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

MEMORANDUM

Date: [placeholder for final date]

SUBJECT: **DRAFT** Review of Agricultural Handler Exposure Task Force (AHETF)
Monograph: "Mixing/Loading of Pesticide Products in Water Soluble Packets" (AHE1014)

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This memorandum presents EPA's review of the occupational handler exposure scenario monograph "Mixing/Loading of Pesticide Products in Water Soluble Packets" (AHE1014) 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. If applicable product labels include instructions for mixing and loading water soluble packets that reflect the practices represented by the monitoring data in this study, EPA recommends use of the data in assessment of exposure and risk to support regulatory decisions. Scientific review of the field and analytical reports (AHE120 – Cañez and Baugher, 2015) that outline the monitoring data collected to support this scenario can be found in separate data evaluation review (DER) memoranda (Crowley, 2016).

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[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 AHE1014: Mixing/Loading of Pesticide Products in Water Soluble Packets (Klonne and Holden, 2015). The AHETF study AHE120 (Cañez and Baugher, 2015) provides 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). The scenario monograph report (AHE1014) that is the subject of this review compiles the exposure monitoring results from AHE120 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 pesticide products in water soluble packets (WSP)[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 – a key assumption in the use of exposure data as "unit exposures" – with 80% statistical power was also met.

Additionally, the AHETF estimate of the slope of log dermal exposure-log amount of active ingredient handled (AaiH) regression was 0.88 (95% CI: 0.53 – 1.22). As the confidence interval includes 1 but not zero, the data is 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 exposure assessment purposes.

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[2] Pesticide Handlers Exposure Database (PHED) Scenario 5: Wettable Powders: Water Soluble Packets.
[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.

After adjustments by EPA for potential inefficiencies of the hand wash and face/neck wipe residue collection methodologies, results of the benchmark objective analyses were nearly identical to those described above. That is, the adjustments did not alter the outcomes of the benchmark analyses and conclusions were unaffected. However, as would be expected, the adjustments to the data result in slightly different estimates of exposure statistics (i.e., means and percentiles) than those calculated without the adjustments. Section 3.2.1 discusses this in more detail.

Select summary statistics for this scenario are presented in Table 1 below, as well as, for comparison, the value previously used (PHED Scenario 5) to assess pesticide exposure/risk for individuals mixing/loading water soluble packets.

Table 1. Unit Exposures (µg/lb ai handled): Mixing/Loading Water Soluble Packets				
Exposure Route[c]	PHED Scenario #5	AHETF[a,b]		
	"Best fit"	Geometric Mean	Arithmetic Mean[d]	95th Percentile[e]
Dermal	9.8	5.95	12.53	44.27
Inhalation	0.24	0.0601	2.60	5.50
[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 3.3.1. [b] 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). [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] 95th 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, in the case of this scenario, formulations enclosed in water soluble packaging) 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., in a bottle or in a 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 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 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 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 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 conduct monitoring for more workers overall 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   2010 HSRB Protocol Review and Comments

The ability of the EPA to use the mixing/loading water soluble packets exposure monitoring 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[5].

The protocol and sampling plan for this exposure data and scenario (AHETF, 2011) was presented to the HSRB in October 2010. The meeting report (HSRB, 2010) stated that the proposed approach would likely generate reliable data for assessing exposure for workers mixing and loading pesticide products in water soluble packets. 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 2010 HSRB AHE120 Protocol Review	
HSRB Comment	**Study Outcome**
There is conflict between the non-random, purposive study design and the statistical methods proposed to analyze the exposure data. Previously the Board said that "there is no statistical theory that can be applied to non-random samples of this type. Thus, the statistical analyses proposed, including mixed model approaches, are not valid."	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 water soluble packets, and the statistical analyses conducted are reasonable to evaluate whether additional monitoring is necessary.
The protocol does not control for ecological, engineering, and statistical factors that may obscure a linear relationship between AaiH and worker exposure.	From a design perspective, the overall goal of the study – to capture the range of expected exposures for this scenario – is admittedly at odds with analyzing the relationship between exposure and AaiH. While controlling for variables other than AaiH would optimize the ability to analyze the relationship, the lack of diversity in those other variables would simultaneously minimize the ability to capture exposure variability.

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

Requiring monitoring to be at least 4 hours may introduce unintended and undesired variability into the results.	A 4-hour minimum was desirable, but not required in the protocol. In fact, 11 of the 25 workers had monitoring times less than 4 hours. However, requirements and/or goals for work time, or, perhaps equivalently, number of tank loads mixed, was intended to minimize the number of non-detect samples in the results. Reviewing the completed data does not show a substantial fraction of the data to be non-detects, therefore the exposure time was adequate from a sampling perspective.
The Board recommended that all field notes for this study report the time on-task as a fraction of the total monitored time, and that the total monitored time and the fraction of the total time on-task be tabulated for this study.	This was not explicitly reported in the field observations. Field observations were very detailed and additional analysis could be conducted to estimate time-on-task. However, the Board's comment was in the context of the 4 hour time requirement, previously addressed above; without the requirement the time-on-task fraction may not be as significant of an issue.

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 AHE120 and reviewed by EPA (Crowley, 2016). No existing studies were deemed acceptable by the AHETF, thus AHE120 was designed to supplant previously used data. 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, 2015).

3.1   Exposure Study Design and Characteristics

This scenario is defined as mixing and loading pesticide products in water soluble packaging[6], 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.

The figures below (from AHE1014 Appendix F; Klonne and Holden, 2015) depict examples of activities for which the exposure data are applicable.

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[6] All products used in AHE120 were wettable powders inside water soluble packaging, however the scenario definition includes all pesticide products (i.e., formulations other than wettable powders) that can be manufactured inside water soluble packaging.

Figure 1: Mixing/Loading WSP Directly in Application Equipment

Figure 2: Mixing/Loading WSP in an Intermediate Pre-Mix Tank

In order to capture the expected range of exposures within this scenario (with a small sample), the monitoring plan for AHE120 (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 water soluble packets 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 only one instance (in Florida) was there enough available workers in a given location such that a random selection could be made from them.

During the initial stages of field monitoring work, the AHETF identified work practices that both the AHETF and EPA agreed were not consistent with the intended use of water soluble packaging as an engineering control intended to reduce exposure potential[7]. These included

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[7] AHETF-EPA conference call on June 21, 2012.

placing the WSPs into baskets hanging over the mix tank and spraying them with water to dissolve the outer packaging or, when WSPs were placed in water in the tank, using overhead solution recirculation to dissolve the outer packaging. These issues resulted in exclusion of monitoring for 6 of the recruited workers[8]. Appendix G of the AHE120 study report provides full details of the excluded monitoring, including field observations, photographs and available exposure monitoring results.

As a result of these issues, specific instructions were provided to workers by the AHETF (outlined in protocol amendments 6, 8 and 13), beyond mixing/loading instructions on the product labels. The instructions were mainly intended to prevent overhead spray of the WSPs in order to dissolve them in the form of use of suspended baskets or overhead recirculation. Thus instructions included having mechanical agitation/recirculation come from the bottom of the mix tank without overhead recirculation, unless the hatch was closed. If overhead circulation is required, the hatch lid should be closed during dissolution. Provided as Appendix B in the AHE120 study report, the mixing instructions in the protocol were as follows[9]:

- Remove any strainer basket from the tank hatch.
- Fill tank to approximately one-third to one-half of the desired final volume of spray.
- Stop adding water and any agitation.
- Add WSPs to the surface of the water in the tank.
- Start mechanical and recirculation agitation from the bottom of tank without using any overhead recirculation.
- If you must work near the tank hatch, close the lid.
- If overhead recirculation cannot be turned off, close the hatch before starting agitation.
- Do not direct water from a hose or fill pipe to break the bags.
- Dissolving the WSPs may take up to 5 minutes or longer, depending on water temperature, hardness and intensity of agitation. Check periodically, avoiding any dusts or re-circulating spray mix.
- When the bags have fully dissolved and the powder has gone into suspension in the water, other products may be added.
- Resume filling the tank with water to the desired level.
- Maintain agitation while filling and driving/flying to the spray site and during application.
- Follow all other label instructions regarding the handling of WSPs.

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 – to

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[8] Monitoring for a total of 9 workers are not represented in the dataset. The 6 as indicated, plus an additional 3: monitoring for 2 workers was not conducted because the outer packaging was broken/breached (and no longer a WSP) and monitoring for 1 worker was terminated due to the addition of WSPs after loading fertilizer which resulted in poor dissolution (product labels instruct users to dissolve WSPs prior to other spray tank additives such as fertilizer).

[9] The feasibility of formal incorporation of these instructions from both a user perspective and regulatory enforcement perspective requires evaluation. In June 2016, EPA initiated this process with an informal discussion with the State FIFRA Issues Research and Evaluation Group (SFIREG). EPA anticipates further discussion with other stakeholders.

satisfy benchmark study objectives. As described above the excluded monitoring resulted in a dataset of 16 MUs. AHE120 initially targeted monitoring in New York, Florida, Louisiana, North Dakota, and California. Following recruiting difficulties the AHETF expanded the targeted states to include Mississippi, Minnesota, and Michigan, but monitoring still extended over a period of 3 years from August 2011 to November 2014. Thus, while AHE120 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 5 clusters intended. Instead of the intended 5 "clusters", the 16 monitored workers ultimately comprised 10 distinct "clusters", when considering spatial proximity as well as a temporal proximity threshold of no more than 90 days apart. The AHETF then applied that data structure for purposes of analysis of within-cluster correlation and the benchmark accuracy objective.

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 workers 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; however diversity in the type of mixing/loading was generally not achieved to the level desired. Most workers mixed and loaded directly into the application equipment as opposed to an intermediate/slurry tank, however, the former is expected to be the most prevalent approach.

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. Though the level of diversity was not achieved within each monitoring area, the overall range of intended amounts of active ingredient handled (i.e., from 3 to 400 lbs) was achieved across all monitoring areas. Thus, ultimately the overall spread of amount of active ingredient handled was approximately 2 orders of magnitude.

For more details on worker characteristics and other monitoring conditions see the monograph submission (AHE1014), and the AHE120 report submission and its corresponding EPA review (Crowley, 2016).

3.2 Exposure Monitoring and Calculations

In AHE120 workers were monitored on actual days of work, handling between 0.92 and 272 lbs of active ingredient (acephate, thiophanate-methyl, or imidacloprid) and mixing and loading between 200 and 9,000 gallons of solution over 2 to 9 separate mixing/loading events in 1 to 10 hours. All workers wore long-sleeved shirts, pants, shoes/socks and chemical-resistant gloves, with some wearing eye protection. No worker wore a respirator.

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, 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 and/or hair.

Additionally, as presented at a June 2007 HSRB meeting, to account for potential residue collection method inefficiencies[10], 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 AHE120 the measurements fell in the second category – on average 34% of total dermal exposure consisted of exposure to the hands and head – thus hand rinse and face/neck wipe measurements have been adjusted upward by a factor of 2 (i.e., multiplied by 2).

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

Total dermal exposure was calculated by summing exposure across all body parts for each individual monitored. Total inhalation exposures were calculated by adjusting the measured air concentration (i.e., ug/L) using a breathing rate of 16.7 L/min representing light activities (NAFTA, 1998), and total work/monitoring time.[11] 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 16 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 EPA's study review of AHE120 (Crowley, 2016).

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[10] The terminology used to describe this are "method efficiency adjusted" (MEA) or "method efficiency corrected" (MEC).
[11] Inhalation Exposure (ug) = collected air residue (ug) x [breathing rate (L/min) ÷ average pump flow rate (L/min)].

MU ID	State	Mix/Load Type	Work/ Monitoring Time (hours)	Solution Mixed (gallons)	AaiH (lbs)	Unit Exposure (ug/lb ai)		
						Dermal		
						Non-MEA	MEA	Inhalation
M3	FL	App. Equip.	6.9	9000	61	6.49	7.04	0.0042
M6	ND	App. Equip.	10.5	4650	212	9.5	14.53	1.08
M7	ND	App. Equip.	3.0	2520	142	8.45	9.96	1.18
M10	FL	App. Equip.	1.5	1500	0.92	5.24	6.74	0.192
M11	CA	Holding tank, then loaded/transferred	8.3	4200	58	4.72	5.51	3.89
M12	LA	Holding tank, then loaded/transferred	1.1	700	24	0.334	0.48	0.00574
M13	CA	App. Equip.	6.1	1500	1.3	8.13	12.45	0.0743
M14	ND	App. Equip.	3.0	1900	58	8.05	8.35	0.000781
M15	MS	App. Equip.	2.7	2250	82	3.16	3.92	0.000561
M18	LA	Intermediate solution tank, then loaded/transfered	0.7	700	73	8.06	9.18	0.0361
M20	MN	Holding tank, then loaded/transferred	4.0	1700	272	1.13	1.18	0.0174
M21	FL	App. Equip.	3.8	3000	21	0.65	1.06	0.0373
M22	FL	App. Equip.	3.8	3000	6.1	8.16	10.21	0.0688
M23	CA	App. Equip.	3.7	200	1.8	36.3	64.72	1.37
M24	CA	App. Equip.	3.7	200	1.7	1.55	2.31	0.0466
M25	CA		2.1	600	2.3	12.6	19.1	1.33

Table 2. Mixing/Loading Water Soluble Packets Exposure Summary

MEA = method efficiency adjustment

Figure 3: Dermal Unit Exposures (ug/lb ai)
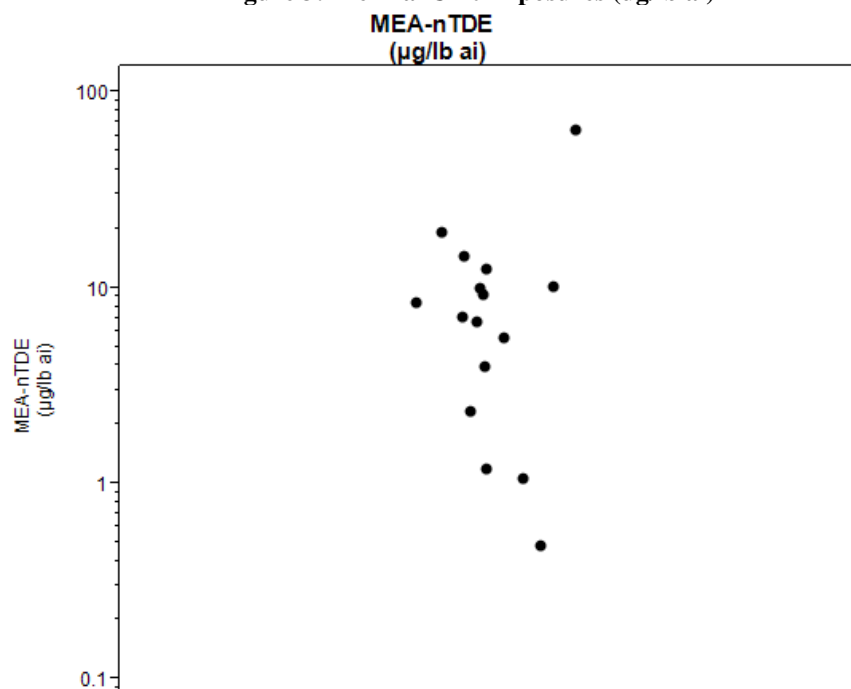
Figure 4: Inhalation Unit Exposures (ug/lb ai)
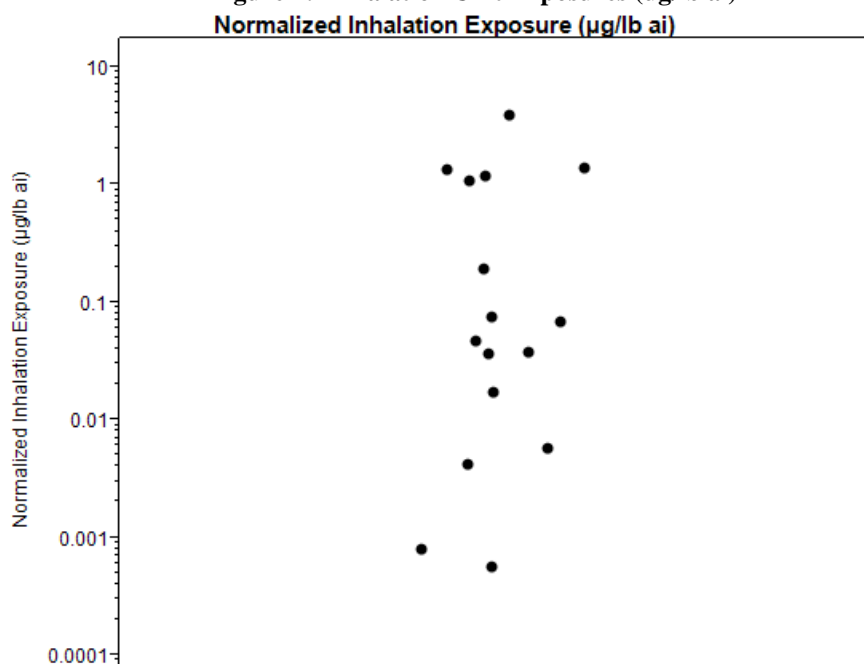
3.3   Evaluation of Scenario Benchmark Objectives

The AHETF monograph details the extent to which the mixing/loading water soluble packets scenario meets objectives described in Section 2.1. The monograph states that both the primary objective (3-fold accuracy) and secondary objective (adequate analytical power to evaluate

proportionality) were met. EPA agrees with the methodologies used to assess these objectives (Appendix D of Klonne and Holden, 2015) and has independently confirmed the results by re-analyzing the data with the AHETF-supplied statistical programming code[12].

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 data structure of 5 clusters each with 5 monitored workers, totaling 25 data points. 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 accuracy objective. However, when AHE120 was conducted, the AHETF was not able to achieve the intended efficient monitoring configurations due to recruitment difficulties, resulting in an extended (> 3 year) monitoring period and, from a data analysis perspective, more clusters than intended. While AHE120 utilized the monitoring areas as intended (NY, FL, LA/MS, ND/MN, and CA), they were not conducted in an efficient temporal manner. For example, the AHETF conducted monitoring in Florida in 2011, 2013, and 2014. Ultimately, the analysis of the benchmark grouped the data from the 5 monitoring areas into 10 clusters, using a 90-day monitoring separation as the threshold. Figure 5 below (from AHE1014 Appendix D Table 2) illustrates the clustering used for analysis of the primary objective.

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[12] A typographical error was identified in the SAS code which used the acronym "OCGB", referencing another AHETF data-based scenario (Open Cab Groundboom). EPA confirmed that the rest of the SAS programming and the data it used were indeed for the mixing/loading WSP scenario, not the OCGB scenario.

Figure 5: AHE1014 Summary of Data 'Clusters'

Cluster	Monitoring Area Code	Monitoring Unit	Monitoring Date	Nearest Town
1	122	M03	11/05/2011	Thonotosassa FL
2	122	M10	01/16/2013	Boca Raton FL
3	122	M21	11/05/2014	Bradenton FL
		M22	11/07/2014	Sebring FL
4	123	M12	08/06/2013	Bastrop LA
5	123	M15	07/30/2014	Dundee MS
		M18	08/06/2014	Gilbert LA
6	124	M06	07/11/2012	Donnybrook ND
		M07	07/12/2012	Tolley ND
7	124	M14	07/16/2014	Bottineau ND
		M20	09/03/2014	Appleton MN
8	125	M11	03/28/2013	Firebaugh CA
9	125	M13	06/18/2014	Kingsburg CA
10	125	M23	11/19/2014	Sanger CA
		M24	11/20/2014	Reedely CA
		M25	11/25/2014	Fresno CA

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, 2015), 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.

EPA performed the method efficiency adjustments on the dermal exposure, utilizing the same (SAS) statistical programming code submitted by the AHETF, except substituting the input data with the MEA data. The primary benchmark of 3-fold accuracy for select statistics was met for both dermal exposure data adjusted and unadjusted for potential hand rinse and face/neck wipe method inefficiencies. Accuracy results for inhalation exposure, though not formally part of the primary objective were much higher than those for dermal, likely due to the larger variability in the inhalation exposure distribution. Results for the unadjusted and adjusted dermal exposure data are presented below in Table 3 and inhalation exposure in Table 4.

Table 3. Mix/Load WSP – Results of Primary Benchmark Analysis for Dermal Exposure						
	Dermal (MEA) [a]			Dermal (non-MEA)		
Statistic	Unit Exposure (ug/lb ai)		fRA_{95}	Unit Exposure (ug/lb ai)		fRA_{95}
	Estimate	95% CI		Estimate	95% CI	
GM_S	5.95	3.25 – 10.78	1.8	4.52	2.47 – 8.21	1.8
GSD_S	3.39	2.21 – 5.17	--	3.32	2.18 – 5.03	--
GM_M	5.95	3.22 – 10.92	1.8	4.52	2.47 – 8.21	1.8
GSD_M	3.39	2.22 – 5.29	--	3.32	2.19 – 5.15	--
ICC	0.00	0.00 – 0.75	--	0.00	0.00 – 0.75	--
GM_S = geometric mean assuming SRS = "exp(average of 16 ln(UE)) values". GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 16 ln(UE)) values" GM_M = variance component model-based geometric mean GSD_M = variance component model-based geometric standard deviation ICC = intra-cluster correlation						
AM_S	11.05	5.51 – 26.93	2.2	7.66	4.17 – 19.49	2.2
AM_U	12.53	5.91 – 28.90	2.2	9.29	4.45 – 20.99	2.2
AM_M	12.53	5.95 – 29.93	2.3	9.29	4.48 – 21.65	2.2
AM_S = simple average of 16 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}						
$P95_S$	64.72	16.24 – 214.9	3.9	36.3	12.1 – 153.8	3.8
$P95_U$	44.27	17.28 – 109.9	2.5	32.5	12.9 – 79.6	2.5
$P95_M$	44.27	17.46 – 113.6	2.6	32.5	13.0 – 82.3	2.5
$P95_S$ = 95th percentile (i.e., the 15th unit exposure out of 16 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 4. Mix/Load WSP – Results of Primary Benchmark Analysis for Inhalation Exposure			
	Inhalation		
Statistic	Unit Exposure (ug/lb ai)		fRA_{95}
	Estimate	95% CI	
GM_S	0.0650	0.0117 – 0.3050	5.1
GSD_S	15.12	5.33 – 43.70	--
GM_M	0.0601	0.0123 – 0.2917	4.9
GSD_M	15.57	5.42 – 47.23	--
ICC	0.54	0.00 – 0.90	--
GM_S = geometric mean assuming SRS = "exp(average of 16 ln(UE)) values". GSD_S = geometric standard deviation assuming SRS = "exp(standard deviation of 16 ln(UE)) values" GM_M = variance component model-based geometric mean GSD_M = variance component model-based geometric standard deviation ICC = intra-cluster correlation			
AM_S	0.583	0.081 – 15.094	24.1
AM_U	2.602	0.136 – 98.285	26.2
AM_M	2.604	0.143 – 128.261	30.0
AM_S = simple average of 16 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}			
$P95_S$	3.89	0.43 – 211.76	22.7
$P95_U$	5.67	0.48 – 54.78	10.8
$P95_M$	5.50	0.50 – 59.19	10.8
$P95_S$ = 95th percentile (i.e., the 15th unit exposure out of 16 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			

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. Upon completion of the study the data can be analyzed to see if it provides a level of precision consistent with that benchmark. Based on the AHETF analysis, 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 of 1.4 (or less) indicates at least 80% statistical power.

As for the primary objective, EPA utilized the MEA dermal exposure data to perform the regression analysis in addition to the AHETF's use of the non-MEA dermal data. There was no substantive effect on the conclusions regarding the secondary objective. 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%, and the 95% confidence interval slope of the mixed-effects regression – preferred since it accounts for within-cluster correlation – excludes 0 and includes 1, suggesting a proportional relationship between exposure and the amount of active ingredient handled is more consistent with the data than an independent one.

The resulting regression slopes and confidence intervals for (MEA and non-MEA) dermal exposure and inhalation exposure are summarized in Table 5.

	Dermal Exposure						Inhalation Exposure		
Model	**Standard (non-MEA)**			**MEA**					
	Est.	**95% CI**	**CI Width**	**Est.**	**95% CI**	**CI Width**	**Est.**	**95% CI**	**CI Width**
Simple Linear	0.88	0.53 – 1.22	0.68	0.82	0.48 – 1.17	0.68	0.67	-0.10 – 1.43	1.53
Mixed-Effects	0.88	0.53 – 1.22	0.68	0.82	0.48 – 1.17	0.68	0.81	-0.19 – 1.82	2.01

Table 5. Summary Results of log-log Regression Slopes

Note: results shown using the Kenward-Rogers denominator degrees of freedom method. AHETF statistical analysis (AHE1014 Appendices D and E) provides results using the Containment method as well. Results were not substantially different.

4.0 Data Generalizations and Limitations

The need for an upgraded generic pesticide handler exposure database has been publicly discussed and established (Christian, 2007). No existing exposure data for mixing and loading

water soluble packets was identified, therefore AHE120 was conducted to supplant data used in regulatory risk assessments. The data will be used generically to assess exposure for workers who mix and load any conventional pesticide formulated in water soluble packaging. However, certain limitations need to be recognized with respect to collection, use, and interpretation of the exposure data.

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.

4.1   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 in water soluble packaging 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.

As described in Section 3.1, the AHETF identified practices and conditions early on in the conduct of AHE120 that they considered outside the scope of the intended practices when mixing/loading WSPs. Subsequent protocol amendments excluded certain practices and provided more explicit instructions for mixing and loading WSPs. Ultimately, monitoring for 9 workers was not included in the final dataset: 6 workers conducted practices considered outside the scope of the AHETF mixing/loading WSP scenario, and monitoring for 3 workers was not conducted or terminated due to improper dissolution or broken packaging (see Section 2.6 and Appendix G of the AHE120 study report). The final dataset submitted by the AHETF – consisting of 16 instead of 25 MUs as a result of data exclusions and/or monitoring termination – represents practices and conditions the AHETF believes are consistent with intended use of WSPs.

EPA agrees with this approach but also recognizes that use of the data is contingent upon product labels containing instructions that are consistent with those practices. As such, EPA risk assessments that use the data will require product label amendments to include mixing/loading instructions that prohibit the practices excluded in the AHETF dataset. EPA will also engage in outreach to the pesticide handler community to determine whether the proposed changes are feasible for these types of products.[13]

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 in water soluble packaging which 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).

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[13] See previous reference to SFIREG engagement.

4.3   Use of "Unit Exposures"

As previously described, 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") 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 water soluble packets. It is important to recognize this as a limitation when making use of the data.

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 AHE120 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 AHE120 loaded and mixed the product directly in the application equipment tank.

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., 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 AHE120, 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 Water Soluble Packets 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 water soluble packets 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 met: upon completion of the study analysis demonstrated that the data provides a level of precision consistent with the pre-study goal of distinguishing complete proportionality from complete independence between dermal exposure and amount of active ingredient handled with 80% statistical power.
- 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.
- Though the desired diversity in the type of mixing/loading activities was not achieved and monitoring exclusions resulted in a total dataset of 16 instead of the intended 25 MUs, EPA does not believe additional monitoring is necessary given the recruitment difficulties experienced by the AHETF.
- 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 pesticide products in water soluble packaging.
- Reliance on the data in human health pesticide risk assessments during the pesticide registration process is contingent on the inclusion of mixing/loading instructions on product labels that are consistent with practices represented by the 16 workers in the dataset.

6.0   References

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Appendix A

Normal and Lognormal Probability Plots of (MEA) Dermal Unit Exposures
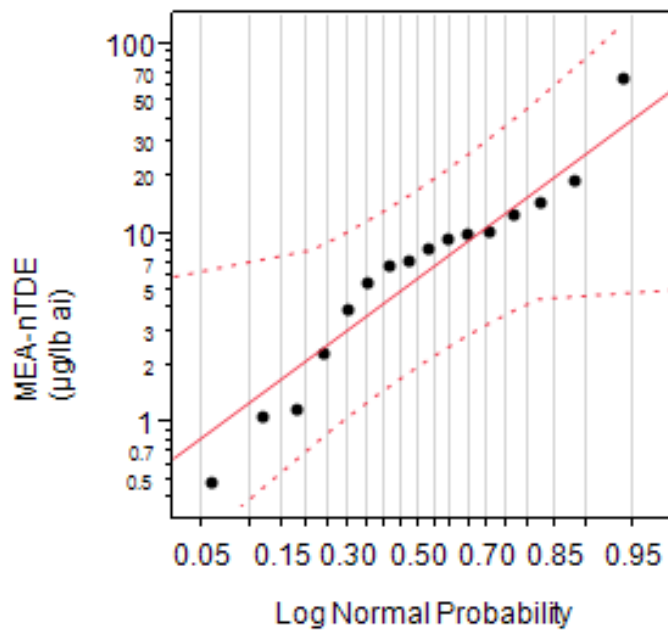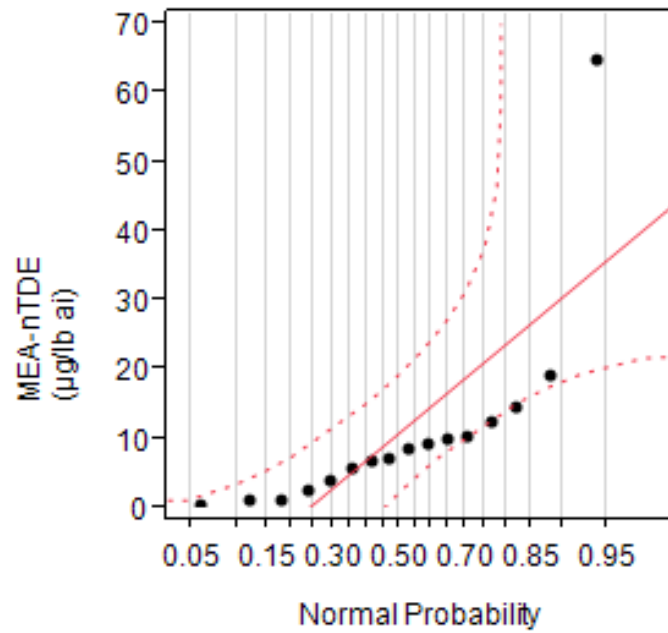
Normal and Lognormal Probability Plots of Inhalation Unit Exposures