyond the 3-fold target in the form of a multiplier to the default exposure estimates used in routine handler exposure assessments for this scenario.

Additionally, all estimates of the slope of log dermal exposure-log amount of active ingredient handled (AaiH) regression included values of 1 but not zero, demonstrating the data are more consistent with a proportional relationship than an independent one. Thus, for this scenario, HED will continue to use the exposure data normalized by the amount of active ingredient as a default condition for regulatory exposure assessment purposes.

Select summary statistics for this scenario are presented in Table 1 below, as well as, for comparison, the value previously used (PHED Scenario 6. All Liquid Formulations: Closed Mixing) to assess pesticide human health exposure/risk for mechanically transferring liquid pesticides.

Table 1. Unit Exposures (µg/lb ai handled): Mechanical Transfer of Liquids

Exposure Route[b]	PHED Scenario #6	AHETF (EPA-revised)[a]				
	"Best fit"	Geometric Mean	Arithmetic Mean[e]		95th Percentile[f]	
Dermal[c,d]	8.6	0.50	3.17	4.02	11.8	13.4
Inhalation	0.083	0.00457	0.0110		0.0403	

[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 3.3.
[b] Results represent dermal exposure under long-sleeve shirt, pants, shoes/socks, and chemical-resistant gloves. For estimates without chemical-resistant gloves, see Table 10 in Section 4.1. Inhalation exposure is without respiratory protection.
[c] Per current EPA policy, dermal unit exposures reflect 2X adjustment of hand and face/neck measurements to address potential inefficiencies in those exposure monitoring methods since the average percent contribution to total dermal exposure by the hands, face, and neck is greater than 20% (see Section 3.2.1).
[d] In addition to the modeled estimates of the arithmetic mean and 95th percentile, additional estimates are presented to reflect a to account for uncertainty beyond the 3-fold target for the arithmetic mean and 95th percentile (i.e., "fRA-adjusted").
[e] Arithmetic Mean (AM) = GM * exp{0.5*((lnGSD)^2)}. "fRA-adjusted" value also shown: 3.17 * (3.8 ÷ 3) = 4.02. See Section 3.3.1.
[f] 95th percentile = GM * GSD^1.645. "fRA-adjusted" value also shown: 11.8 * (3.4 ÷ 3) = 13.4. See Section 3.3.1.

2.0 Background

The following provides background on the AHETF objectives and review 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 estimate worker exposures associated with major agricultural and non-agricultural handler scenarios. A scenario is defined as a pesticide handling task based on activity such as mixing/loading or application. Other factors such as formulation (e.g., liquids,

granules, etc.) application equipment type (e.g., tractor-mounted boom sprayers, powered handgun sprayers, etc.) are also key criteria for defining some 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 current data, an engineering control (e.g., vehicles with enclosed cabs, closed mixing/loading systems) or additional personal protective equipment/clothing may also be a key element of the scenario.

AHETF studies use dosimetry methods intended to define pesticide handler dermal and inhalation exposures, attempting to represent the chemical exposure "deposited on or to-the-skin" or "in the breathing zone." For the purposes of pesticide handler exposure assessment, dermal and inhalation exposures are expressed as "unit exposures" – exposure per mass of pesticide 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). Scenario-specific unit exposures are then used generically to predict exposure for other chemicals and/or application conditions such as 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 – granule, liquid concentrate, dry flowable, etc.), packaging (e.g., in a bag or jug), mixing/loading process (e.g., open pour versus closed system), 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 one chemical loaded using a closed system can be used to estimate exposure for loading another chemical in the same manner. 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, exposure is assumed to double.

The AHETF approach for monitoring occupational handler exposure was based on criteria – reviewed by EPA 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 and 2010), 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 to 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 of the geometric mean, arithmetic mean, and 95th percentile dermal unit exposures. To meet this primary objective AHETF proposed an experimental design with a sufficient number of monitored individuals across a set of monitoring locations. Note that this "fold relative accuracy" (fRA) objective does not apply to normalized inhalation exposure, though estimates are provided for reference.

- The secondary objective is the ability to evaluate the assumption of proportionality between dermal exposure and amount of active ingredient handled (AaiH) in order to

inform use of the AHETF data generically across application conditions. 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 maximize logistical/cost efficiency while minimizing the number of participating workers, the AHETF developed a study design employing a 'cluster' strategy. A cluster, from a sample size perspective, is defined as a set of workers monitored in spatial and temporal proximity. For AHETF purposes, clusters are generally defined by a few contiguous counties in a given U.S. state (or states). Importantly, in terms of a sampling strategy, there is assumed to be some level of correlation within clusters. So, while cluster sampling is logistically more efficient and cost effective, within-cluster correlation may result in the need to conduct monitoring for more workers overall than if cluster sampling were not employed.

Though for most handler scenarios the optimal configuration for the AHETF is 5 regional clusters each consisting of 5 participants[7], (i.e., a "5 x 5" strategy), for AHE500 the AHETF employed slightly alternative (but equivalent) designs to augment existing data (AHE13 and AH501) and target the aforementioned quantitative objectives. Per the original 2011 sampling plan, for "non-returnable" pesticide containers – containers that will be rinsed and discarded – a "7 x 3" strategy was employed while a "5 x 3" plan was conducted for "returnable containers" – containers that are returned to a distributor or refilled on-site). To accommodate the analysis for the secondary objective, the AHETF partitions the practical AaiH range handled into strata, and then strives to "assign" participants to separate strata so participants within the same cluster are handling different amounts and the overall range is covered. In general, the strata of AaiH for any given scenario is commensurate with typical commercial production agriculture and EPA regulatory assumptions with respect to amount of solution that might be prepared in a workday.

2.2 2011 HSRB Protocol Review and Comments

The ability of the EPA to use the AHETF mechanical transfer of liquids data to support 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[8]. The protocol and sampling plan for this exposure data and scenario (AHETF, 2011a and 2011b) was presented to the HSRB in October 2011. The meeting report (HSRB, 2012) stated that the proposed approach would "likely generate scientifically reliable data, useful for assessing the exposure of workers using closed systems to load liquid pesticide products from returnable or nonreturnable containers"[9].

[7] Together with the conditions under which the active ingredient is handled, the workers are often referred to as "monitoring units" (MUs).
[8] http://www2.epa.gov/programs-office-science-advisor-osa/human-studies-review-board
[9] https://archive.epa.gov/osa/hsrb/web/pdf/hsrb_meeting_final_report_for_october_2011-certified.pdf

The following table outlines issues raised by the HSRB and how/whether the issue was addressed in the protocol or completed study. HSRB issues/comments are quoted directly or paraphrased from the 2011 meeting report.

Table 2. Summary of 2011 HSRB AHE500 Protocol Review		
2011 HSRB Comment		**Study Outcome**
The Board urged the Agency and sponsors to be cautious about including these older data in the AHED exposure data, particularly if they are substantially different from the data collected using the proposed design and protocols		The final dataset continues to include data from "older" studies. The data has been adequately reviewed based on contemporary criteria and does not appear substantially inconsistent/different from the newly collected data to warrant its exclusion.
There is some concern that the proportionality premise regarding levels of residues and amount of active ingredient handled might not hold for these scenarios.	Detailed observations should occur during the conduct of the exposure so that any incidental worker contacts with contaminated surfaces are noted.	The observations and notes taken during the study did in fact lead to the AHETF being able to identify certain exposure patterns. This study was the largest effort to date by the AHETF in terms of quantitative tabulation and analysis of the observation notes.
	The Board suggested that the sponsors and Agency consider the value of measuring surface contamination at the start of the study; if there were a background residue present prior to the conduct of the study, this existing residue would contribute to the total exposure and should be quantified.	Surface residue measurements were not collected. While the proposal has merit, EPA considers it outside the scope of the study.
It was suggested that no upper limit be imposed on the AaiH of participants using closed systems to load liquid pesticide products from nonreturnable containers.		The amount of active ingredient handled across all workers in the studies was very diverse, representative of what would be handled with the systems and adequate to support data analysis objectives.
Criteria should be developed before the conduct of the study to ensure that the closed systems included within these studies comply with the provision within the Agency's WPS that such systems must be functioning properly. These criteria should describe how 'proper function' will be (or were) determined and by whom. Such criteria are expected to be a part of scientifically reliable data collection process and to ensure compliance with the WPS.		The protocol for AHE500 states: "Prior to use in the study, the closed system and mixing/loading procedures shall be evaluated and discussed by the Study Director or a designated researcher to ensure the system is operating properly and the anticipated procedures do not involve open pouring. This examination will include ensuring no significant leaks; discussing how connections will be made between containers and closed systems and between systems and hoses or tanks; and ensuring the system meets one of the four system types discussed above." The AHE500 study report notes as a deviation from protocol (deviation #4 and #6) that this was not always possible. Despite this deviation, systems were characterized during recruitment by the potential participants themselves, AHETF staff evaluated the system prior to monitoring and properly documented the systems and their operation during the

Table 2. Summary of 2011 HSRB AHE500 Protocol Review	
2011 HSRB Comment	**Study Outcome**
	monitoring; in no instance did the Study Director or designee prematurely terminate monitoring due to a malfunctioning system.
A suggestion was made to consider the addition of cotton gloves, to be worn over the handlers' chemical protective gloves. While the Board did not question the rationale to place the focus of these studies on hand exposures inside chemical protective gloves, it felt that being able to measure both unprotected and protected hand exposures would greatly increase the value of this study.	Exposure to hands outside chemical resistant gloves were not measured; results therefore do not represent "bare hand" exposure. EPA will explore if and how exposures need to represent bare hand exposure during mechanical transfer of liquid pesticides (see Section 4.1).

2.3 2020 HSRB Review and Comments

[placeholder for summary of January 2020 HSRB comments and how EPA responds/addresses them]

3.0 Exposure Study Conduct and Monitoring Results

Field monitoring and analytical results, as well as protocol amendments and deviations, were reported in AHE500 and the existing data study submissions (AHE13 and AH501) and reviewed by EPA (Crowley, 2020; Arthur, 2007; EPA, 1998). Data from AHE500 – an additional 22 data points – was designed to supplement existing data. No protocol amendments or deviations were considered to adversely affect the study results.

Table 3. AHETF Mechanical Transfer of Liquids Studies				
Study ID		**Study Title**	**Existing or New Data**	**EPA Data Review**
AHE#	**EPA MRID**			
AHE13	46763702 (amended) 46634105 (original)	Determination of Dermal and Inhalation Exposure to Workers During Closed-System Loading and ULV Application of a Liquid Pesticide Product to Cotton	Existing study (n=9)	Arthur, 2007
AH501	42685901	Evaluation of Worker Exposures to Tribufos During Aerial and Ground Applications of DEF 6 to Cotton	Existing study (n=7)	EPA, 1998 (study reviewed as part of PHED
AHE500	50846201	Determination of Dermal and Inhalation Exposure to Workers during Closed System Loading of Liquids in Returnable and Non-Returnable Containers	New study; protocol reviewed by HSRB in 2011 (n=22)	Crowley, 2020

The following sections summarize the conduct of the studies, the exposure monitoring results and the scenario benchmark statistical analyses presented in the AHETF scenario monograph AHE1022.

3.1 Exposure Study Design and Characteristics

As described by the AHETF, this pesticide handler scenario involves the "mechanical transfer of liquids (MTL) using closed systems from a variety of product containers to various tanks or

application equipment…connecting/disconnecting pumps and hoses to product containers and to pre-mix or spray tanks; operating controls or valves to affect the transfer; and in some cases, rinsing the container..." (AHE1022). These systems conform to EPA's Worker Protection Standard (WPS, 40 CFR §170.240 (d)(4)) because they "enclose the pesticide to prevent it from contacting handlers or other persons".[10] Although some points in the transfer setup can be slightly open, the engineering control precludes workers from manually pouring liquids.
EPA agrees that the AHETF studies represent the diversity of possible types of systems used to mechanically transfer liquid pesticides. Three important characteristics of the monitoring data are described below.

- Container type
    - "Returnable" where the product package (e.g., a bulk container of more than 100 gallons) can be returned to the manufacturer or distributor or refilled on-site; and,
    - "Non-returnable" referring to plastic jugs or drums (e.g., 5-gallon jug or 55-gallon drums) that are disposed of or rinsed/re-used.
- System type
    - Suction/Extraction: extraction via pump and hose from a probe inserted into container; probes are often integrated into returnable/refillable containers but are also often user-fabricated and inserted loosely into the containers; mechanism necessary to rinse probe prior to removal
    - Gravity Flow: container is placed inverted onto system which opens the container and product flows into tank with container rinsing mechanism incorporated
    - Container Breach: system punctures container and contents flow into tank via gravity with integration of puncturing device and rinsing mechanism; typically used with smaller containers
- Degree of openness
    - Completely closed: a seamless transfer from the extraction of product concentrate to filling of application equipment tank.
    - Not completely closed: in various places the system is not completely sealed or seamlessly connected throughout. For example, a system which empties solution into an open tank hatch or a suction/extraction system with a gap between the extraction probe and the container opening.

The figures below (from AHE1022 Appendix F; Bruce and Holden, 2019a) depict examples of activities for which the exposure data are applicable.

[10] Note the referenced WPS regulation at the time of the study was 40 CFR §170.240 (d)(4). That has since been revised and "closed systems" are currently covered under a revised Worker Protection Standard at 40 CFR §170.305 and §170.607. While the revision slightly updates descriptions of closed systems, EPA does not consider the revision to effect the outcome or use of the AHETF data.

Figure 1: Returnable / Suction-Extraction / Completely Closed

Figure 2: Non-returnable / Suction – Extraction / Not Completely Closed

Figure 3: Returnable / Gravity Feed / Completely Closed

Figure 4: Non-returnable / Container Breach / Not Completely Closed

In order to capture the expected range of exposures with a relatively small sample and augment existing data from AHE13 and AH501, the monitoring plan/protocol for AHE500 (AHETF, 2011a and 2011b) outlined a strategy to target a diverse set of conditions such as geographic areas/U.S. states, types of mechanical transfer systems, container size, transfer set-up and different workers/employers. Monitoring data based on that strategy would then augment existing data from AHE13 and AH501, respectively, which, while the data were acceptable, represented a more limited set of conditions (e.g., same system types, repeat samples on the same worker). While certain conditions were targeted, thereby potentially restricting the sampling population, recruiting procedures were developed to minimize bias in the selection of employers and subjects. As described in detail in the study, there were three recruitment phases. The phases involved winnowing down the initial universe list of employers in the monitoring area who may

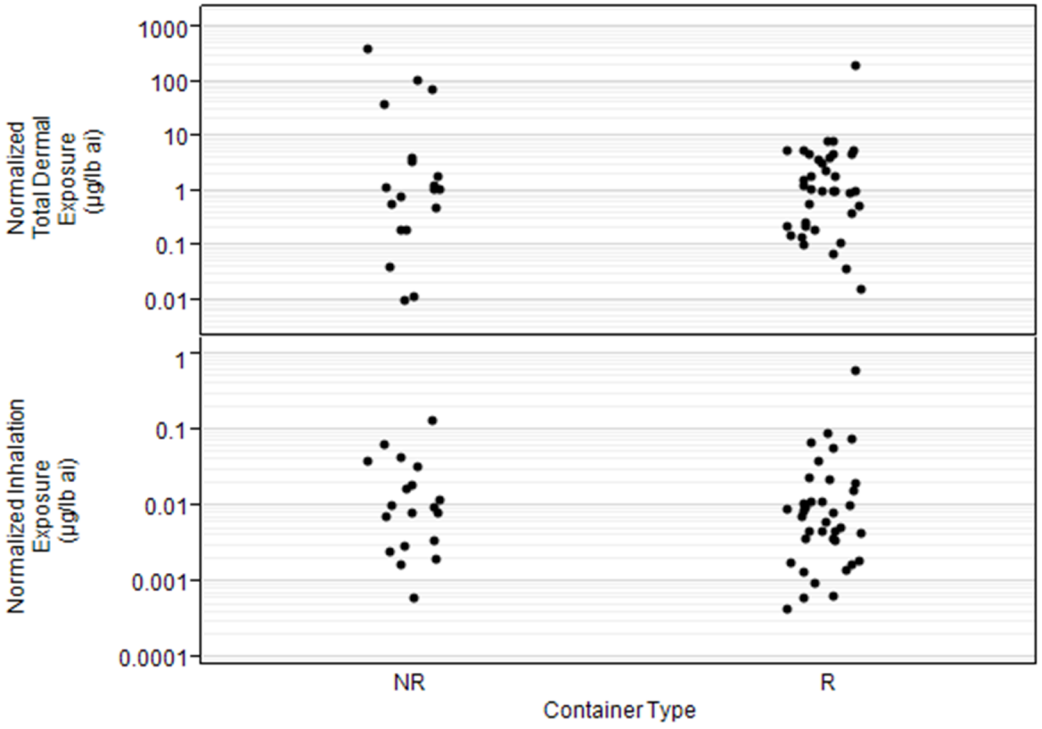
use mechanical transfer systems through processes to identify subsequent lists of "qualified employers" and then "potentially eligible" employers. After confirming eligibility, AHETF scheduled and conducted monitoring of workers. Randomization in the process included random calling from the Employer Universe List – typically a few thousand names – where a Qualified Employer List was developed of those who use closed systems (approximately 10% of the Employer Universe List). Random calling was then made of those on the Qualified Employer List to determine willingness to participate (again, about 10% of the Qualified List). Non-response (i.e., inability to contact, interview refusals) was typical for the AHETF monitoring program - approximately 75% across the monitoring areas. Finally, in no instance was there an opportunity at the final stage of identifying participants to randomly select from a pool of multiple workers who volunteered.

The sampling plan for this scenario (AHETF, 2011) originally proposed a split into two "sub-scenarios": returnable and non-returnable containers. For both sub-scenarios a 'cluster' sampling strategy was employed as a cost-effective approach that would also satisfy benchmark data analysis objectives. For the returnable container sub-scenario, a '3 x 5' design – monitoring of a total of 15 different workers, 3 workers in each of 5 separate 'clusters' or monitoring areas monitored around approximately the same time – was used; a total of only 15 additional monitoring events were necessary to augment the existing returnable container data from AHE13 and AH501. For the non-returnable container sub-scenario, a completely new dataset was proposed as no existing data was available for non-returnable containers. For this sub-scenario a '3 x 7' design was proposed – monitoring of a total of 21 different workers, 3 workers in each of 7 separate 'clusters'. All 21 intended monitoring samples for non-returnable containers and all 15 intended monitoring samples of returnable containers were collected from AHE500 to complement the existing 15 from AHE13 and 7 from AH501. However, the cost-effective sampling design was not achieved – due to recruitment difficulties, considering both spatial and temporal differences, monitoring was conducted in more clusters than designed. From a statistical sampling perspective this likely resulted in more independent measurements but was more costly from a logistical and resource perspective. With two non-returnable container monitoring samples from AHE500 invalidated due to analytical issues or deviation from normal worker activity[11] there were 19 non-returnable container monitoring samples and 37 returnable container monitoring samples for a total data set of 56 monitoring samples across 13 U.S. states dating from 1991-2016.

Post-study analysis resulted in significant changes to the final dataset proposed for use. First, despite the pre-study assumptions about differences between returnable and non-returnable containers, AHETF analysis demonstrated that there are not significant differences and the AHETF proposed to combine all 56 monitoring samples into a single dataset representing all types of container types used to mechanically transfer liquid pesticides. A separate AHETF submission (Bruce and Holden, 2019b) presents the analysis for the proposed combination saying "…results indicate no statistically significant differences in exposure potential for returnable versus non-returnable containers" and the following figure provides a visual comparison.

[11] Samples for worker M23 were analytically invalid and samples for worker M2 were never analyzed due to inappropriate rinsing and clean up activity. More detail provided in EPA's review of AHE500 (Crowley, 2020).

Figure 5: Normalized Dermal and Inhalation Exposure by Container Type



Next, the same AHETF submission outlines an analysis of the combined 56 data points, identifying an activity that significantly increases the potential for dermal exposure. Because the AHETF noted that their dataset did not result in marked dermal exposure differences in comparison to standard "open pouring" of liquid pesticide products, various data characteristics were tabulated and analyzed to attempt to identify potential causes of higher dermal exposure potential. These activities included:

- Removing unrinsed extraction probes (i.e., "contaminated stingers")
- Disconnecting contaminated product transfer hoses
- Rinsing empty test substance containers with an open system
- Rinsing empty test substance containers with a closed system
- Leaks in test substance or spray mixture transfer systems
- Repairs involving test substance or spray mixture transfer systems
- Rinsing gloves during the monitoring interval

The AHETF found that for suction/extraction types of systems removing chemical extraction probes from the container prior to rinsing them within the container had a statistically significant relationship with dermal exposure potential. The following figures provide a graphical presentation of the data followed by a photographic representation of the activity.

Figure 6: Normalized Dermal Exposure by Un-rinsed Extraction Probe Removal

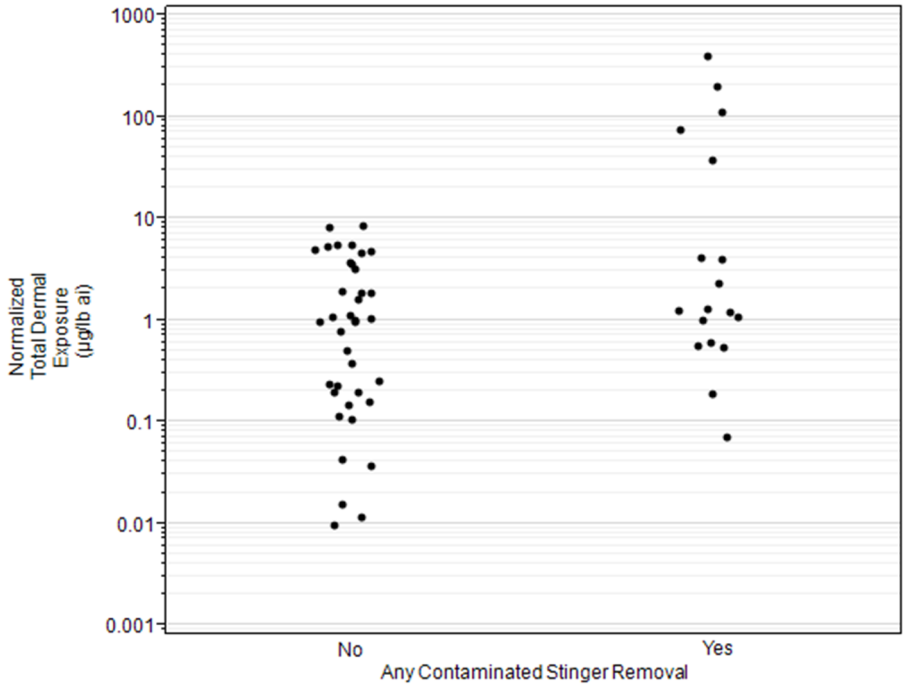


Figure 7: Removing Un-rinsed Extraction Probe

A total of 18 monitored workers removed an extraction probe without first rinsing it – 12 workers from AHE500 and 6 from AHE13. As shown by the potential for unexpectedly high dermal exposure, this activity appears to void the engineering control and the AHETF proposed excluding these 18 data points from the dataset used for regulatory purposes. EPA had the AHETF analysis independently validated (Attachment 1) and agrees with utilizing a dataset that

does not represent removing unrinsed extraction probes (n=38). EPA believes that the practice of rinsing chemical extraction probes prior to their removal from pesticide containers is consistent with the intent of closed systems. However, to the extent the dataset is needed for regulatory purposes, summary statistics are also provided in Section 4.1 for those workers who used suction/extraction systems but removed extraction probes prior to rinsing them (n=18).

As monitoring was conducted across 25 years and 13 different U.S. states, both spatial and temporal diversity is represented in the sample. While the same workers were monitored more than once in the existing AHE13 and AH501 studies ("repeat measures"), the AHE500 protocol specified that no worker should be monitored twice. In one instance, and only after combination of the monitoring data for both returnable and non-returnable containers, did the AHE500 dataset have a worker with more than one sample. The system types were reasonably diverse with an approximately even split between returnable and non-returnable container types and various system types represented (suction/extraction, container breach, gravity flow). The following table provides a summary of monitoring characteristics.

Table 4. Mechanical Transfer of Liquid Summary (AHE13 / AH501 / AHE500)

Study	Worker	Date	State	Product Container Type[1]	System Type[2]	Completely Closed	Solution Prepared (gallons)	Duration (hours)
AH501	A	10/2/1991	CA	R	S/E	Yes	4075	4.8
		10/2/1991	CA	R	S/E	Yes	4175	4.1
		10/4/1991	CA	R	S/E	Yes	5285	4.8
	E	10/2/1991	CA	R	S/E	Yes	4075	4.8
		10/2/1991	CA	R	S/E	Yes	3805	4.1
		10/4/1991	CA	R	S/E	Yes	3025	4.5
		10/4/1991	CA	R	S/E	Yes	5305	4.8
AHE13	A	10/18/2004	TX	R	G	Yes	853	6.1
		10/19/2004	TX	R	G	Yes	967	9.8
		10/21/2004	TX	R	G	Yes	562	10.1
	B	10/18/2004	TX	R	G	Yes	633	2.7
		10/19/2004	TX	R	G	Yes	970	10.0
		10/21/2004	TX	R	G	Yes	443	9.8
	E	10/25/2004	TX	R	S/E	No	235	0.6
	F	10/25/2004	TX	R	G	Yes	607	7.7
	G	10/25/2004	TX	R	G	Yes	446	4.9
AHE500	C	11/29/2012	FL	R	S/E	Yes	5880	6.1
	H	3/9/2013	MS	NR	S/E	No	3525	3.3
	K	5/30/2013	MI	R	G	Yes	1500	2.7
	A	6/13/2013	FL	R	G	No	1350	2.5
	P	10/11/2013	WA	R	G	No	1200	1.5
	Q	11/13/2013	WA	NR	CB	No	13420	5.9
	S	5/7/2014	MI	R	G	Yes	3200	3.6
	N	7/4/2014	MI	R	G	Yes	8075	8.9
	U	10/3/2014	WA	R	G	No	1250	2.2
	AA	6/9/2015	NE	R	S/E	No	unknown	3.9
		7/11/2015	NE	NR	S/E	No	1041	4.7
	AB	6/19/2015	CO	R	G	Yes	5634	5.6
	W	6/27/2015	CO	NR	S/E	Yes	540	2.3
	AK	4/4/2016	LA	NR	S/E	No	2250	2.1
	AF	4/5/2016	LA	NR	S/E	No	1200	2.2

Table 4. Mechanical Transfer of Liquid Summary (AHE13 / AH501 / AHE500)								
Study	**Worker**	**Date**	**State**	**Product Container Type[1]**	**System Type[2]**	**Completely Closed**	**Solution Prepared (gallons)**	**Duration (hours)**
	AH	4/12/2016	NE	NR	CB	No	330	2.2
	AG	4/13/2016	NE	R	G	Yes	2974	8.6
	AI	4/15/2016	NE	R	G	No	716	2.0
	AM	6/4/2016	MI	NR	G	No	3000	4.3
	AN	6/23/2016	NE	NR	G	Yes	1500	2.5
	Z	7/21/2016	GA	NR	S/E	No	800	1.2
	AO	9/21/2016	CO	R	G	Yes	2000	2.4
[1] NR = non-returnable; R = returnable [2] G = Gravity Flow; S/E = suction/extraction; CB = container breach								

Also, per protocol for study AHE500, the amount of active ingredient handled by the workers was diversified – mainly to supplement the range of amount of active ingredient handled in the existing studies in order to accommodate the secondary (regression analysis) study objective – but also to potentially add indirect variability to the dataset. Across all three studies there was a wide range of active ingredient handled, from 86 to 9603 lbs, just over 2 orders of magnitude. Overall, this amount of active ingredient handled corresponded to workers handling between 20 and 970 gallons of liquid concentrate product, preparing between 235 and 13,420 gallons of dilute solution.

3.2 Exposure Monitoring and Calculations

This section briefly describes how exposure was measured, the final dermal and inhalation exposure results used in statistical analyses, and how those results were analyzed.

3.2.1 Monitoring Methods

Dermal exposure was measured using 100% cotton "whole body dosimeters" (WBD) underneath normal work clothing (e.g., long-sleeved shirt, long pants, socks and shoes), hand rinses (collected at the end of the day and during restroom and lunch breaks), face/neck wipes, socks (AHE13 only), and patches (hat and upper chest/back, AH501 only). Per AHETF goals, monitoring was conducted to represent exposure for workers wearing long-sleeve shirts, pants, shoes/socks, chemical-resistant gloves and no respiratory protection. Differences in monitoring methods across studies were appropriately noted by the AHETF:

- Hand measures: immersing hands in a plastic bag with ethanol in AH501 vs. pouring an aqueous surfactant solution over hands in AHE13 and AHE500.
- Inhalation measures: only the front section (filter plus front sorbent section) was analyzed in AH501; the tubes were analyzed in their entirety (filter, front section, and back section) in AHE13; and OVS tubes were separated into front (filter plus front sorbent) vs. back sorbent sections and analyzed separately in AHE500
- Socks used to measure exposure to feet in AHE13 only
- Patches used to measure head exposure in AH501 only

Patches used in AH501 (typically 100 cm^2 patches) were extrapolated to the total face/neck area. Then, in order to simulate total head exposure, all face/neck values – those measured using the standard wipe method or the patches in AH501 – were adjusted to extrapolate to portions of the head covered by hair; additional extrapolations were also done to areas covered by eye protection or use of respirators. Total dermal exposure was then calculated for each worker by summing exposure across all their body part measurements.

Additionally, as presented at a June 2007 HSRB meeting, to account for potential residue collection method inefficiencies[12], EPA follows the rules below to determine whether to adjust the hand and face/neck field study measurements:

- if measured exposures from hands, face and neck constitute less than 20% of total dermal exposure as an average across all workers, no action is required;
- if measured exposure from hands and face/neck constitutes between 20% and 60% of total dermal exposure, the measurements shall be adjusted upward by a factor of 2, or submission of a validation study to support the residue collection method;
- if measured exposure from hands and face/neck constitutes greater than 60% of total dermal exposure, a validation study demonstrating the efficiency of the residue collection methods is required.

Across all 3 studies, the dermal exposure measurements fell in the second category – on average approximately 51% of total dermal exposure consisted of exposure measured using hand washes and face/neck wipes.

Total inhalation exposures were calculated by adjusting the measured air concentration (i.e., µg/L) using a breathing rate of 16.7 L/min representing light activities (NAFTA, 1998), and total work/monitoring time[13].

3.2.2 Dermal and Inhalation Exposure Results

Following calculation of total dermal and inhalation exposure as described in Section 3.2.1 above, dermal and inhalation "unit exposures" (i.e., µg/lb ai handled) are then calculated by dividing the summed total exposure by the amount of active ingredient handled. Both dermal and inhalation exposure samples are adjusted as appropriate according to recovery results from field fortification samples and, though alternate methods can be applied by data users (e.g., maximum likelihood estimation), residues with results less than analytical limits use the "½ analytical limit" (either ½ LOD or LOQ) convention. Across all 3 studies only a small number of dermal exposure samples were non-detects and none had a non-detect inhalation (OVS front section) sample.

A summary of the 38 monitored workers is provided in Table 5 below, with data plots shown in Figures 8 and 9.

[12] The terminology used to describe this are "method efficiency adjusted" (MEA) or "method efficiency corrected" (MEC)

[13] Inhalation exposure (µg) = collected air residue (µg) x [breathing rate (L/min) ÷ average pump flow rate (L/min)]. Pump flow rate typically 2 L/min.

Table 5. Mechanical Transfer of Liquids Unit Exposure Summary									
Study	**Worker**	**Product Container Type**	**System Type**	**Completely Closed**	**Solution Prepared (gallons)**	**Duration (hours)**	**AaiH (lbs)**	**Unit Exposure (µg/lb ai)**	
								Dermal (MEA)	**Inhalation**
AH501	A	R	S/E	Yes	4075	4.8	1531	1.44	0.0102
		R	S/E	Yes	4175	4.1	1569	6.27	0.0398
		R	S/E	Yes	5285	4.8	1191	2.79	0.0664
	E	R	S/E	Yes	4075	4.8	1531	1.67	0.0113
		R	S/E	Yes	3805	4.1	1430	12.75	0.0587
		R	S/E	Yes	3025	4.5	682	13.07	0.0911
		R	S/E	Yes	5305	4.8	1196	6.30	0.0761
AHE13	A	R	G	Yes	853	6.1	8445	3.28	0.00466
		R	G	Yes	967	9.8	9573	5.73	0.00834
		R	G	Yes	562	10.1	5564	5.54	0.00926
	B	R	G	Yes	633	2.7	6267	2.25	0.0045
		R	G	Yes	970	10.0	9603	4.90	0.0079
		R	G	Yes	443	9.8	6267	5.90	0.0162
	E	R	S/E	No	235	0.6	2327	0.33	0.0004
	F	R	G	Yes	607	7.7	6009	1.45	0.0111
	G	R	G	Yes	446	4.9	4415	0.18	0.0050
AHE500	C	R	S/E	Yes	5880	6.1	2203	0.28	0.0096
	H	NR	S/E	No	3525	3.3	527	0.23	0.0016
	K	R	G	Yes	1500	2.7	87.6	0.59	0.0016
	A	R	G	No	1350	2.5	861	0.12	0.0006
	P	R	G	No	1200	1.5	137	2.89	0.0013
	Q	NR	CB	No	13420	5.9	443	0.01	0.0030
	S	R	G	Yes	3200	3.6	207	1.70	0.0034
	N	R	G	Yes	8075	8.9	815	0.31	0.0018
	U	R	G	No	1250	2.2	514	1.89	0.0038
	AA	R	S/E	No	unknown	3.9	768	0.235	0.0020
		NR	S/E	No	1041	4.7	434	0.943	0.0073
	AB	R	G	Yes	5634	5.6	863	0.42	0.0037
	W	NR	S/E	Yes	540	2.3	495	0.02	0.0006
	AK	NR	S/E	No	2250	2.1	178	1.13	0.0427
	AF	NR	S/E	No	1200	2.2	535	1.27	0.0122
	AH	NR	CB	No	330	2.2	158	0.08	0.0025
	AG	R	G	Yes	2974	8.6	234	7.89	0.0238
	AI	R	G	No	716	2.0	1065	0.03	0.0043
	AM	NR	G	No	3000	4.3	243	6.82	0.0080
	AN	NR	G	Yes	1500	2.5	85.9	3.35	0.0081
	Z	NR	S/E	No	800	1.2	150	0.29	0.0163
	AO	R	G	Yes	2000	2.4	109	0.06	0.0014

Figure 8: Dermal (MEA) Unit Exposures (ug/lb ai)

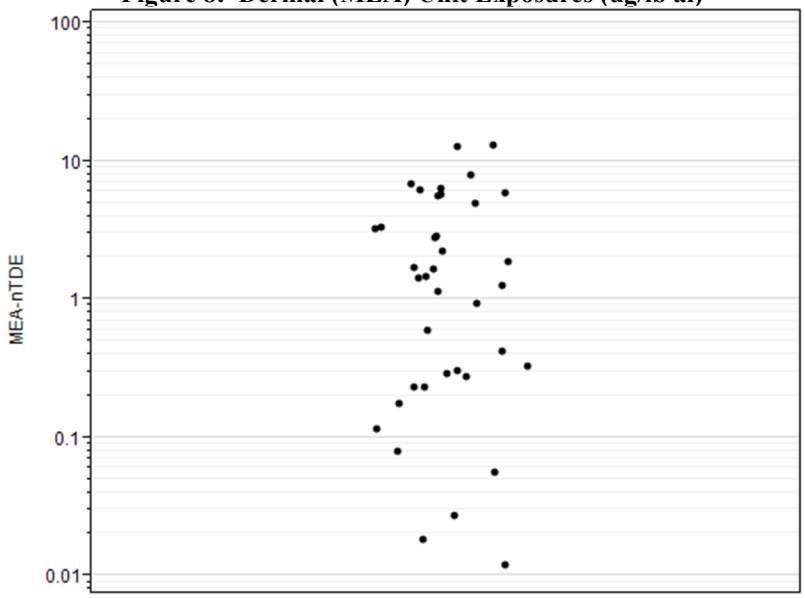
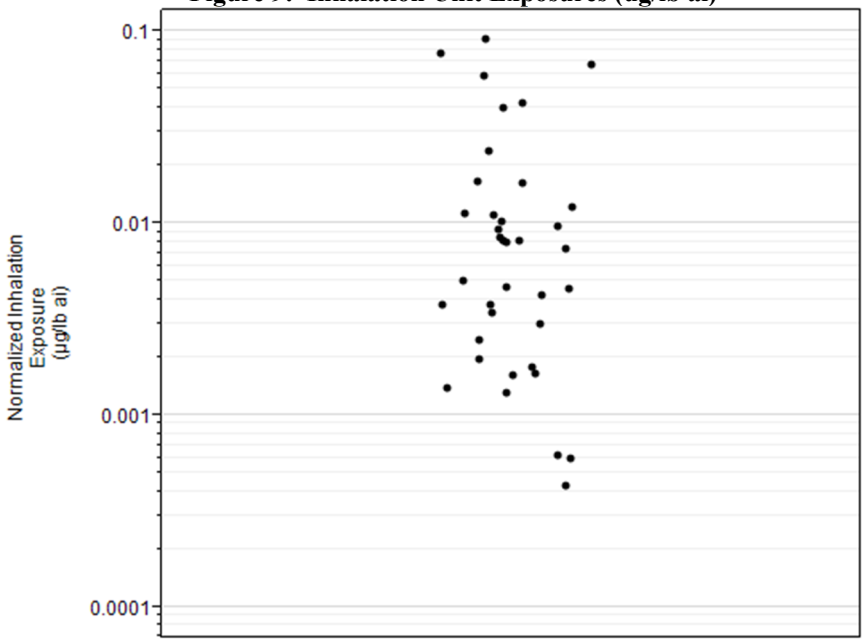


Figure 9: Inhalation Unit Exposures (ug/lb ai)



3.3 Evaluation of Scenario Benchmark Objectives

The AHETF monograph details the extent to which the results of the completed study meet the objectives described in Section 2.1. The monograph states that the primary objective (3-fold accuracy) was not met while the secondary objective (adequate analytical power to evaluate proportionality) was met. EPA agrees with the methodologies used to assess these objectives (Appendix D of Bruce and Holden, 2019a) and has independently confirmed the results by re-

analyzing the data with the AHETF-supplied statistical programming code (AHE1022 Appendix E).

3.3.1 Primary Objective: fold Relative Accuracy (fRA)

The primary benchmark objective for AHETF scenarios is for select dermal exposure 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" or fRA).

First, the AHETF evaluated the structure of the final dataset in comparison to the intended study design. The initial study design envisioned a (cost-effective and analytically-equivalent) data structure. Importantly, as uncertainty can be underestimated if independence is assumed, the AHETF incorporated the potential correlation of monitoring within the same cluster when demonstrating that the planned study design and sample size would satisfy the primary (accuracy) analytical objective. However, when AHE500 was conducted, the AHETF was not able to achieve the intended efficient monitoring configurations due to recruitment difficulties and, from a data analysis perspective resulted in more clusters than intended. Ultimately, analysis of all 3 studies included grouping the data into 16 clusters and additional sub-clusters. Figure 10 below (from AHE1022 Appendix D Table 2) illustrates the clustering used for analysis of the primary objective.

Figure 10: AHE1022 Summary of Data 'Clusters'

Study (Monitoring Area)	Cluster ID	Sub-Cluster ID	MU IDs	Date of MU	Nearest City	State
AH501-M-1	1	1a	1, 2, 3, 4	10/2/99	Corcoran	CA
			6, 7, 8	10/4/99		
AHE13	2	2a	1, 2	10/18/04	Garden City	TX
			3, 4	10/19/04		
			7, 8	10/21/04		
			12, 14, 15	10/25/04		
AHE500 (501/511)	3	3a	M19	6/19/15	Lamar	CO
		3b	M21	6/27/15	Olathe	
	4	4a	M34	6/21/16	Stratton	CO
AHE500 (502/512)	5	5a	M01	11/29/12	Felda	FL
	6	6a	M08	6/13/13	Palm Bay	FL
	7	7a	M33	7/21/16	Nashville	GA
AHE500 (503/513)	8	8a	M07	5/30/13	Howell	MI
	9	9a	M12	5/7/14	Union	MI
		9b	M15	7/4/14	Lennon	
	10	10a	M29	6/4/16	Ionia	MI
AHE500 (504/514)	11	11a	M18	6/9/15	Albion	NE
		11b	M22	7/11/15	Albion	
	12	12a	M26	4/12/16	Fairmont	NE
		12b	M27	4/13/16	Axtell	
		12c	M28	4/15/16	Adams	
		12d	M32	6/23/16	Ravenna	
AHE500 (505/515)	13	13a	M10	10/11/13	Royal City	WA
		13b	M11	11/13/13	Warden	
	14	14a	M17	10/3/14	Moses Lake	WA
AHE500 (506)	15	15a	M03	3/9/13	Morgan City	MS
AHE500 (507)	16	16a	M24	4/4/16	Monterey	LA
			M25	4/5/16		

Next, the AHETF demonstrated both dermal and inhalation unit exposures were shown to fit lognormal distributions reasonably well; lognormal probability plots (and normal probability plots, for comparison) are provided as Attachment 2. Finally, 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 within-cluster correlations.
    - Monitoring conducted in different studies and/or different monitoring areas were in different clusters
    - Monitoring conducted near the same town and no more than a week apart were considered an additional sub-cluster. This occurred in clusters 1, 2, and 16 (see Figure 10).

- Though the AHETF recognized that there were repeat measurements for the same worker (AH501: 2 workers totaling 7 samples; AHE13: 2 workers totaling 6 samples; AHE500: 1 worker totaling 2 samples), the variance component model did not include a 3rd level of clustering to account for potential correlation within the same worker. In correspondence with EPA, the AHETF noted that the sub-clustering overlaps with within-worker clustering so is largely already accounting for within-worker correlation. EPA also had a separate "ad hoc" AHETF analysis validated (Attachment 1) that showed no significant changes when including a 3rd worker-level component.

As presented in Appendix C of the AHETF Governing Document (AHETF, 2008 and AHETF, 2010) and Appendix D of the scenario monograph (Bruce and Holden, 2019a), the 95% confidence limits for each of these estimates were obtained by generating 10,000 parametric bootstrap samples. Then, the fRA_{95} 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.

Utilizing both the final datasets and the statistical programming code submitted by the AHETF (in SAS), EPA confirmed the statistical analysis results in the AHETF submission. EPA then used the revised data based on the method efficiency adjustment (MEA) outlined in Section 3.2.1 in the same AHETF SAS code, substituting the input data with the EPA-revised data (output from SAS provided in Attachment 3). For both the AHETF data and the EPA-revised dataset, the primary benchmark of 3-fold accuracy for select dermal exposure statistics were not met. Accuracy results for inhalation exposure, though not formally part of the primary objective, were better than those for dermal exposure. Results for the AHETF-submitted and EPA-revised dermal exposure data are presented below in Table 6 and inhalation exposure in Table 7.

Table 6. Mechanical Transfer of Liquids – Results of Primary Benchmark Analysis for Dermal Exposure

Statistic	Dermal (EPA-revised)[a]			Dermal (AHETF)		
	Unit Exposure (ug/lb ai)		fRA_{95}	Unit Exposure (ug/lb ai)		fRA_{95}
	Estimate	95% CI		Estimate	95% CI	
GM_S	0.93	0.17 – 1.44	2.9	0.627	0.116 – 0.899	2.8
GSD_S	6.43	3.81 – 12.53	--	6.65	3.87 – 12.10	--
GM_M	0.50	0.23 – 1.09	2.2	0.322	0.147 – 0.703	2.2
GSD_M	6.86	3.99 – 12.16	--	6.82	4.03 – 11.96	--
ICC_1	0.00	0.00 – 0.68	--	0.00	0.00 – 0.66	--
ICC_2	0.67	0.12 – 0.88	--	0.61	0.00 – 0.86	--
GM_S = geometric mean assuming SRS = "exp(average of 38 ln(UE)) values". GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 38 ln(UE)) values" GM_M = variance component model-based geometric mean GSD_M = variance component model-based geometric standard deviation ICC_1 = intra-class correlation for data in the same cluster but different sub-clusters ICC_2 = intra-class correlation for data in the same cluster and sub-cluster						
AM_S	2.75	0.68 – 11.58	4.4	1.93	0.448 – 7.29	4.2
AM_U	5.25	0.75 – 18.4	4.8	3.77	0.503 – 10.8	4.5
AM_M	3.17	0.92 – 13.6	3.8	2.03	0.603 – 8.59	3.8
AM_S = simple average of 38 unit exposures AM_U = arithmetic mean based on $GM_S = GM_S*\exp\{0.5*((\ln GSD_S)\text{^}2\}$ AM_M = variance component model-based arithmetic mean = $GM_M* \exp\{0.5*((\ln GSD_M)\text{^}2\}$						
$P95_S$	12.8	2.82 – 72.7	4.9	8.12	1.87 – 45.2	4.8
$P95_U$	19.8	2.83 – 53.6	4.3	14.1	1.92 – 32.3	4.1

$P95_M$	11.8	3.5 – 39.4	3.4	7.57	2.28 – 24.9	3.3
$P95_S$ = 95th percentile (i.e., the 37th unit exposure out of 38 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.						

Table 7. Open Pour Loading Granules – Results of Primary Benchmark Analysis for Inhalation Exposure

Statistic	Inhalation		
	Unit Exposure (ug/lb ai)		fRA_{95}
	Estimate	95% CI	
GM_S	0.00644	0.00227 – 0.00918	2.0
GSD_S	3.91	2.57 – 5.53	--
GM_M	0.00457	0.00254 – 0.00818	1.8
GSD_M	3.76	2.61 – 5.58	--
ICC_1	0.39	0.00 – 0.73	--
ICC_2	0.52	0.00 – 0.82	--
GM_S = geometric mean assuming SRS = "exp(average of 38 ln(UE)) values". GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 38 ln(UE)) values" GM_M = variance component model-based geometric mean GSD_M = variance component model-based geometric standard deviation ICC_1 = intra-class correlation for data in the same cluster but different sub-clusters ICC_2 = intra-class correlation for data in the same cluster and sub-cluster			
AM_S	0.0153	0.00453 – 0.0246	2.4
AM_U	0.0163	0.00475 – 0.0272	2.4
AM_M	0.0110	0.00525 – 0.0248	2.2
AM_S = simple average of 38 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}			
$P95_S$	0.0761	0.0152 – 0.141	3.1
$P95_U$	0.0606	0.0157 – 0.104	2.6
$P95_M$	0.0403	0.0173 – 0.0951	2.3
$P95_S$ = 95th percentile (i.e., the 37th unit exposure out of 38 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			

As the primary objective was not met – results showed accuracy of the dermal exposures estimates approximately 3.8-fold at the arithmetic mean and 3.4-fold at the 95th percentile – EPA will quantitatively incorporate the uncertainty beyond the 3-fold target in the form of a multiplier to the default dermal exposure estimates used in routine handler exposure assessments (see Table 1).

3.3.2 Secondary Objective: Evaluating Proportionality

The secondary objective of the study design is to evaluate whether characteristics of the resulting data (i.e., the variability and correlation structure, the range of AaiH, etc.) are consistent assumptions used when designing the study to have 80% statistical power to distinguish between complete proportionality from complete independence between dermal exposure and amount of active ingredient handled. Upon completion of the study, the data can be analyzed to determine if it provides a level of precision consistent with that benchmark. Based on analysis of the AHETF submission, as well as results based on EPA revisions to the dermal exposure dataset, this benchmark was met.

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. A proportional relationship would mean that doubling the amount of active ingredient handled would double exposure. 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. For the dermal exposure results, the width of the regression confidence interval for dermal exposure was less than 1.4, demonstrating that the study was adequately powered to detect complete independence from complete proportionality.

As for the primary objective, EPA assessed the secondary objective using both the AHETF-submitted dermal exposure data and using a revised dermal exposure dataset that included the MEA adjustment. In comparison to the results from the AHETF submission, there was no substantive effect on the conclusions regarding the secondary objective when using the EPA-revised dataset. For both, the width of the confidence interval for dermal exposure was less than 1.4, indicating the power to detect complete independence from complete proportionality was greater than 80%. The resulting regression slopes and confidence intervals for (AHETF and EPA-revised) dermal exposure and inhalation exposure are summarized in Table 8.

Table 8. Summary Results of log-log Regression Slopes

Model	Dermal Exposure						Inhalation Exposure		
	AHETF			EPA-Revised					
	Est.	95% CI	CI Width	Est.	95% CI	CI Width	Est.	95% CI	CI Width
Simple Linear	1.45	1.01 – 1.89	0.88	1.36	0.93 – 1.8	0.88	1.16	0.82 – 1.49	0.66
Mixed-Effects	1.25	0.55 – 1.95	1.4	1.17	0.47 – 1.87	1.4	1.14	0.62 – 1.67	1.05

Note: results shown using the Kenward-Rogers denominator degrees of freedom method. AHETF statistical analysis (AHE1022 Appendices D and E) provides results using the Containment method as well. Results were not substantially different.

For both dermal and inhalation exposure the 95% confidence interval slope of the mixed effects model includes 1 and excludes 0, suggesting a proportional relationship between exposure and the amount of active ingredient handled is more consistent with the data than an independent one. See Figures 11 and 12 below (from AHE1022 Appendix D).

Figure 11: Dermal vs AaiH Log-log Regression

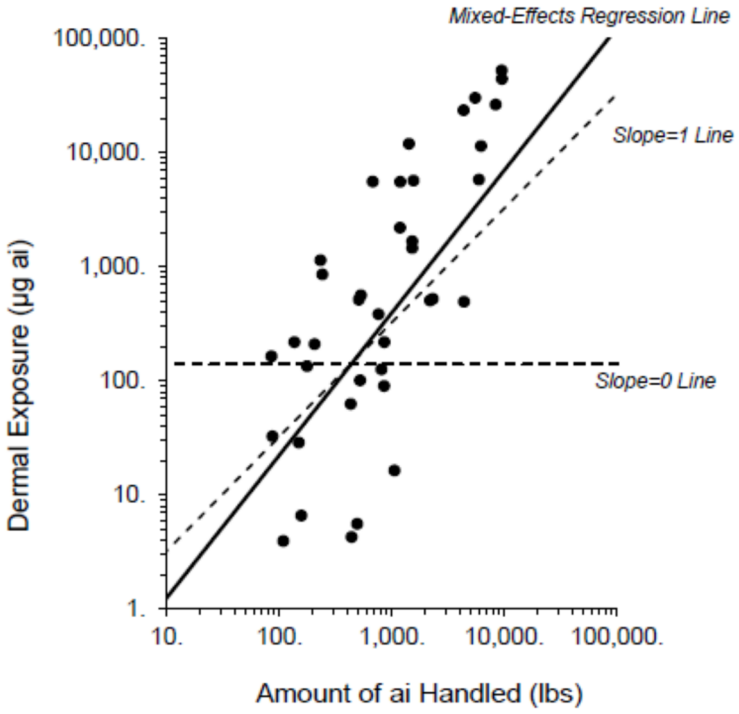
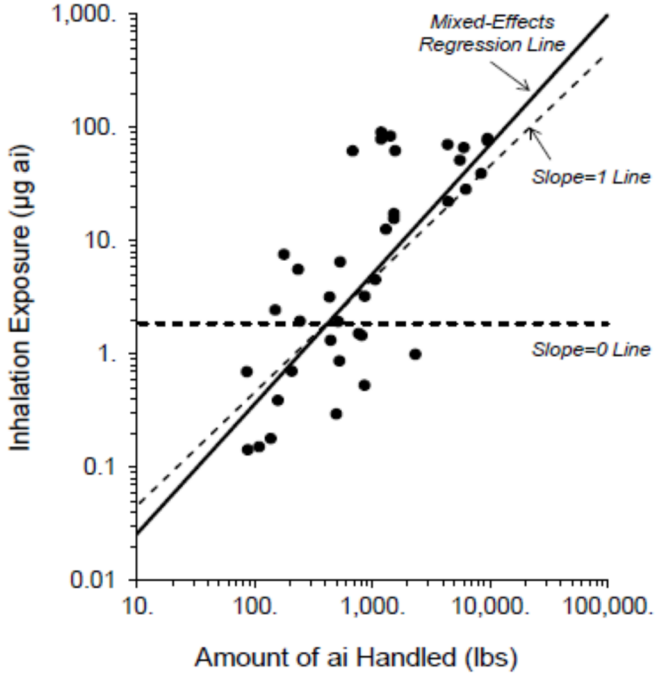


Figure 12: Inhalation vs AaiH Log-log Regression



4.0 Data Generalizations and Limitations

The need for an upgraded generic pesticide handler exposure database has been publicly discussed and established (Christian, 2007). While existing exposure data for mechanically transferring liquid pesticides was available, only two studies totaling 15 samples were considered of sufficient quality for the AHETF database. Therefore, AHE500 was conducted to supplement the existing data and the new composite dataset used in regulatory risk assessments. The data will be used generically for current and future pesticide products to assess exposure and risk for workers mechanically transferring liquid pesticide products into pesticide application equipment. However, certain limitations need to be recognized with respect to collection, use, and interpretation of the exposure data.

4.1 Generic Use in Exposure Assessment

Though specific active ingredients were monitored in AH501, AHE13 and AHE500, the data are considered reliable for use in a generic fashion (i.e., for any pesticide active ingredient). That said, use of the data generically in a regulatory context implies that the pesticide active ingredient being reviewed has a use pattern consistent with the activities and conditions represented by the data for this scenario. Additionally, the availability of this data does not preclude additional consideration or use of acceptable available chemical- and scenario-specific studies, biomonitoring studies, or other circumstances in which exposure data can be acceptably used in lieu of these data.

Because this data represents some specific use patterns, the following need to be considered when using the data in regulatory risk assessments:

- Use of suction/extraction style systems with proper rinsing of the extraction probe within the product container
    - As the AHETF identified that removal of the extraction probe prior to rinsing can lead to increased exposure potential, pesticide use instructions, training, or product labels will need to be more specific as to this aspect of suction/extraction style closed systems. The results show that not rinsing the probes prior to their removal is inconsistent with the closed system requirements.
    - As described throughout this review, all dermal exposures (e.g., Tables 1, 5, and 6) represent workers who did not remove unrinsed extraction probes when using suction/extraction systems (n=38). AHETF did submit all the data to EPA, including the 18 workers who removed unrinsed extraction probes. While those data are not proposed for use in assessing risk for workers mechanically transferring liquid pesticides with closed systems, the data may have other regulatory uses, including risk assessment of workers that use probes to extract liquids without engineering controls. EPA utilized AHETF's SAS programming from Bruce and Holden, 2019b to estimate the distribution of exposures for workers using suction/extraction systems without rinsing probes. The following figure and table provide a brief summary of all the exposure data (output from SAS is provided in Attachment 3).

Figure 13: Dermal and Inhalation Exposures with and without Unrinsed Probes

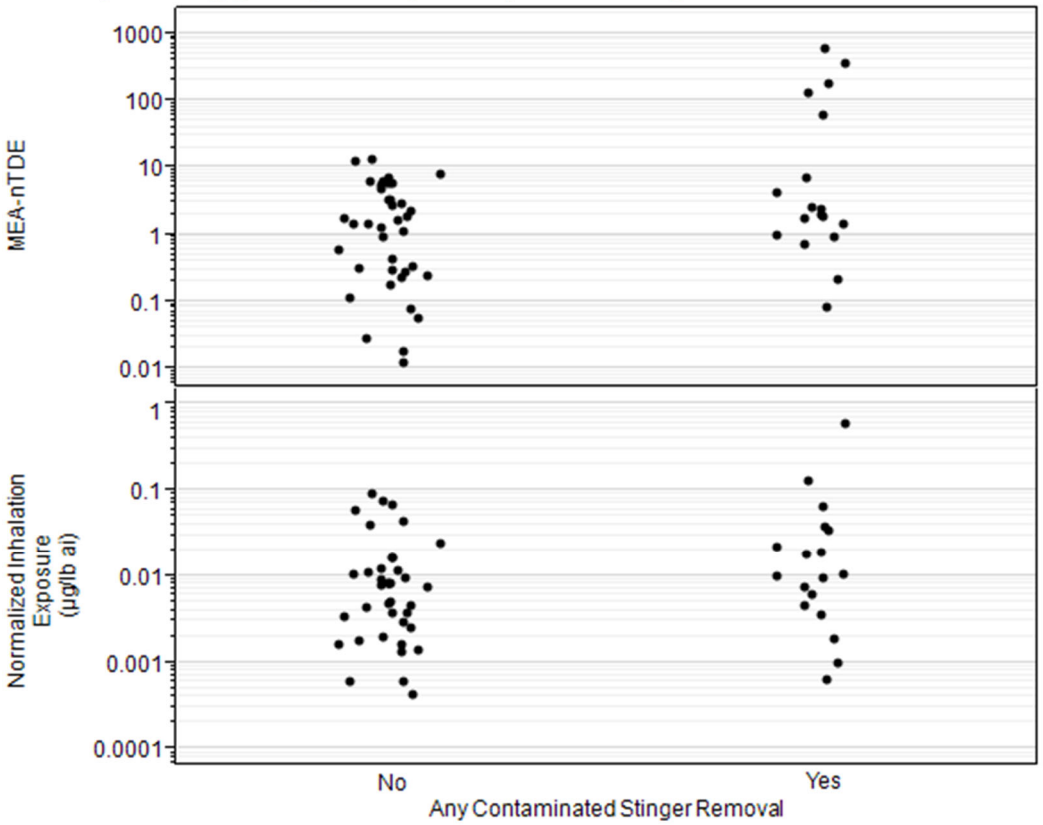


Table 9. Comparison of Data with and without Unrinsed Probe Extraction				
Statistic	**Dermal (ug/lb ai)**		**Inhalation (ug/lb ai)**	
	Mechanical Transfer, excluding unrinsed extraction probe (n=38)[1]	**Non-Engineering Control S/E Transfer[2] (n=18)**	**Mechanical Transfer, excluding unrinsed extraction probe (n=38)[1]**	**Non-Engineering Control S/E Transfer[2] (n=18)**
Arithmetic Mean	4.02	2600	0.011	0.078
95th Percentile	13.4	2670	0.0403	0.3

[1] From Table 1, EPA-revised (MEA) mixed model estimates, with fRA-adjustment.
[2] Mixed model estimates from Bruce and Holden 2019b, substituting EPA-revised (MEA) dermal data and including fRA-adjustment: AM_M 350 ug/lb ai * (22.3/3) = 2600 ug/lb ai and $P95_M$ 847 ug/lb ai * (9.44/3) = 2670 ug/lb ai.

- Use of chemical-resistant gloves
    - EPA's Worker Protection Standard allows – for certain categories of pesticides – for reduction in required PPE when using closed systems[14]. For example, for some pesticides, whereas workers would normally be required to wear chemical-resistant gloves, they would not be required if a closed system is used to load the

[14] Both the regulation existing at the time AHE500 was conducted (40 CFR §170.240) and the revised version (40 CFR §170.607) include the PPE exception.

chemical. However, as previously described, per protocol, the AHETF data represents workers wearing chemical-resistant gloves during the entire mechanical transfer process. As a good industrial hygiene practice the AHETF believes that EPA should consider removing the exception to the requirement to wear chemical-resistant gloves when using closed systems and that their data best matches that situation.

Data users need to be cognizant that risk assessments using the AHETF data "as-is" represent workers wearing chemical-resistant gloves, despite the "PPE exception criteria" outlined in EPA's Worker Protection Standard. Due to the potential for workers to take advantage of the regulation that relaxes the requirement to wear chemical-resistant gloves when mechanically transferring liquid pesticides, EPA altered the AHETF data to back-calculate "bare hand" exposures by assuming chemical-resistant gloves provide 90% protection. Revised dermal exposure estimates representing "bare hand" exposure were substituted in the AHETF's SAS programs (Bruce and Holden, 2019a and 2019b) and summary results are presented in the table below. These values can then be used by risk assessors that need to consider exposures during mechanical transfer of liquid pesticides with and without chemical-resistant gloves.

Table 9. Comparison of Data with and without Unrinsed Probe Extraction

Statistic	Dermal (ug/lb ai)			
	With Chemical-resistant Gloves		Without Chemical-resistant Gloves	
	Mechanical Transfer, excluding unrinsed extraction probe (n=38)[1]	Non-Engineering Control S/E Transfer[1] (n=18)	Mechanical Transfer, excluding unrinsed extraction probe (n=38)[2]	Non-Engineering Control S/E Transfer[3] (n=18)
Arithmetic Mean	4.02	2600	30.44	33,526
95th Percentile	13.4	2670	96.6	27,666

[1] From Table 9.
[2] Uses SAS programming from Bruce and Holden 2019a with substitution of EPA-revised MEA data and additional revision for "bare hands" by dividing hand exposure values by 0.1 (i.e., chemical-resistant gloves assumed to provide 90% protection). Includes fRA adjustment: AM_M 22.83 ug/lb ai * (4.5/3) = 30.44 ug/lb ai and $P95_M$ 80.6 ug/lb ai * (3.6/3) = 96.6 ug/lb ai.
[3] Mixed model estimates from Bruce and Holden 2019b with substitution of EPA-revised MEA data and additional revision for "bare hands" by dividing hand exposure values by 0.1 (i.e., chemical-resistant gloves assumed to provide 90% protection). Includes fRA adjustment: AM_M 3618 ug/lb ai * (27.8/3) = 33526 ug/lb ai and $P95_M$ 7757 ug/lb ai * (10.7/3) = 27666 ug/lb ai.

4.2 Applicability of AHETF Data for Volatile Chemicals

The data generated in this study are acceptable to use as surrogate data for assessing mechanical transfer of other conventional liquid pesticides, which are generally chemicals of low volatility. EPA does not expected that this dataset would be used to support regulatory decisions for high volatility pesticides (e.g., fumigants).

4.3 Use of "Unit Exposures"

As previously described, for the purposes of pesticide handler exposure assessment, dermal and inhalation exposures are expressed as "unit exposures" – exposure per mass of pesticide handled. This format provides a very simple exposure model from which to extrapolate data generically to other chemicals with different application rates. Underlying use of the data in that format is the assumption that exposure is proportional to the amount of active ingredient handled. In other words, if one doubles the amount of pesticide handled, exposure is assumed to double.

For this AHETF data, statistical analyses demonstrated that the data were more consistent with a proportional relationship between exposure and the amount of active ingredient handled than an independent one. Thus, EPA will continue to recommend use of the exposure data normalized by the amount of active ingredient handled as a default condition.

4.4 Representativeness and Extrapolation to Exposed Population

Targeting and selecting specific monitoring characteristics (i.e., "purposive sampling" or "diversity selection") as well as certain restrictions necessary for logistical purposes (e.g., selection of certain monitoring areas known to mechanically transfer liquid pesticides to ensure a large pool of potential participants, requiring potential participants to use certain pesticides to ensure laboratory analysis of exposure monitoring matrices, and requiring selection of workers who normally wear the scenario-defined minimal PPE), render the data neither purely observational nor random to allow for characterization of the dataset as representative of the population of workers mechanically transferring liquid pesticides. It is important to recognize this as a limitation when making use of the data.

It appears however, that the final dataset has captured routine behavior as well as limiting the likelihood of "low-end" or non-detect exposures via certain scripting aspects (e.g., adequate product loading/transferring durations), both of which are valuable for regulatory assessment purposes. And, as outlined in the AHE500 study submission and EPA's review of AHE500, an informal survey of local experts did not suggest that the monitoring was atypical for each monitoring area. Also, construction and use of master lists of potential growers/employers/companies 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.

5.0 Conclusions

EPA has reviewed the AHETF Mechanical Transfer of Liquids scenario monograph and concurs with the technical analysis of the data as well as the evaluation of the statistical benchmark objectives. Conclusions are as follows:

- Deficiencies in the data EPA currently uses to estimate dermal and inhalation exposure for mechanical transfer of liquid pesticides have been recognized and the need for new data established.
- The primary (quantitative) objective was not met: estimates of the arithmetic mean and 95th percentile dermal exposures were not shown to be accurate within 3-fold with 95%

confidence. As a result, EPA will incorporate a multiplier to the dermal exposure data to incorporate the additional uncertainty beyond the target 3-fold level.

- The secondary (quantitative) objective was met: results of the log-log regression analysis demonstrate that the study was adequately powered to distinguish proportionality from independence between dermal exposure and AaiH.
- The relationship between both dermal and inhalation exposure and the amount of active ingredient handled was more consistent with a proportional relationship than an independent one. EPA will continue to recommend using exposures normalized by AaiH as a default condition for exposure assessment purposes.
- The AHETF data are representative of two specific conditions:
    - Workers wearing chemical-resistant gloves during all activities, not necessarily of the WPS exception criteria for closed systems that might allow workers to handle products with bare hands; and
    - Proper rinsing of chemical extraction probes when using suction/extraction type systems
- The AHETF data developed and outlined in the monograph and this review represent the most reliable data for assessing exposure during mechanical transfer of liquid pesticides to application equipment.

6.0 References

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Attachment 1
Statistical Review of Issues on Closed System Loading of Liquids

MEMORANDUM

To:	Matthew Crowley, EPA
From:	Jonathan Cohen, ICF
Cc:	Diana Hsieh, EPA; David Miller, EPA; Dave Burch, ICF
Date:	November 12, 2019
Re:	Statistical Review of Issues on Closed System Loading of Liquids

Summary

ICF was asked by EPA to review the Agricultural Handler Exposure Task Force (AHETF) report "Closed System Loading of Liquids (CSLL), Rationale for a Single Monograph: Mechanical Transfer of Liquids (MTL)", 7 October, 2019, with particular focus on the validity of the analyses used to justify combining the data for the returnable and non-returnable containers and excluding data from monitoring units where the handlers removed "contaminated stingers," which are transfer probes contaminated with pesticide. ICF found that both findings were supported by the data.

AHETF Analyses

The combined data set consists of 56 monitoring units (MUs), of which 37 had returnable containers ("R") and 19 had non-returnable containers ("NR"). Of the 56 MUs, 18 of them were cases where the handler removed "contaminated stingers," which are transfer probes contaminated with pesticide, and the other 38 MUs had no removal of contaminated stingers. To account for potential clustering, the MUs were first clustered by the combination of study, monitoring area, and year. The MUs less than a week apart were then clustered into sub-clusters.

AHETF did an analysis of variance of the logarithms of the normalized dermal and inhalation exposure (exposure divided by amount of amount of active ingredient handled) to compare the geometric means between R and NR scenarios and found that the geometric means were not statistically significantly different at the 5% level. For normalized total dermal exposure, the ratio of the estimated geometric mean of NR to the estimated geometric mean of R was 1.96 with a p-value of 0.3547. More precisely, the "geometric mean of NR" is an abbreviation for the geometric mean of the normalized exposure for MUs using non-returnable containers, and similarly for other geometric means. For normalized hand exposure, the ratio of the estimated geometric mean of NR to the estimated geometric mean of R was

2.07 with a p-value of 0.3471. For normalized inhalation exposure, the ratio of the estimated geometric mean of NR to the estimated geometric mean of R was 1.69 with a p-value of 0.2919. The fitted statistical model was a log-normal mixed model with nested random effects for the two levels of clustering. This analysis of variance was used to justify combining the R and NR data.

AHETF used the same mixed model analysis of variance of all 56 MUs to compare the normalized total dermal exposure and normalized hand wash exposure between MUs with removal of contaminated stingers ("RCS") and MUs without RCS ("No RCS"). They found that the geometric means were statistically significantly different at the 5% level. For normalized total dermal exposure, the ratio of the estimated geometric mean of RCS to the estimated geometric mean of No RCS was 5.81 with a p-value of 0.0015. For normalized hand exposure, the ratio of the estimated geometric mean of RCS to the estimated geometric mean of No RCS was 3.83 with a p-value of 0.0243. This analysis of variance was used to justify exclusion of the MUs with RCS.

ICF was given a copy of the data, SAS code, and SAS outputs from the AHETF analyses. ICF reviewed the SAS code and reran the SAS programs. ICF determined that the code was correct, reran the code on the data, and obtained the same results. ICF also identified a few issues to be investigated, as discussed below.

Clustering by worker

The AHETF analyses clustered the data spatially and temporally but did not account for potential correlations between data from the same worker. AHETF were asked about this by EPA staff and AHETF responded that they did not use worker in the statistical modeling as a third nested sub-sub-cluster cluster partially to avoid overcomplicating the clustering model and also because the within subcluster correlation was quite large. However, to address this issue, AHETF reran the benchmark model for the 38 MUs without removal of contaminated stingers using a third nested sub-sub-cluster and submitted the results to EPA. The results using the third nested sub-sub-cluster were very similar to the results with only clusters and sub-clusters. For example, for normalized total dermal exposure the original analysis with clusters and sub-clusters had an estimated geometric mean of 0.314 (fold relative accuracy 2.116) and the revised analysis with clusters, sub-clusters, and sub-sub-clusters had an estimated geometric mean of 0.318 (fold relative accuracy 2.132). Also for normalized total dermal exposure, the original analysis with clusters and sub-clusters had an estimated arithmetic mean of 1.838 (fold relative accuracy 3.554) and the revised analysis with clusters, sub-clusters, and sub-sub-clusters had an estimated arithmetic mean of 1.850 (fold relative accuracy 3.400).

ICF was given a copy of the data, SAS code, and SAS outputs from the AHETF analyses with a worker sub-sub-cluster. ICF reviewed the SAS code and reran the SAS programs. ICF determined that the code was correct, reran the code on the data, and obtained the same results.

ICF was concerned that the worker random effect might have an impact on the analysis of variance of the effects of returnable versus non-returnable containers for all 56 MUs. The original analysis with clusters and sub-clusters showed that the estimated ratio of the geometric means for normalized total dermal exposure was 1.96 (p-value 0.3547) and the estimated ratio of the geometric means for normalized hand exposure was 2.07 (p-value 0.3471). ICF reran the analysis to include a worker effect. However, instead of forcing the worker effect to be nested within the sub-cluster random effect, ICF's analysis treated the worker effect as an independent random effect. This choice only impacts cluster 11 since for that cluster the same worker was assigned to different sub-clusters 11a and 11b because those

MUs were separated by about one month. The revised analysis with clusters, sub-clusters, and worker effects showed that the estimated ratio of the geometric means for normalized total dermal exposure was 1.84 (p-value 0.3154) and the estimated ratio of the geometric means for normalized hand exposure was 1.89 (p-value 0.3168). Therefore, the impact of including a worker effect does not change the numerical results by very much and leads to the same conclusion of no statistically significant difference at the 5% level between R and NR.

Equal Variances Assumption

The mixed model analyses of variance used by AHETF to compare the R and NR geometric means and to compare the RCS and No RCS geometric means assumed that the random effects variances were the same for all the MUs. Note that these random effects are for the logarithms of the normalized exposure. Examination of Figure 2 of the report suggests that this equal variance assumption may be unrealistic and that it is plausible that the R and NR data might have unequal variances. ICF repeated the mixed model analyses of variance on the 56 MUs using an alternative mixed model where the three random effects (cluster, sub-cluster, and residual) can have different variances for the R and NR MUs.

If equal variances are assumed for the R and NR data, then for normalized total dermal exposure the ratio of the estimated geometric mean of NR to the estimated geometric mean of R is 1.96 with a p-value of 0.3547. Under the same assumption, for normalized hand exposure the ratio of the estimated geometric mean of NR to the estimated geometric mean of R is 2.07 with a p-value of 0.3471. ICF repeated the analysis allowing for different variances between the R and NR groups of the random effects for the cluster, sub-cluster, and residual. Using this alternative model, for normalized total dermal exposure the ratio of the estimated geometric mean of NR to the estimated geometric mean of R is 2.22 with a p-value of 0.3721. For normalized hand exposure the ratio of the estimated geometric mean of NR to the estimated geometric mean of R is 2.64 with a p-value of 0.3428. Therefore, eliminating the equal variances assumption did not change the conclusion that the geometric means for R and NR are not significantly different at the 5% level.

A similar result was found for the comparison between the RCS and No RCS data. If equal variances are assumed for the R and NR data, then for normalized total dermal exposure, the ratio of the estimated geometric mean of RCS to the estimated geometric mean of No RCS is 5.81 with a p-value of 0.0015. Under the same assumption, for normalized hand exposure, the ratio of the estimated geometric mean of RCS to the estimated geometric mean of No RCS is 3.83 with a p-value of 0.0243. If equal variances are not assumed for the R and NR data, then for normalized total dermal exposure, the ratio of the estimated geometric mean of RCS to the estimated geometric mean of No RCS is 6.17 with a p-value of 0.0222. If equal variances for the R and NR data are not assumed for normalized hand exposure, the ratio of the estimated geometric mean of RCS to the estimated geometric mean of No RCS is 6.00 with a p-value of 0.0225. Therefore, eliminating the equal variances assumption did not change the conclusion that the geometric means for RCS and No RCS are significantly different at the 5% level.

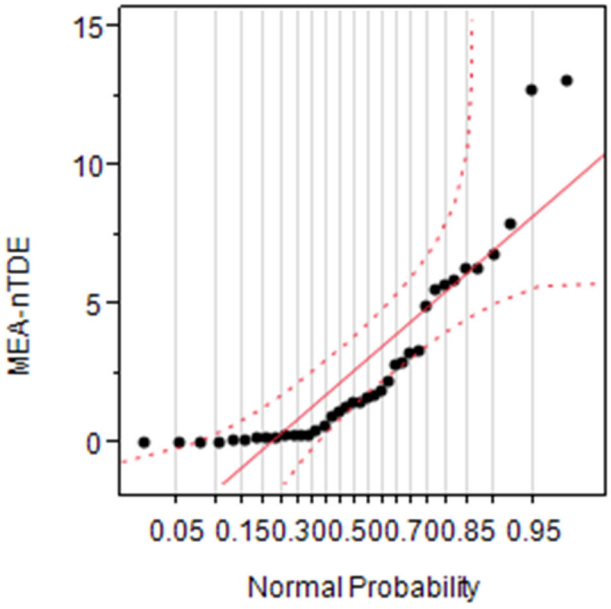
Potential Outlier

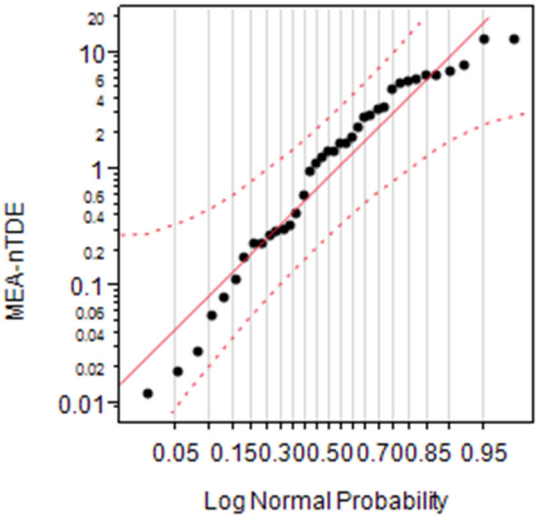
ICF examined the impact of the potential outlier for MU M30 in cluster 19, sub-cluster 19a, a returnable container MU, which had very high normalized exposure values compared to other returnable container MUs. For that MU, the total normalized dermal exposure was 195.6 µg/lb ai and the normalized inhalation exposure was 0.592 µg/lb ai. M30 was a MU with removal of a contaminated stinger. The normalized dermal exposure is more than 20 times higher than the next highest R normalized dermal

exposure and the normalized inhalation exposure is more than 6 times higher than the next highest R normalized inhalation exposure. To evaluate whether the results of the AHETF statistical analyses were strongly related to this potential outlier, ICF repeated some of the analyses of the total dermal exposure data after excluding this MU.

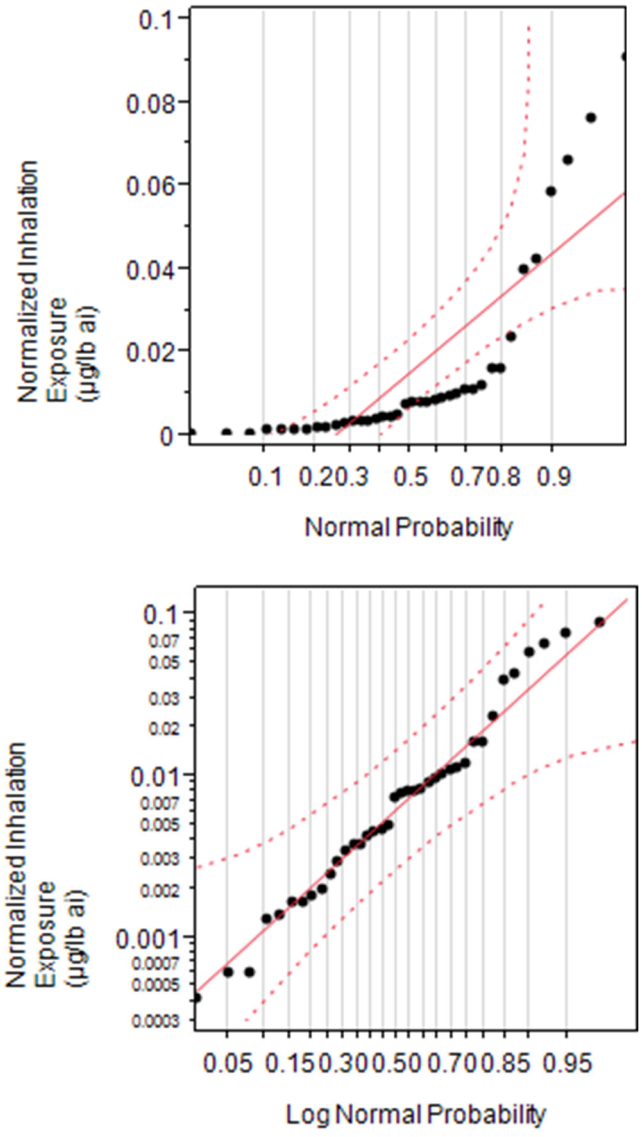
As noted above, for normalized total dermal exposure using all 56 MUs and assuming equal variances for the R and NR data, the ratio of the estimated geometric mean of NR to the estimated geometric mean of R is 1.96 with a p-value of 0.3547; if the potential outlier is removed, then the ratio of the estimated geometric means increases to 2.44 with a p-value of 0.2081. For normalized total dermal exposure using all 56 MUs and assuming equal variances for the R and NR data, the ratio of the estimated geometric mean of RCS to the estimated geometric mean of No RCS is 5.81 with a p-value of 0.0015; if the potential outlier is removed, then the ratio of the estimated geometric means decreases to 5.15 with a p-value of 0.0026. For normalized total dermal exposure using all 56 MUs and not assuming equal variances for the R and NR data, the ratio of the estimated geometric mean of NR to the estimated geometric mean of R is 2.22 with a p-value of 0.3721; if the potential outlier is removed, then the ratio of the estimated geometric means increases to 2.93 with a p-value of 0.2086. All these results show that the main conclusions of no statistically significant differences between R and NR and statistically significant differences between RCS and No RCS do not entirely rely on the potential outlier.

Attachment 2
Normal and Lognormal Probability Plots of Dermal Unit Exposures (ug/lb ai)





Normal and Lognormal Probability Plots of Inhalation Unit Exposures



Attachment 3
Output from AHETF SAS program substituting input data with EPA-revised data

Re-run of "MTL w/o RCS" (n=38) with EPA's MEA revision (Section 3.3.1 and Table 6)

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

NFvar	GEvar	Component	Variance	PctTot	SD	GSD
REvar						
DermAaiH	NrmDerm	V1	0.00000	0.000	0.00000	1.00000
Derm			2.48713	67.062	1.57706	4.84072
			1.22156	32.938	1.10524	3.01996
			3.70869	100.000	1.92580	6.86061

Log-Scale Residual Variance Structure

Analysis of Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

REvar=Derm NFvar=DermAaiH GEvar=NrmDerm

Summary of Estimates and Bootstrap Confidence Intervals

(10000 Bootstrap Replicates, Seed = 81633215)

Analysis of Normalized Exposure

Statistic	Est	LoCL	HiCL	HiCL/ LoCL	HiCL/ Est	fRA95
GSDs	6.42716	3.80697	12.53149	.	.	.
GSDm	6.86061	3.98774	12.15596	.	.	.
TGC1	0.00000	0.00000	0.67553	.	.	.
TGC2	0.67062	0.12122	0.88091	.	.	.
GMs	0.92948	0.17213	1.43625	5.39995	1.54522	2.88468
GMm	0.49559	0.22633	1.08715	2.18973	2.19363	2.19149
AMs	2.74713	0.67749	11.57562	4.05486	4.21371	4.38146
AMu	5.24705	0.74875	18.39641	7.00777	3.50605	4.77733
AMm	3.16562	0.92277	13.64417	3.43055	4.31011	3.80635
P95s	12.74632	2.81764	72.70525	4.52376	5.70402	4.93977
P95u	19.82964	2.83004	53.60045	7.00684	2.70305	4.29936

	11.77119	3.49907	39.41133	3.36409	3.34812	3.35026
P95m	6.42716	4.19491	9.82020	.	.	.
	0.92948	0.51026	1.69407	1.82157	1.82260	1.82226
iGSDs	2.74713	1.71629	15.38531	1.60062	5.60050	3.00963
iGMs	5.24705	2.03370	15.14053	2.58005	2.88553	2.71065
iAMs	12.74632	6.95094	96.45140	1.83376	7.56700	3.91850
iAMu	19.82964	7.73488	49.71122	2.56366	2.50691	2.53085
iP95s						
iP95u						

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

NFvar	GEvar	Component	Variance	PctTot
DermAaiH	NrmDerm	V1	0.00000	0.000
			2.64634	68.638
			1.20915	31.362
			3.85548	100.000

REvar

Derm

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

REvar	NFvar	GEvar	Log-Scale Residual Variance Structure	PDFM	Parameter	Est	LoCL	HiCL	Width
Derm	DermAaiH	NrmDerm	Mixed	KenRog	A	-1.73782	-6.05136	2.57572	.
						1.16926	0.47205	1.86646	1.39441
Derm	DermAaiH	NrmDerm	Mixed	Contain	A	-1.73782	-6.49352	3.01788	.
						1.16926	0.47561	1.86290	1.38728
Derm	DermAaiH	NrmDerm	Simple	*	A	-2.53592	-5.55425	0.48241	.
						1.36453	0.92661	1.80245	0.87584

Analysis of Exposure vs NF

Regression Coefficients and CLs

V2

V3

Vtot

Derm	DermAaiH	NrmDerm	Slope=0	KenRog		A	5.37987	4.41652	6.34322	.
							0.00000	.	.	.
Derm	DermAaiH	NrmDerm	Slope=1	KenRog		A	-0.70200	-1.51990	0.11591	.
							1.00000	.	.	.

B

B

MUID	ID	Sub ClusID	MonDate	Town	State	Nr CSrems	Derm AaiH
	2	2a	10/20/2004	Garden City	TX	3	7504.0
	2	2a	10/20/2004	Garden City	TX	4	9504.0
	2	2a	10/25/2004	Garden City	TX	2	1713.0
5	2	2a	10/25/2004	Garden City	TX	1	2426.0
6	2	2a	10/26/2004	Garden City	TX	2	2683.0
Clus							
11	2	2a	10/26/2004	Garden City	TX	1	4851.0
13	20	20a	03/12/2013	Winnie	TX	11	660.0
16	15	15a	03/14/2013	Marks	MS	2	139.0
17	6	6b	04/26/2013	Moore Haven	FL	1	548.0
M04	13	13c	09/25/2013	Toledo	WA	1	176.0
M05	17	17a	06/18/2014	Eloy	AZ	1	135.0
M06	17	17a	06/19/2014	Eloy	AZ	2	1428.0
M09	14	14a	10/02/2014	Moses Lake	WA	5	445.0
M13	18	18a	06/22/2015	Lake Odessa	MI	4	337.0
M14	19	19a	06/08/2016	Mt. Angel	OR	4	91.9
M16	10	10b	06/14/2016	Marlette	MI	1	76.4
M20	21	21b	10/11/2016	Runnelstown	MS	6	286.0
M30	7	7b	10/14/2016	St. Matthews	SC	1	89.8
M31							
M35							
M36							

Listing of Relevant Input Data
CSLL Scenario: Just RCS

---------- REvar=Derm NFvar=DermAaiH GEvar=NrmDerm ----------

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

	Estimate
	75.5749836
	161.6923258

	5.1115643
	13.1149671
	0.0845336
	0.0845336
	0.2110842
	1.0113333
	2.1561919
	59.1632048
	359.9782372
	603.5732984
	603.5732984

---------- REvar=Inh NFvar=InhAaiH GEvar=NrmInh ----------

Statistic	Estimate
AMs	0.0541328
GMs	0.1379033
GSDs	0.0122697
Min	5.4317883
P05s	0.0006331
P10s	0.0006331
P25s	0.0009754
P50s	0.0044943
P75s	0.0103847
P90s	0.0335575
P95s	0.1307972
Max	0.5919643
	0.5919643

Statistic	NFvar	GEvar	Component	Variance	PctTot	SD	GSD
AMs							
SDs							
GMs							
GSDs							
Min							
P05s							
P10s							
P25s							
P50s							
P75s							

	DermAaiH	NrmDerm	V1	4.88726	71.533	2.21071	9.1222
Derm				0.05734	0.839	0.23946	1.2706
				1.88753	27.627	1.37387	3.9506
				6.83212	100.000	2.61383	13.6513
	InhAaiH	NrmInh	V1	1.27001	44.088	1.12695	3.0862
Inh				0.00646	0.224	0.08035	1.0837
				1.60418	55.688	1.26656	3.5486
				2.88065	100.000	1.69725	5.4589

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

---------- REvar=Derm NFvar=DermAaiH GEvar=NrmDerm ----------

Summary of Estimates and Bootstrap Confidence Intervals

(M10000 Bootstrap Replicates, Seed = 81653215)

Analysis of Normalized Exposure

Statistic	Est	LoCL	HiCL	LoCL	HiCL/ Est	fRA95
Vtot	13.11497	4.64910	36.69120	.	.	.
GSDs	13.65128	4.80678	38.37658	.	.	.
GSDm	0.71533	0.00000	0.85490	.	.	.
TGC1	0.02948	0.00000	0.88166	.	.	.
TGC2	5.11156	1.91707	70.51263	2.6663	13.7947	6.0702
GMs	11.49606	2.65329	48.54045	4.3328	4.2224	4.2802
GMm	75.57498	13.55229	1864.70939	5.5765	24.6736	19.4034
AMs	140.27582	19.33111	12639.03247	7.2565	90.1013	23.1697
AMu	350.04660	23.34135	11637.73656	14.9968	33.2462	22.2882
AMm	603.57330	78.64227	24575.04842	7.6749	40.7159	18.5787
P95s	352.46604	69.78300	10483.97641	5.0509	29.7446	12.1717
P95u	846.72614	86.11298	7533.84077	9.8327	8.8976	9.4360
P95m	13.11497	5.52364	31.31202	.	.	.
iGSDs	5.11156	1.55328	16.75357	3.2908	3.2776	3.2852
iGMs	75.57498	9.43215	748.80912	8.0125	9.9082	12.2196
iAMs	140.27582	14.65593	2443.86198	9.5713	17.4218	12.3967
iAMu						

	603.57330	52.33080	11151.34791	11.5338	18.4755	18.9591
iP95s	352.46604	53.66256	2259.76050	6.5682	6.4113	6.4932

iP95u

---------- REvar=Inh NFvar=InhAaiH GEvar=NrmInh ----------

Statistic	Est	LoCL	HiCL	LoCL	HiCL/ Est	fRA95
	5.43179	2.92676	9.72536	.	.	.
	5.45891	2.99183	10.48603	.	.	.
GSDs	0.44088	0.00000	0.73311	.	.	.
GSDm	0.00401	0.00000	0.76784	.	.	.
ICC1	0.01227	0.00651	0.05214	1.8857	4.24921	2.83212
ICC2	0.01838	0.00720	0.04594	2.5521	2.49973	2.51896
GMs	0.05413	0.01703	0.25929	3.1794	4.78996	4.10099
GMm	0.05137	0.01974	0.36065	2.6023	7.02079	4.25122
AMs	0.07759	0.02089	0.37469	3.7146	4.82900	4.19911
AMu	0.59196	0.07046	2.75805	8.4015	4.65915	6.94330
AMm	0.19848	0.06952	1.23342	2.8549	6.21446	4.21281
P95s	0.29972	0.07392	1.19862	4.0549	3.99913	4.03200
P95u	5.43179	3.07624	9.62597	.	.	.
P95m	0.01227	0.00561	0.02678	2.1884	2.18264	2.18598
iGSDs	0.05413	0.01420	0.15909	3.8119	2.93882	3.46391
iGMs	0.05137	0.01629	0.19936	3.1528	3.88106	3.48780
iAMs	0.59196	0.05663	1.92358	10.4530	3.24949	6.92113
iAMu	0.19848	0.05757	0.67341	3.4473	3.39293	3.42136

iP95s----------

iP95u

Est/

Re-run of "MTL w/o RCS" (n=38) with EPA's MEA revision and "bare hands" back-calculation (Section 4.1 and Table 10)

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

NFvar	GEvar	Component	Variance	PctTot	SD	GSD
REvar						
DermAaiH	NrmDerm	V1	0.00000	0.000	0.00000	1.00000
			3.78139	88.096	1.94458	6.99069
Derm			0.51098	11.904	0.71483	2.04383
			4.29236	100.000	2.07180	7.93912
InhAaiH	NrmInh	V1	0.48397	28.931	0.69568	2.00508
			0.41331	24.707	0.64289	1.90197
Inh			0.77557	46.362	0.88067	2.41251
			1.67286	100.000	1.29339	3.64512

~~Log-Scale Residual Variance Structure~~

Analysis of Normalized Exposure

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

---------- REvar=Derm NFvar=DermAaiH GEvar=NrmDerm ----------

Statistic	Est	LoCL	HiCL	HiCL/ LoCL	HiCL/ Est	fRA95
V3						
Vtot	6.37164	4.02106	15.87286	.	.	.
	7.93912	4.43968	14.50475	.	.	.
GSDs	0.00000	0.00000	0.67327	.	.	.
GSDm	0.88096	0.55048	0.95339	.	.	.
V2	4.24395	0.87907	8.21606	4.82775	1.93595	3.05905
V3	2.66909	1.15447	6.13159	2.31197	2.29726	2.30724
Vtot						
GMm						

Summary of Estimates and Bootstrap Confidence Intervals

(10000 Bootstrap Replicates, Seed = 81653215)

Analysis of Normalized Exposure

	12.92502	4.09146	88.29202	3.15902	6.83109	5.18759
AMs	23.57484	4.42317	173.47011	5.32985	7.35827	5.94422
	22.82643	5.87234	116.14569	3.88711	5.08821	4.48717
AMu	65.70617	16.77470	583.15261	3.91698	8.87516	5.72666
AMm	89.25760	16.69332	408.27208	5.34691	4.57409	4.89102
P95s	80.60400	22.36066	290.04622	3.60472	3.59841	3.59951
P95u	6.37164	4.17515	9.68801	.	.	.
P95m	4.24395	2.39085	7.64570	1.77508	1.80155	1.78636
iGSDs	12.92502	7.76546	67.76217	1.66443	5.24271	2.99702
iGMs	23.57484	9.31561	67.90165	2.53068	2.88026	2.70966
iAMs	65.70617	31.38885	429.76662	2.09330	6.54073	3.86215
iAMu	89.25760	35.50618	223.28254	2.51386	2.50155	2.50580
iP95s						
iP95u						

Re-run of "JustRCS" (n=18) with EPA's MEA revision and "bare hands" back-calculation (Section 4.1 and Table 10)

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

REvar	NFvar	GEvar	Component	Variance	PctTot	SD	GSD
Derm	DermAaiH	NrmDerm	V1	5.23092	70.122	2.28712	9.8465
			V2	0.53331	7.149	0.73028	2.0757
			V3	1.69554	22.729	1.30213	3.6771
			Vtot	7.45977	100.000	2.73126	15.3522
Inh	InhAaiH	NrmInh	V1	1.27001	44.088	1.12695	3.0862
			V2	0.00646	0.224	0.08035	1.0837
			V3	1.60418	55.688	1.26656	3.5486
			Vtot	2.88065	100.000	1.69725	5.4589

Log-Scale-Residual-Variance-Structure

Analysis of Normalized Exposure

Normalized Exposure Characterization and Benchmark Evaluation: Scenario CSLL

---------- REvar=Derm NFvar=DermAaiH GEvar=NrmDerm ----------

Summary of Estimates and Bootstrap Confidence Intervals

Statistic	Est	LoCL	HiCL	HiCL/ LoCL	HiCL/ Est	fRA95
GSDs	16.96971	4.84612	44.99400	.	.	.
GSDm	15.35220	5.09836	45.15502	.	.	.
TGC1	0.70122	0.00000	0.87910	.	.	.
TGC2	0.23928	0.00000	0.90354	.	.	.
GMs	30.28448	12.93402	589.35325	2.3415	19.461	6.7601
GMm	86.82063	18.86144	404.87596	4.5788	4.663	4.6271

(10000 Bootstrap Replicates, Seed = 81653215)

Analysis of Normalized Exposure

	593.76429	106.60756	19254.55379	5.5696	32.428	25.0098
AMs	1667.58619	158.08561	208452.65370	10.5486	125.003	30.7501
	3618.19565	190.97188	170398.45741	18.9462	47.095	27.7876
AMu	4263.18063	604.91030	249849.73511	7.0476	58.606	20.7594
AMm	3190.46752	559.90997	122537.03638	5.6982	38.407	14.4985
P95s	7757.10669	690.87996	78780.77148	11.2279	10.156	10.7233
P95u	16.96971	6.55443	44.20351	.	.	.
P95m	30.28448	8.16819	111.78647	3.7076	3.691	3.7007
iGSDs	593.76429	65.64473	9258.87906	9.0451	15.594	19.7978
iGMs	1667.58619	116.94840	50805.51191	14.2592	30.466	19.6615
iAMs	4263.18063	391.34685	142646.28944	10.8936	33.460	25.4535
iAMu	3190.46752	402.31708	24637.01632	7.9302	7.722	7.8306
iP95s						
iP95u						