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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: [placeholder for final date]

SUBJECT: **DRAFT** Review of Agricultural Handler Exposure Task Force (AHETF) Monograph: "Open Pour Mixing/Loading of Wettable Powders" (AHE1015)

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FROM: Matthew Crowley, Biologist
Chemistry and Exposure Branch
Health Effects Division

THROUGH: David J. Miller, Chief
Chemistry and Exposure Branch
Health Effects Division

TO: Richard Dumas
Pesticide Re-evaluation Division

This memorandum presents EPA's review of the occupational handler exposure scenario monograph "Open Pour Mixing/Loading of Wettable Powders" (Klonne and Holden, 2016; AHE1015) submitted by the Agricultural Handler Exposure Task Force. It reflect comments and advice provided by the Human Studies Review Board following its review in July 2016[1].

The AHETF satisfactorily followed the study protocols, sampling design, and data analysis plan. EPA considers the mixing/loading wettable powder scenario complete and its results are recommended for use in routine assessment of exposure and risk. Scientific review of the field and analytical reports (AHE80 – Rosenheck and Baugher, 2016; AHE39 – Klonne, 2007) that outline the monitoring data collected to support this scenario can be found in separate data evaluation review (DER) memoranda (Crowley, 2016 and Williams and Crowley, 2016).

[1] [placeholder for HSRB report]

1.0 Executive Summary

This document represents the Health Effects Division (HED) review of the Agricultural Handler Exposure Task Force (AHETF) Study AHE1015: Open Pour Mixing/Loading of Wettable Powders (Klonne and Holden, 2016). The AHETF studies AHE80 (Rosenheck and Baugher, 2016) and AHE 39 (Klonne, 2007) provide the exposure monitoring field and analytical results, including laboratory analyses; details can be found in both the submitted study reports and corresponding EPA reviews (Crowley, 2016 and Williams and Crowley, 2016). The scenario monograph report (AHE1015) that is the subject of this review compiles the exposure monitoring results from AHE80 and AHE39 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 specific scenario sampling and data analysis plan (AHETF, 2011). 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 used to assess exposure and risk for this scenario.[2] The data are considered the most reliable data for assessing exposure and risk to individuals mixing and loading wettable powder formulation pesticides[3] while wearing the following personal protective equipment (PPE): long-sleeved shirts, long pants, shoes, socks, chemical-resistant gloves, and no respirator[4]. Importantly, the data represents exposure during mixing and loading only – it does not represent exposures during the application of pesticide spray solutions.

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 and 95th percentile. This objective was met: AHETF results showed accuracy of approximately 2-fold at the arithmetic mean and 95th percentile. The secondary objective to evaluate proportionality versus independence between dermal 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.

Additionally, the AHETF estimate of the slope of log dermal exposure-log amount of active ingredient handled (AaiH) regression was 0.62 (95% CI: -0.13 – 1.37). Because the confidence interval of the slope includes both 0 and 1 a proportional relationship cannot be distinguished from an independent one. The AHETF additionally demonstrated that the results of the secondary objective are greatly influenced by the dermal exposure of a single worker, M13, whose dermal exposure was very different from other workers. Given these results, EPA will investigate other options for using the data for risk assessment purposes, but in the near-term,

[2] Pesticide Handlers Exposure Database (PHED) Scenario 4: Wettable Powders: Open Bag.
[3] The data are not applicable to volatile chemicals (e.g., fumigants).
[4] 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.

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 this scenario are presented in Table 1 below, as well as, for comparison, the value previously used (PHED Scenario 4) to assess pesticide exposure/risk for individuals mixing/loading wettable powder pesticide formulations.

Table 1. Unit Exposures (μg/lb ai handled): Mixing/Loading Wettable Powders

Exposure Route	PHED Scenario #4	AHETF[a,b]		
	"Best fit"	Geometric Mean	Arithmetic Mean[d]	95th Percentile[e]
Dermal[c]	170	27.0	57.5	204
Inhalation	43.4	0.466	2.75	10.4

[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] Unlike other AHETF datasets, dermal exposures do not reflect any adjustment of hand and face/neck measurements to address potential inefficiencies in those exposure monitoring methods. The average percent contribution to total dermal exposure by the hands, face, and neck in this data was less than 20%, which per current EPA policy, does not trigger any adjustments (see Section 3.2).
[c] Exposure values represent long sleeve shirt, pants, shoes/socks, chemical-resistant gloves, and no respirator.
[d] Arithmetic Mean (AM) = GM * exp{0.5*((lnGSD)^2)}
[e] 95^{th} percentile = GM * GSD^1.645

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) application equipment type (e.g., tractor-mounted boom sprayers, backpack sprayers) 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, an engineering control (e.g., enclosed cabs on tractors) 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 chemical 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 – 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 mixing/loading one chemical can be used to estimate exposure during mixing/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 expected 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 the geometric mean, arithmetic mean, and 95^{th} 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" (*f*RA) objective does not apply to normalized inhalation exposure, though estimates are provided for reference.

- The secondary objective is to evaluate the assumption of proportionality between dermal exposure and amount of active ingredient handled (AaiH) in order to be able to use 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 95^{th} 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 efficiently 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 state. 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, correlation may result in the need to collect more overall samples than if cluster sampling were not employed.

Though other configurations may also satisfy study objectives, for most handler scenarios the optimal configuration for the AHETF is 5 regional clusters each consisting of 5 participants. The 25 total participants together with the conditions under which the worker handles the active ingredient are 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 EPA handler risk assessments with respect to amount of area that could be treated or amount of dilute solution that could be sprayed in a work day.

2.2 2011 HSRB Protocol Review and Comments

The ability of the EPA to use the mixing/loading wettable powder 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[5].

The protocol and sampling plan for this exposure data and scenario (AHETF, 2011) was presented to the HSRB in January 2011. The meeting report (HSRB, 2011) stated that the proposed approach would likely generate reliable data for assessing exposure for workers mixing and loading wettable powder pesticide formulations. However, various issues were raised. The following table outlines issues raised by the HSRB and how/whether the issue was addressed in the protocol or completed study.

Table 2. Summary of 2011 HSRB AHE80 Protocol Review

HSRB Comment	Study Outcome
AaiH allocation might result in more workers handling middle-range than extremes, resulting in less-than-expected statistical power	The AHETF and EPA were satisfied that the pre-study simulations and analyses demonstrated that the study would meet objective if carried out accordingly. However, as described in Section 3.3.2 below, because sulfur was the only active ingredient used and has relatively high application rates, the intended low levels of AaiH were not achieved. This was the likely cause of not meeting the secondary objective.
The validity of the primary objective is questionable without the population being clearly defined.	As described in Section 4.4 below, while the study design was not a truly random selection of participants – many of the logistical and analytical necessities of the study simply prevent it from being that – the exposures are a reasonable representation of all U.S workers mixing/loading wettable powder pesticide, and the primary objective is a reasonable benchmark to guide the number of workers to monitor.
Clarify the mixing/loading type/sub-scenario requirement for each monitoring area.	The final protocol (AHETF, 2011) called for each monitoring area to have more than one of the three specified mixing/loading types (direct, pre-mix solution, or pre-mix concentrate), but noted it may not be possible. The study was unable to meet this goal – most workers mixed only directly in the spray equipment tank.
The monitored exposures may not represent equipment specialized	Though the design intended otherwise, the monitored workers mixed/loaded wettable powders only in airblast or groundboom sprayer equipment, mostly of large tank size capacity. As previously mentioned, the goals for diversity

[5] http://www2.epa.gov/programs-office-science-advisor-osa/human-studies-review-board

for smaller loads or small acreage.	in mixing/loading "types" were not achieved, however the data represent a reasonable foundation from which to estimate exposures for regulatory purposes. Additionally, as outlined in the study submission and EPA's review for AHE80, an informal survey of local experts did not suggest that the monitoring was atypical for each monitoring area.

2.3 2016 HSRB Review and Comments

[placeholder]

3.0 Exposure Study Conduct and Monitoring Results

Field monitoring and analytical results, as well as protocol amendments and deviations, were reported in AHE80 and AHE39 and reviewed by EPA (Crowley, 2016 and Williams and Crowley, 2016). Monitoring of five (5) workers mixing/loading wettable powders in AHE39 was conducted in 2006[6]; AHE80 was designed to supplement AHE39 with an additional 20 workers with the completed study submitted to EPA in 2016. 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 (Klonne and Holden, 2016).

3.1 Exposure Study Design and Characteristics

This scenario is defined as mixing and loading wettable powder pesticide formulations, either directly in pesticide application equipment or in an intermediate slurry/pre-mix tank, while wearing a long-sleeved shirt, long pants, shoes, socks, chemical-resistant gloves, and no respirator. Between studies AHE80 and AHE39, dermal and inhalation exposure monitoring was conducted for 24 different workers[7] and reported in the AHETF submissions:

- "Determination of Dermal and Inhalation Exposure to Workers During Mixing/Loading Wettable Powders in the United States" (AHE80; Rosenheck and Baugher, 2016); and,
- "Determination of Dermal and Inhalation Exposure to Workers in Idaho During Pre-Plant Incorporated Applications to Sweet Corn Using Open Cab Groundboom Equipment and During Open Pour Mixing/Loading a Wettable Powder Pesticide Product" (AHE39; Klonne, 2007).

The figures below (provided by the AHETF) depict examples of activities for which the exposure data are applicable.

[6] The first subject was enrolled in exposure study AHE39 prior to the effective date of the EPA rule regarding protection of human subjects. As such, the HSRB is not required to review study AHE39, although it has been reviewed by EPA. EPA's ethics review concluded that there is no regulatory barrier, from an ethics standpoint, to EPA relying on AHE39 in actions taken under FIFRA or §408 of FFDCA.

[7] The original sampling plan called for monitoring a total of 25 workers – 20 additional workers in AHE80 to supplement the existing data from AHE39. Monitoring for one worker in AHE80 (worker M15) was not conducted due to a malfunctioning water source.

Figure 1: Mixing/Loading Wettable Powder Directly in Application Equipment

Figure 2: Mixing/Loading Wettable Powder in an On-board Inductor Tank

Figure 3: Mixing Wettable Powder in a Slurry Bucket then Loading into Spray Tank

Considering the existing data available in AHE39 (5 workers monitored in Idaho in 2006), in order to capture the expected range of exposures within this scenario (with a small sample), the monitoring plan for AHE80 (AHETF, 2011) outlined a strategy to target a diverse set of conditions in terms of geographic areas, types of equipment tanks/containers types, workers, and other potential exposure factors. The 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 wettable powders through processes to identify subsequent lists of "qualified employers" and then "potentially eligible" employers. After confirming eligibility, AHETF scheduled and conducted monitoring of workers. In no case were there enough available workers in a given monitoring area such that a random selection could be made among them.

The sampling plan for this scenario (AHETF, 2011) outlined a '5x5' design – monitoring of a total of 25 different workers, 5 workers in each of 5 separate 'clusters' or monitoring areas – that would satisfy benchmark study objectives. With the existing dataset of 5 monitored workers from study AHE39 representing 1 cluster, the study protocol for AHE80 specified 4 additional monitoring locations each consisting of 5 workers to complete the '5x5' design. AHE80 thus included new monitoring in New York, Michigan, Florida, and California to augment the existing monitoring data in Idaho from AHE39.

Due to the decreasing use of wettable powders and the limited number of wettable powder products, recruitment for AHE80 proved difficult and monitoring extended over a period of 3 years from October 2011 to November 2014. The end result was monitoring for 19 additional workers (monitoring for one worker was not conducted due to a malfunctioning water source). Thus, while AHE80 covered the intended (spatial) monitoring areas, when considering the temporal differences resulting from the extended period of monitoring, the dataset resulted in more than the additional 4 clusters intended. The AHETF, for purposes of analysis of within-cluster correlation and the accuracy objective, grouped the final dataset (24 total monitored workers – 19 from AHE80 and 5 from AHE39) into 9 clusters using a threshold of 90-days between monitoring and 15 sub-clusters using a threshold of 5 days between monitoring.

As monitoring was conducted across 3 years and 5 different U.S. states, both spatial and temporal diversity is represented in the sample. There were no repeat measurements on the same worker, and all except for two workers in AHE39 were employed by a different farm/grower/company. The monitoring plan called for no piece of equipment to be used multiple times by different workers and for use of different types of mixing/loading procedures in the same monitoring area (e.g., directly in the application equipment, use of intermediate pre-mix tanks, etc.). Diversity in equipment was achieved with only two workers mixing/loading in the same pesticide application equipment (in AHE39); however, diversity in the type of mixing/loading was generally not achieved – most workers mixed and loaded directly into the application equipment.

Also, per protocol, the amount of active ingredient handled by the workers was diversified – mainly to accommodate the secondary study objective – but also to potentially add indirect variability to the dataset. However, the level of diversity in amount of active ingredient handled was less than desired. The monitoring plan called for a range of approximately 400-fold, from a low-end of 5 lbs active ingredient to a high-end of 2000 lbs of active ingredient. Again due to low use and availability of wettable powder products, sulfur was the only active ingredient utilized by the workers recruited in AHE80. Sulfur has relatively high application rates, which resulted in an inability to achieve lower amounts of active ingredient handled. Other active ingredients – thiophanate-methyl and permethrin – were identified in the study protocol as additional potential surrogates, both of which have rates lower than sulfur; however, per protocol, the AHETF does not require anyone to use products that they do not want to use. Thus, ultimately, the overall spread of amount of active ingredient handled was only 17-fold, and then only 2- to 9-fold within monitoring areas.

For more details on worker characteristics and other monitoring conditions see the monograph submission (AHE1015), and the study report submissions (AHE80 and AHE39) and their corresponding EPA reviews (Crowley, 2016 and Williams and Crowley, 2016).

3.2 Exposure Monitoring and Calculations

In AHE80 and AHE39 workers were monitored on actual days of work, handling between 55 to 925 lbs of active ingredient (diazinon and sulfur), mixing and loading between 300 and 12,500 gallons of solution over 3 to 25 separate mixing/loading events in 1 to 10 hours. All workers wore long-sleeved shirts, pants, shoes/socks and chemical-resistant gloves; some wore eye protection or respirators.[8]

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), and face/neck wipes. 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. In order to simulate total head exposure without eye protection or respirators, face/neck wipe samples for those workers who did use eye protection and/or respirators were adjusted to extrapolate to portions of the head covered by protective eyewear, respirators, and/or hair.

Additionally, as presented at a June 2007 HSRB meeting, to account for potential residue collection method inefficiencies[9], 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.

For these studies, the measurements fell in the first category – on average 11% of total dermal exposure consisted of exposure to the hands and head – thus hand rinse and face/neck wipe measurements have not been corrected for any potential method inefficiencies.

Inhalation exposure was measured using a personal air sampling pump and glass fiber filter cassette cartridges. The cassette cartridge is attached to the worker's shirt collar to continuously sample air from the breathing zone.

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[8] All work attire met the requirements of the product labels and EPA's Worker Protection Standard. Respirators were worn at worker preference, but not required by product labels.

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

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 16.7 L/min representing light activities (NAFTA, 1998), and total work/monitoring time.[10] Dermal and inhalation unit exposures (i.e., ug/lb ai handled) are then calculated by dividing the summed total exposure by the amount of active ingredient handled.

A summary of the 24 mixer/loader MUs is provided in Table 2 below, with data plots shown in Figures 3 and 4. All field measurements were adjusted by their corresponding field fortification recovery values. In addition, 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. More details on exposure measurements, field fortification sampling, and other laboratory measurements can be found in the respective study reviews of AHE80 and AHE39 (Crowley, 2016 and Williams and Crowley, 2016).

Table 2. Mixing/Loading Wettable Powder Exposure Summary

Study	MU ID	State	Mix/Load Type	Work/ Monitoring Time (hours)	Solution Mixed (gallons)	AaiH (lbs)	Unit Exposure (ug/lb ai)	
							Dermal	Inhalation
AHE80	M1	FL	Pre-mix/Slurry (on-board inductor)	3.4	3000	54.6	237	13.5
AHE80	M2	NY	App. Equip.	3.2	1800	108	108	3.91
AHE80	M3	NY	App. Equip.	7.3	5500	300	12.2	0.809
AHE80	M4	NY	App. Equip.	9.1	12500	685	89.8	3.39
AHE80	M5	NY	App. Equip.	5.4	6500	438	71.0	0.930
AHE80	M6	FL	App. Equip.	2.8	5000	97.0	46.8	2.98
AHE80	M7	FL	App. Equip.	3.5	4000	196	29.3	0.059
AHE80	M8	CA	App. Equip.	9.1	4500	316	45.6	0.758
AHE80	M9	CA	App. Equip.	3.8	2400	93.6	6.31	0.127
AHE80	M10	CA	App. Equip.	1.8	2400	96.0	7.74	0.127
AHE80	M11	CA	App. Equip.	4.9	1500	69.9	17.1	0.235
AHE80	M12	MI	App. Equip.	3.5	920	118	40.4	2.81
AHE80	M13	MI	Pre-mix (Holding tanks)	3.4	6100	925	0.637	0.089
AHE80	M14	MI	App. Equip.	2.5	1600	346	45.4	0.505
AHE80	M16	MI	App. Equip.	8.1	2000	122	20.8	0.082
AHE80	M17	NY	App. Equip.	0.6	1500	79.8	38.5	0.031
AHE80	M18	FL	App. Equip.	2.5	3000	143	34.3	1.62
AHE80	M19	CA	App. Equip.	1.8	710	71.7	10.9	0.171
AHE80	M20	FL	Pre-mix/Slurry (on-board inductor)	2.5	3000	71.7	27.4	0.079
AHE39	M1	ID	Pre-mix/Slurry	9.9	700	138	23.7	4.25
AHE39	M2	ID	Pre-mix/Slurry	8.3	300	59.1	52.6	2.50
AHE39	M3	ID	Pre-mix/Slurry	9.1	300	59.1	12.1	3.91
AHE39	M4	ID	Pre-mix/Slurry	8.4	500	98.5	44.0	3.42
AHE39	M5	ID	Pre-mix/Slurry	8.2	500	98.5	133	10.3

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

Figure 3: Dermal Unit Exposures (ug/lb ai)

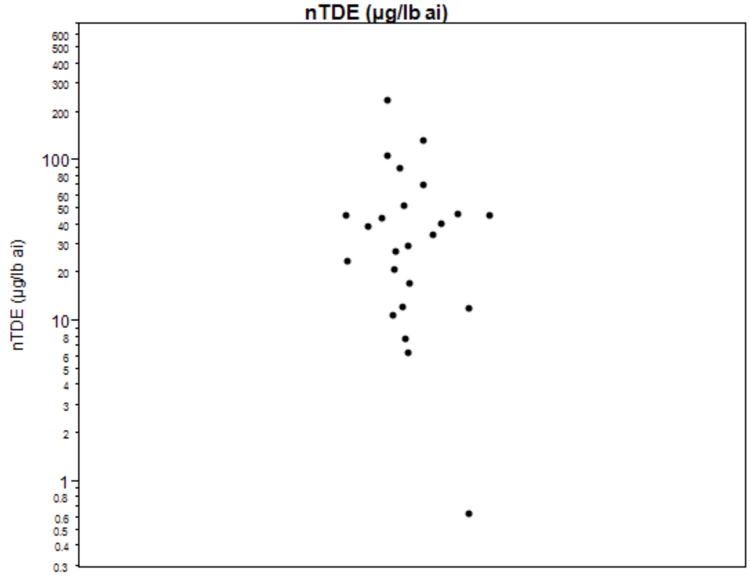
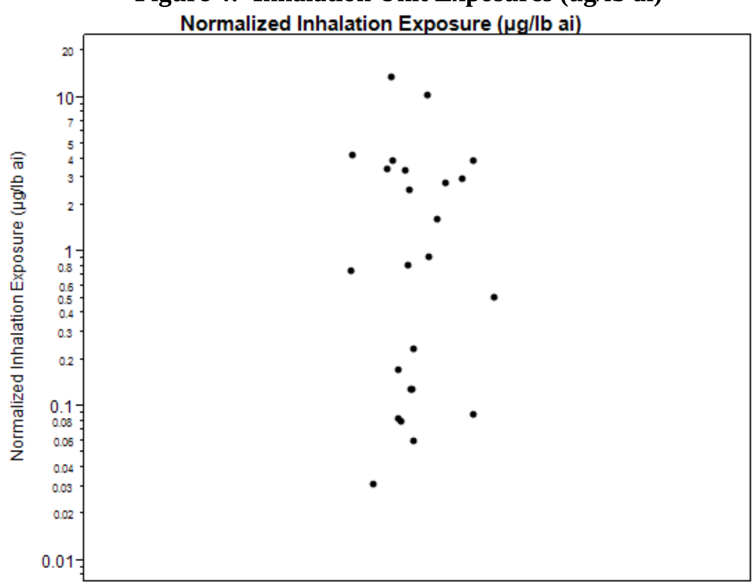


Figure 4: Inhalation Unit Exposures (ug/lb ai)



3.3 Evaluation of Scenario Benchmark Objectives

The AHETF monograph details the extent to which the mixing/loading wettable powder scenario meets objectives described in Section 2.1. The monograph states that while the primary objective (3-fold accuracy) was met, the secondary objective (adequate analytical power) was not. EPA agrees with the methodologies used to assess these objectives (Appendix D of Klonne and Holden, 2016) and has independently confirmed the results by re-analyzing the data with the AHETF-supplied statistical programming code.

3.3.1 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" or fRA).

First, the AHETF evaluated the structure of the final dataset in comparison to the intended study design. The initial study design assumed a total of 25 monitored workers: 5 clusters each consisting of 5 monitored workers. The pre-existing data, AHE39, represented 1 cluster, while the newly planned study, AHE80, would constitute the remaining 4 additional clusters. Importantly when demonstrating that the planned study design would satisfy the accuracy objective, knowing that uncertainty can be underestimated if independence is assumed, the AHETF incorporated the potential correlation of monitoring within the same cluster.

However, when AHE80 was conducted, the AHETF was not able to achieve the intended '4 x 5' efficient monitoring configuration due to recruitment difficulties. This resulted in an extended (3 year) monitoring period and, from a data analysis perspective, more clusters than intended. While AHE80 utilized the 4 monitoring areas as intended – NY, FL, MI, and CA – the temporal variability was more than anticipated. For example, the AHETF conducted monitoring in Florida in 2011, 2012, and then again in 2014. Ultimately, the analysis of the benchmark grouped the data from the 5 monitoring areas into 9 clusters (using a 90-day monitoring separation as the threshold, and then a total of 15 sub-clusters (using a 5-day monitoring threshold within each cluster). Figure 5 below (from AHE1015 Appendix D Table 3) illustrates the clustering used for analysis of the primary objective.

Figure 5: AHE1015 Summary of Data 'Clusters'

Monitoring Area	Monitoring Unit	Monitoring Date	Nearest Town	Cluster	Sub-Cluster
39-ID	39-M3	06/01/2006	Weiser ID	1	1
	39-M2	06/02/2006	Payette ID		
	39-M4	06/02/2006	Payette ID		
	39-M1	06/03/2006	Payette ID		
	39-M5	06/04/2006	Payette ID		
81-NY	M2	05/14/2012	Williamson NY	2	2
	M3	05/15/2012	Wolcott NY		
	M4	05/16/2012	Sodus NY		
	M5	05/18/2012	Williamson NY		
	M17	05/28/2014	Burt NY	3	3
82-FL	M1	10/19/2011	Zolfo Springs FL	4	4
	M6	10/10/2012	Fort Pierce FL	5	5a
	M7	11/01/2012	Haines City FL		5b
	M18	11/06/2014	Lake Placid FL	6	6a
	M20	12/18/2014	Wauchula FL		6b
83-MI	M12	04/26/2013	St. Joseph MI	7	7a
	M13	05/24/2013	Suttons Bay MI		7b
	M14	06/03/2013	Central Lake MI		7c
	M16	06/15/2013	Elk Rapids MI		7d
84-CA	M8	03/27/2013	Selma CA	8	8a
	M9	03/28/2013	Del Rey CA		
	M10	03/29/2013	Selma CA		
	M11	04/12/2013	Kingsburg CA		8b
	M19	11/26/2014	Fresno CA	9	9

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 Appendix A. 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 MU correlations, as noted above.

As presented in Appendix C of the AHETF Governing Document (AHETF, 2008 and AHETF, 2010) and Appendix D of the scenario monograph (Klonne and Holden, 2016), the 95% confidence limits for each of these estimates were obtained by generating 10,000 parametric bootstrap samples. Then, the fRA for each was determined as the maximum of the two ratios of the statistical point estimates with their respective upper and lower 95% confidence limits. The primary benchmark of 3-fold accuracy for select statistics was met for dermal exposure data. Though not subject to the same objective as dermal exposure, accuracy results for inhalation were higher than those for dermal, likely due to the larger variability in the inhalation exposure distribution. A summary of the results is presented in Table 3 below.

Table 3. Mixing/Loading Wettable Powders – Results of Primary Benchmark Analysis						
Statistic	**Dermal**			**Inhalation[a]**		
	Unit Exposure (ug/lb ai)		**fRA_{95}**	**Unit Exposure (ug/lb ai)**		**fRA_{95}**
	Estimate	**95% CI**		**Estimate**	**95% CI**	
GM_S	28.6	15.1-48.3	1.8	0.739	0.148-1.476	3.2
GSD_S	3.34	2.37-4.89	--	6.09	3.17-13.27	--
GM_M	27.0	15.2-47.8	1.8	0.466	0.178-1.240	2.6
GSD_M	3.42	2.39-5.16	--	6.58	3.35-13.37	--
ICC_C	0.00	0.00-0.54	--	0.00	0.00-0.74	--
ICC_S	0.25	0.00-0.75	--	0.83	0.07-0.95	--
GM_S = geometric mean assuming SRS = "exp(average of 24 ln(UE)) values". GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 24 ln(UE)) values" GM_M = variance component model-based geometric mean GSD_M = variance component model-based geometric standard deviation ICC_C = intra-class correlation for data in the same cluster but different subclusters ICC_S = intra-class correlation for data in the same subcluster						
AM_S	48.1	26.7-117.0	2.1	2.36	0.49-10.45	5.0
AM_U	59.2	28.2-122.5	2.1	3.78	0.55-18.57	5.6
AM_M	57.5	28.8-128.4	2.1	2.75	0.67-17.54	5.0
AM_S = simple average of 24 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}						
$P95_S$	133	68-494	2.8	10.3	1.5-45.5	6.3
$P95_U$	208	87-461	2.3	14.4	2.0-52.0	5.1
$P95_M$	204	89-491	2.3	10.4	2.4-47.1	4.3
$P95_S$ = 95th percentile (i.e., the 23rd unit exposure out of 24 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] Accuracy results for inhalation exposure are presented but, unlike dermal exposure, are not subject to the 3-fold threshold study objective.						

In a separate analysis, EPA added another hierarchy/grouping consisting of U.S. state to evaluate whether any different conclusions would be drawn using an alternative model. The AHETF's model consisted of subjects (n=24) nested within the 5-day monitoring time threshold (15 clusters) nested within "U.S. state by 90-day monitoring threshold" (9 clusters). To this EPA added a third, higher level grouping by U.S. state, resulting in a model consisting of subjects (n=24) nested within the 5-day monitoring time threshold (15 clusters) nested within "U.S. state by 90-day monitoring threshold" (9 clusters) nested within U.S. state (5 clusters). This model did not result in substantively different estimates of statistics (e.g., GM, GSD, etc.) compared with the model used by the AHETF. Thus, EPA found the data structure used by the AHETF to evaluate this benchmark to be reasonable.

3.3.2 Secondary Objective: Evaluating Proportionality

The secondary objective of the study design is to be able to distinguish, with 80% statistical power, complete proportionality from complete independence between dermal exposure and amount of active ingredient handled. 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 of 1.4 (or less) indicates at least 80% statistical power. Upon completion of the study the data can be analyzed to see if it provides a level of precision consistent with that benchmark. As shown in Table 5 below, for dermal exposure, the width of the confidence interval for the slope of the mixed-effects regression – preferred since it accounts for within-cluster correlation – is greater than 1.4; therefore, this benchmark was not met.

The results for worker M13 were unique in the dataset – this worker handled the most active ingredient (925 lbs of sulfur) but had the lowest dermal exposure (589 µg), a result that was at odds with the rest of the data. This worker's hand and head exposure were similar to the rest of the dataset, but exposure to the rest of the body was the lowest. While the AHETF did not discuss any problems or issues related to this worker's exposure or any issues related to analytical issues, they did investigate the effect of excluding this result on the relationship between exposure and the amount of active ingredient handled[11]. Additionally, though not subject to the secondary benchmark, the AHETF evaluated the relationship between inhalation exposure and the amount of active ingredient handled. The resulting regression slopes and confidence intervals for dermal exposure (with and without M13) and inhalation exposure are summarized in Table 5.

Table 5. Summary Results of log-log Regression Slopes

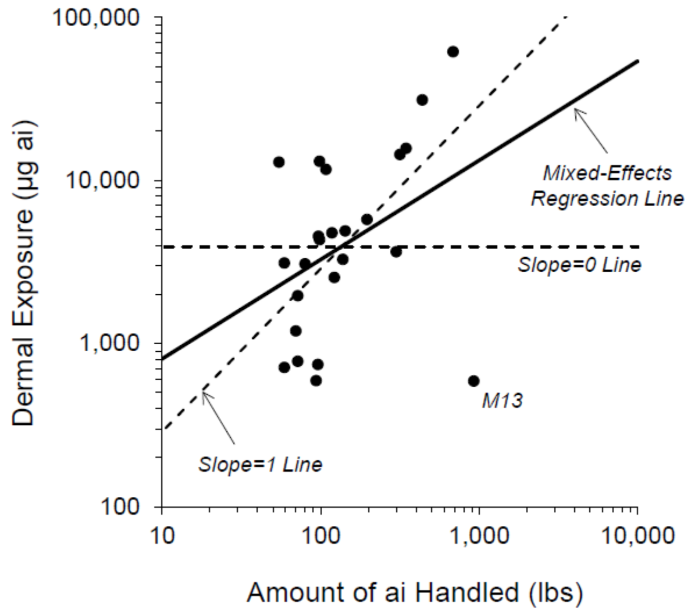
Model	Dermal Exposure						Inhalation Exposure		
	Including M13			Excluding M13					
	Est.	95% CI	CI Width	Est.	95% CI	CI Width	Est.	95% CI	CI Width
Simple Linear	0.64	-0.02-1.29	1.31	1.22	0.63-1.81	1.18	0.75	-0.25-1.76	2.01
Mixed-Effects	0.62	-0.13-1.37	1.50	1.21	0.50-1.92	1.43	1.13	0.30-1.96	1.66

Note: results shown using the Kenward-Rogers denominator degrees of freedom method. AHETF statistical analysis (AHE1015 Appendices D and E) provides results using the Containment method as well. Results were not substantially different.

For dermal exposure, the slope of the mixed-effects regression – preferred since it accounts for within-cluster correlation – is 0.62 with a 95% confidence interval that includes both 0 and 1, an inconclusive result regarding the relationship between exposure and the amount of active ingredient handled. Figure 6 below (from AHE1015 Appendix D) shows a plot of dermal exposure versus amount of active ingredient handled, with M13 identified.

[11] Although the AHETF conducted this sensitivity analysis, they did not propose to exclude exposure for M13 from the dataset and EPA has no reason to and does not intend to rely on results that exclude worker M13.

Figure 6: Dermal Exposure (µg) vs. AaiH (lb ai)



Without exposure for worker M13, however, the slope of the mixed-effects regression is 1.21 with a 95% confidence interval that excludes 0 and includes 1, a result that is consistent with a proportional relationship between exposure and the amount of active ingredient handled. As discussed in Section 3.1 above, the use in AHE80 of only sulfur with its relatively high application rates likely prevented the AHETF from monitoring exposure resulting from use of low amounts of active ingredient. The range of amount of active ingredient handled was only 17-fold compared to the nearly 100-fold range in dermal exposure. As in any regression, slope estimates are sensitive to the range in both the independent and dependent variables. The range in the amount of active ingredient might in this case be too small, resulting in the inconclusive results shown here. Importantly, while it had an effect on estimates of the slope and confidence intervals, it did not have an effect on the overall results: whether M13 is excluded or not, the secondary benchmark would not have been met.

For inhalation exposure, the mixed-effects regression slope is 1.13, with a 95% confidence intervals that excludes 0 and includes 1, suggesting a proportional relationship is more consistent with the data than an independent relationship. Worker M13 did not have similar analytical effects for inhalation exposure as for dermal exposure. In terms of the secondary objective, the width of the confidence interval was greater than 1.4, indicating the power to detect complete independence from complete proportionality was less than 80%.

4.0 Data Generalizations and Limitations

The need for an upgraded generic pesticide handler exposure database has been publicly discussed and established (Christian, 2007). Existing exposure data for mixing and loading wettable powders was identified (AHE39) and then supplemented by study AHE80 to constitute the completed scenario. The data will be used generically to assess exposure for workers who mix and load any conventional pesticide formulated as a wettable powder. 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

The data comprising this scenario are acceptable for use in assessing exposure for workers who mix and load any conventional pesticide formulated as a wettable powder while wearing a long-sleeve shirt, pants, shoes/socks, and chemical-resistant gloves. Importantly, 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, even for this specific scenario, the availability of this data 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.

4.2 Applicability of AHETF Data for Volatile Chemicals

The data generated in this study are acceptable to use as surrogate data for assessing for workers who mix and load any conventional pesticide formulated as a wettable powder, which, as solid formulations, are generally chemicals of low volatility. Since they are not typically formulated as solid or powder formulations, it is 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, statistical analyses were inconclusive regarding support for use of the exposure data normalized by the amount of active ingredient handled. As a result, alternative uses of the data and/or additional exposure 'models' can be investigated. However, 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. Given the nature of routine exposure assessments to assume high levels of amounts of active ingredient handled for purposes of making regulatory decisions, the assumption of proportionality is likely a conservative approach.

4.4 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 certain U.S. states to ensure a large pool of potential applicators; requiring potential applicators 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), made the studies comprising this scenario neither purely observational nor random to allow for characterization of the dataset as representative of the population of workers who mix and load wettable powder pesticide formulations. It is important to recognize this as a limitation when making use of the data.

Additionally, diversity in both the type of mixing/loading activity and the amount of active ingredient handled, as described in the protocol and pre-study goals, were not achieved. In AHE80 a study goal was to have each monitoring area include a variety of different mixing/loading techniques (e.g., one worker loading directly into the application equipment, another worker mixing in a slurry bucket, etc.), however, most workers in AHE80 loaded and mixed the product directly in the application equipment tank. With respect to the amount of active ingredient handled, as for other variables, the goal was to have diversity within each monitoring area as well as across all monitoring areas, but the preponderance of sulfur as the active ingredient in wettable powder products of choice and its corresponding relatively high application rates may have limited the AHETF's ability to achieve the low-end of the range. In terms of representativeness of the data, these may be limitations.

It appears however, that the dataset has captured routine behavior as well as limiting the likelihood of "low-end" or non-detect exposures via certain scripted aspects (e.g., monitoring time and tank loading targets), both of which are valuable for regulatory assessment purposes. And, as outlined in the study submission and EPA's review of AHE80, 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 Mixing/Loading Wettable Powder 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 data EPA currently uses to estimate dermal and inhalation exposure for workers mixing/loading wettable powders have been recognized and the need for new data established.
- The primary (quantitative) objective was met: estimates of the arithmetic mean and P95 dermal exposures were shown to be accurate within 3-fold with 95% confidence.
- The secondary (quantitative) objective was not met: the dataset does not provide the ability 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 inconclusive. Despite this result, EPA will continue using exposures normalized by AaiH as a default condition for exposure assessment purposes, but will investigate alternative approaches in the future.

- Though the lack of diversity in the type of mixing/loading activities or the amount of active ingredient handled were not achieved may limit the representativeness of the data, given the recruitment difficulties experienced by the AHETF for AHE80, EPA does not believe additional monitoring needs to be conducted.
- The AHETF data developed and outlined in the monograph and this review represent the most reliable data for assessing exposure to workers who mix and load wettable powder pesticide formulations.

6.0 References

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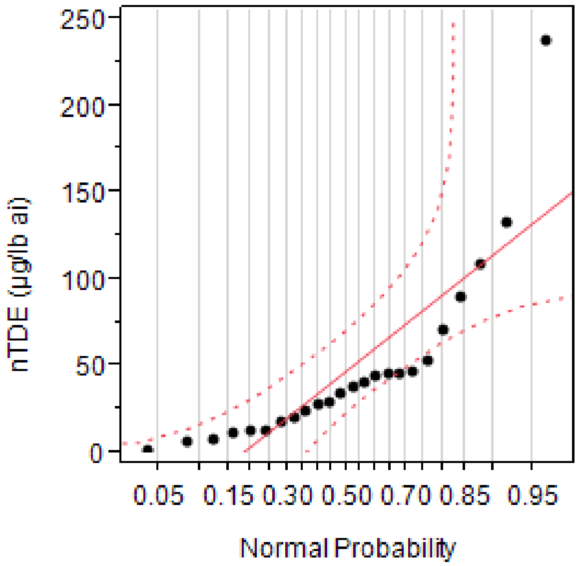
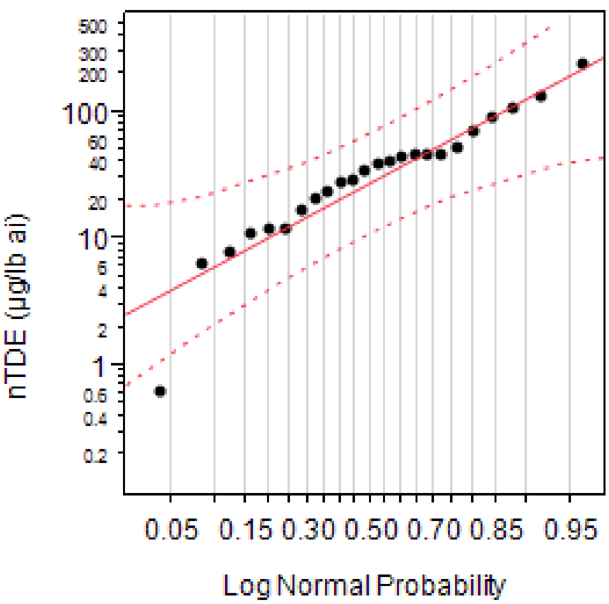
Appendix A

Normal and Lognormal Probability Plots of Dermal Unit Exposures





Normal and Lognormal Probability Plots of Inhalation Unit Exposures