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

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

September 26, 2011

MEMORANDUM

SUBJECT: Science and Ethics Review of AHETF Scenario Design and Protocol AHE500 for Exposure Monitoring of Workers During Closed System Loading of Returnable and Non-Returnable Containers in the United States

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REF: Collier, R. (2011) Closed System Loading of Liquids Scenarios Submission. Unpublished protocol dated August 2, 2011, prepared for the Agricultural Handler Exposure Task Force under Sponsor ID AHE500, 438 p.

We have reviewed the referenced proposal from both scientific and ethics perspectives. Scientific aspects of the proposed research are assessed in terms of the recommendations of the EPA Guidelines Series 875 and of the EPA Human Studies Review Board (HSRB). Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the HSRB. Below is a summary of the conclusions reached in our science and ethics reviews.

Science Review

- The protocol addresses the technical aspects of applicable exposure monitoring guidelines and is likely to produce scientifically valid and useful data.

- Given the importance in this study of capturing information about observed worker behavior, the AHETF should provide study observers with a list of specific types of behaviors that should be noted in the field log, to complement the general information provided in SOP AHETF-10.C.5.

Ethics Review

- The protocol meets the applicable ethical requirements of 40 CFR part 26, subparts K and L.

- Please make the following revisions before moving forward with the research:

    - Add a statement to the consent form that explains to subjects that if, after their participation in the study, they experience symptom that they believe is related to their participation in the study, they should contact the Study Director immediately. A telephone number should be provided.

    - The AHETF should develop procedures for handling such a call and document those procedures in a new or existing SOP.

- The AHETF should incorporate the forthcoming guidance from the HSRB about how to provide personal exposure results to subjects.

A. Responsiveness to Previous EPA and HSRB Comments

Previous EPA and/or HSRB Comments applicable to this protocol	Is the comment reflected or addressed in this protocol?
1. Add risks from exposure to the surrogate chemicals as one of the risks associated with participation in this study.	**Yes.**
2. Do not identify the receipt of exposure results as a benefit to the subjects.	**Yes**
3. Clarify "greater than minimal risk".	**Yes.** The protocol clearly states that the reason that the study is classified as "greater than minimal risk" is because of the risk of heat-related illness due to subjects wearing an extra layer of clothing.
4. The Board recommended that AHETF clarify how witnesses will be selected for workers who self-identify as non-readers. It needs to be clarified that these witnesses are not associated with the research project.	**Yes.** SOP AHETF-11.I.3 was revised to remove the option of the Study Director choosing a witness, and to clarify that witnesses will be selected by the subject.

Previous EPA and/or HSRB Comments applicable to this protocol	Is the comment reflected or addressed in this protocol?
5. The Board recommended that language about a subject's right to refuse medical treatment language be revised as follows: "You may refuse medical treatment unless the medical professional decides (based on established criteria) that you are too sick to make a decision about getting medical treatment." In addition, it recommended that in an appropriate SOP, the criteria for decision-making capacity are provided as guidance for medical professionals who perform this function in AHETF research.	**Partially.** The language in the consent form reads: "You may refuse medical treatment unless the medical professional decides that you are too sick to make a decision about getting medical treatment." SOP AHETF-11.H.3 was appropriately revised to include a statement recognizing a subject's right to refuse medical treatment. However, the SOP does not specify the criteria that will be used by the medical professional to make that decision. SOP AHETF-11.H.3 should be further revised to include such criteria.

B. Completeness and Contents of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. All required elements are present. EPA's checklist is appended to this review as Attachment 6.

C. Summary Assessment of the Scenario Design[1]

1. **Scenario Design:** The AHETF protocol AHE500 describes two study designs for closed mixing loading scenarios to be in their database: 1) closed system loading of liquids packaged in non-returnable containers (CSLL-NR); and 2) closed system loading of liquids packaged in returnable containers (CSLL-R). EPA's Worker Protection Standard (WPS) defines closed systems as those that are "designed by the manufacturer to enclose the pesticide to prevent it from contacting handlers or other people while it is being handled. Such systems must function properly and be used and maintained in accordance with the manufacturer's written operating instructions." The use of closed mixing loading systems permits handlers to wear less Personal Protective Equipment (PPE) than required by pesticide labeling for open mixing/loading, including in some cases not wearing chemical resistant gloves. However, for both AHETF closed system loading scenarios addressed in this protocol, the handler attire shall consist of long sleeved shirts, long pants, shoes plus socks. The PPE shall include chemical resistant gloves and protective eyewear when subjects are using closed systems that operate under pressure. The requirement of CSLLs on pesticide labels is a widely used regulatory option to mitigate handler risks for highly toxic pesticides such as some organophosphates.

   The AHETF anticipates that recruitment will be challenging for both scenarios because of CSLL variability and the reasons CSLLs are used (e.g., toxic pesticides or

[1] Supporting details are in Attachment 1.

convenience/efficiency for large spraying operations). The latter consideration suggests that fewer numbers of users of these equipment types would be available in a given study area compared to widely used equipment such as ground boom or airblast sprayers.

The AHETF recognizes the highly variable nature of CSLLs and also notes the diminishing number of CSLL manufacturers. The AHETF also acknowledges that custom made systems built and used by growers or contract spray operators are common. Thus it is possible that the participants in the two CSLL studies could be operating any number of systems provided they meet the broad requirements of a closed liquid loading system as defined by the WPS (i.e., enclosed and prevent contact). Closed loading liquid systems may be broadly categorized as: suction/extraction, container breach and direct drop/gravity feed. Suction extraction is widely used for returnable containers while container breach and some direct drop/gravity feed systems are available for smaller non-returnable containers.

For the CSLL-NR scenario, there are no acceptable existing studies. To develop the new data, AHETF have selected a seven by three (clusters by subjects) study configuration for the CSLL-NR scenario. This will result in a total of 21 Monitoring Units (MUs) for the CSLL-NR scenario. This configuration was used by the AHETF for two previous scenarios (backpack and handgun applicators in Rights of Way sites) and reviewed favorably by the Board in October 2010. Because this is a mix/load scenario and not an application scenario, the Task Force has a large number of surrogate active ingredients (13) available for consideration for the CSLL-NR scenario.

There are existing data available for the CSLL-R scenario; however, additional data need to be collected. There are two existing clusters (California and Texas) with 22 MUs. Five new clusters with 3 MUs per cluster are proposed. Up to nine surrogate active ingredients packaged in returnable containers are available for use in the CSLL-R study.

EPA intends to use these data to estimate daily dermal and inhalation exposures of pesticide handlers loading pesticides formulated as liquids and handled using a variety of CSLLs. The Agency has always encouraged the use of closed mixing/loading systems (for example by reducing the required PPE if such systems are used). However, these data will be used primarily in risk assessments to characterize the impact of such systems to mitigate open mixing loading exposure/risks of concern.

2. Sampling Design:

Five and seven new clusters (monitoring areas) each having 3 monitoring units (MUs) have been proposed for the CSLL-R and CSLL-NR scenarios. To do this AHETF will:

- Identify geographic areas associated with the use of more toxic pesticides (excluding fumigants) increasing the likelihood of closed system usage
- Stratify CSLL use areas by EPA growing regions
- Identify the predominant surrogate pesticide-using states and provinces in the EPA growing regions

- Select one major agricultural state likely to support an efficient study configuration and to have an ample supply of handlers. For these two scenarios, the AHETF selected the entire state to be the monitoring area due to anticipated problems with recruitment. The recruitment concern is being able to identify participants using diverse close mixing/loading systems using the clothing/PPE scenario desired by the AHETF.

The AHETF have purposively selected the following states for the proposed monitoring sites by scenario. Three MUs are proposed for each state/monitoring area.

Proposed Study Sites		
State	CSLL-NR	CSLL-R
Florida	yes	yes
Michigan	yes	yes
Nebraska	yes	yes
Arizona	yes	yes
Washington	yes	yes
Mississippi	yes	**no***
Texas	yes	**no***

* Existing studies were conducted in Texas and California.

EPA agrees that the selected states are likely to provide regional, climatic and agronomic variability in addition to being areas where closed liquid loading systems are used. This scenario addresses the exposures of individuals using closed systems to mix/load liquids (package in returnable and non-returnable containers) into a variety of tanks including those connected to application equipment. These scenarios do not address the exposures of individuals making pesticide applications.

After the monitoring areas are identified, the next stage of the diversity selection process involves delineating the practical range of amount of active ingredient handled (AaiH) for the two closed system mixing/loading scenarios. For the CSLL-NR scenario, three bands (strata) ranging from 12 to 800 pounds AaiH are proposed with the upper band (311 to 800) likely to be filled by mixer/loaders supporting aerial applications. For the CSLL-R scenario, three bands ranging from 60 to 2,400 pounds AaiH are proposed. Past studies have shown that AaiH is associated with exposure and is a meta-factor associated with differences in equipment and mixing/loading and spraying practices. The lower band of the AaiH for the CSLL-R is likely to be filled by mixer/loaders supporting ground sprays. The range of each stratum is two-fold. The AHETF assert that this characteristic ensures that when there is one MU per stratum, an order of magnitude in AaiH will be achieved. The scenario specific AaiH strata are as follows:

CSLL-NR

- 12 to 30 lbs AaiH
- 31 to 310 lbs AaiH
- 311 to 800 lbs AaiH

CSLL-R

- 60 to 119 lbs AaiH
- 120 to 1,200 lbs AaiH
- 1,201 to 2400 AaiH

The next stage of sample selection results in identifying the growers whose crops will be treated and the workers whose exposure will be monitored. As with other agricultural pesticide scenarios, growers who agree to cooperate with the research and to have their crop treated with any of surrogate pesticides must be identified before study participants can be recruited.

The AHETF process for identifying handler subjects recruited from growers or commercial pesticide application firms includes five steps:

- Contacting resources such as Farm Market ID and Meister Media Worldwide to identify growers using closed mixing/loading systems
- Assembling a list of growers from all resources contacted and eliminating duplicates
- Assembling a list of commercial applicators in each state from sources such as pesticide applicator licensing authorities and the National Agricultural Aviation Association.
- Combine both grower and commercial applicator lists
- Putting the list of growers into random order
- Contact a random subsample from the combined grower and commercial applicator list (i.e., employer list), one at a time, in the sequence of the randomized list, to determine whether the grower is 'eligible' to participate
- Placing eligible employers into a "working pool"

Screening of employers for eligibility will continue until the pool contains somewhat more employers with somewhat more handlers than are needed to fill three MUs in each cluster. From each employer in the working pool, the following range of information will be compiled:

- The employer is willing to cooperate with the AHETF
- The employer has the necessary mixing/loading equipment
- The employer has at least one handler with experience with the CSLL equipment
- The employer will permit AHETF to recruit their employee(s)
- The employer has sufficient acreage that the minimum AaiH can be mixed/loaded
- The employer is willing to use a least one of the surrogates

This process of identifying cooperating growers is basically sound. EPA has accepted this approach.

When selecting MUs, the following restrictions will be enforced to increase diversity within the cluster:

- No two MUs obtained for the same scenario can monitor the same worker
- No two workers in the same monitoring area used for the same scenario can have the same employer
- If an employer has previously contributed a worker to an MU in a different monitoring area for the same scenario, then it is preferable that this same employer not contribute a worker to another monitoring area.
- It is preferable that no two MUs obtained for the same scenario in the same monitoring area be in the same AaiH stratum
- Each MU in a monitoring area must differ with respect to at least one of the following characteristics: type of closed system, container size, and transfer set-up (i.e., transfer directly to a spray tank or transfer to a mix tank and then to a spray tank). Ideally, each MU will utilize a different system type, but it is likely that it will be difficult to locate all systems in all monitoring areas. In addition, completely closed systems are most desirable.

The growers and/or commercial pesticide applicator companies in the chosen configuration provide the pool of handlers from which handlers will be recruited to fill each of the three MU slots. If selected growers or handlers drop out as the time of the field study approaches, additional handlers appropriate to fill out the MU design may be recruitable from among those employed by growers and commercial firms already in the working pool of eligible entities. If there are too few handlers available in the pool to complete a revised efficient configuration, the working pool can be expanded by approaching more growers or commercial firms from the original randomized list. If the original randomized list is exhausted without finding enough interested handlers to complete the field study design, another list will be generated. Alternatively, the AHETF may consider monitoring as soon as there is an eligible participant if recruitment proves to be too difficult.

1. **Choice of Surrogate Materials:** The surrogate pesticides and their possible packaging types for the two scenarios are delineated in the following table. These pesticides have a wide range of application rates that should help fill the AaiH strata in each monitoring area.

Surrogate Pesticide	Available in NR Containers	Available in R Containers
Carbaryl	yes	no
Chlorothalonil	yes	possible
Dacthal (DCPA)	yes	no
Fosamine	yes	yes
Glyphosate	yes	yes
Imazapyr	yes	yes
Imidacloprid	yes	limited
Malathion	yes	yes
Simazine	yes	possible
Sulfur	yes	unknown
Thiophanate-Methyl	yes	unknown

2,4-D	yes	yes
2,4-DB	yes	yes

C. Summary Assessment of the Scientific Aspects of the Study Design[2]

1. Statistical design and sample size determination:

Existing Data for the CSLL-NR Scenario:
Since there are no acceptable existing data, the AHETF will collect 21 MUs based on a seven cluster by three MU design to adequately address the CSLL-NR scenario.

Existing Data for the CSLL-R Scenario:
There are seven MUs from the purchased study AH501-M-1 that will be used to address this scenario. These MUs involved two workers on two days, however, and thus do not represent completely independent measurements. Worker A was measured twice on day one and once on day two. Worker E was measured twice on day one and day two. Thus, these MUs represent three cases of 2 MUs collected using the same worker on the same day. These MUs also include three cases of 2 MUs by the same worker on the same day. There are also 15 MUs from AHE13 that are applicable to the CSLL-R scenario, but some workers were utilized for more than one MU. EPA agrees with AHETF that these data alone are not sufficient for a complete CSLL-R scenario, and so additional data are warranted. The structure of these existing data was summarized by the AHETF as follows:

Structure of AH501 Data for the CSLL-R Scenario:

Study	Location and Dates	Worker ID	**Amounts of Active Ingredient Handled by MUs (lbs.*), each on Separate Day.**			
			1		**2**	
AH501-M-1	Cocoran, CA October 2 and 4, 1991	A	1,531	1,569	1,569	
		E	1,531	1,430	682	1,196

*Amounts rounded to nearest pound

Structure of AHE13 Data for the CSLL-R Scenario:

Study	Location and Dates	Worker ID	**Amounts of Active Ingredient Handled by MUs (lbs.*), each on Separate Day.**

[2] Supporting details are in Attachment 2.

Study	Location and Dates	Worker ID	**Amounts of Active Ingredient Handled by MUs (lbs.*), each on Separate Day.**		
AHE13	Garden City, TX October 18 - 25, 2004	A	8,455	9,573	5,564
		B	6,267	9,603	4,386
		C	1,713	2,683	7,504
		D	2,426	4,851	9,504
		E	2,327		
		F	6,009		
		G	4,415		

*Amounts rounded to nearest pound

Reference Distribution:

Sample sizes are determined by using a random sampling reference model which is reasonably close to the actual diversity selection process. Sample sizes that would be appropriate under the reference model are then assumed to be reasonable for the study.

The AHETF reference model assumes that:

• Normalized exposure is log-normally distributed with a known geometric standard deviation (GSD). This also means that the logarithm of normalized exposure is normally distributed with a known standard deviation SD=Log(GSD).

• There will be N_C new monitoring areas and N_M new MUs per area. The total number of new MUs in a scenario is, therefore, $N = N_C \times N_M$.

• There may be correlation between the (logarithm of) normalized exposures of MUs if they have been efficiently configured to form a single cluster in a monitoring area. This is referred to as intra-cluster correlation, or simply ICC.

Based on analyses of exposure from a number of available monitoring studies, Appendix C of the AHETF Governing Document derived a default relative variation structure consisting of a geometric standard deviation (GSD) of 4 and an intracluster correlation (ICC) of 0.3. AHETF used these values of the reference parameters (GSD and ICC) to determine the sample size.

Because the CSLL-R scenario has existing MUs from previously-conducted studies to consider, the AHETF made the following assumptions for this scenario only:

• Each different location in the existing data corresponds to a different cluster.

• The same lognormal distribution, GSD, and ICC apply for existing MUs. However, because some existing MUs were conducted by the same worker and some workers conducted two MUs per day, there may also be non-zero within-worker correlation (IWC) and/or within-worker-day correlation (IDC).

The Number and Configuration of New MUs:

Based on interviews with growers and commercial application companies, AHETF identified several factors that make obtaining MUs especially difficult for these scenarios:

• Suitable closed systems are not commonly in use.

• Commercially available systems are not readily available for some system types.

• Handlers that do use appropriate systems sometimes wear additional PPE that are contrary to the design criteria for these scenarios, such as chemical-resistant clothing or aprons.

• Diversity in system type is desirable within each monitoring area.

According to the AHETF it is less costly to keep the number of monitoring areas as small as possible and have a large number of MUs per area. Because of the above complications, however, designs with a smaller number of MUs per monitoring area are more likely to be attainable for all the areas selected. Therefore, the configuration size is restricted to N_M=3 for all new MUs.

Appendix C of the Governing Document describes the simulation methodology needed to calculate sample sizes when the reference model used is cluster sampling from a lognormal distribution. These simulations determine accuracy or power given the number and configuration of MUs. For the scenarios discussed in this review, the simulations require that the structure of any existing MUs be held constant and only the number of new MUs is varied. It is the combination of existing and new MUs that must satisfy the benchmark objectives:

1. **Primary Objective**: Estimates of the geometric mean, the arithmetic mean, and the 95th percentile of normalized dermal exposure generally need to be accurate to within approximately 3-fold of their actual population value assuming the reference random sampling model applies.
2. **Secondary Objective:** If the reference model was true, and AaiH is assumed to be the normalizing factor of interest for each scenario, there should be at least 80% statistical power to distinguish complete proportionality from complete independence between dermal exposure and AaiH.

Using the simulation approach described in page 35 of the AHETF document entitled: "Closed System Loading of Liquids in Returnable and Non-Returnable Containers" it

was found that for the CSLL-NR scenario 7 new clusters with 3 MUs each are required to meet the primary benchmark. For the CSLL-R scenario, the primary objective is satisfied if the two existing clusters of 22 MUs are augmented with 5 new monitoring areas of 3 MUs each.

MU and Cluster configuration for the CSLL-NR and CSLL-R:

Scenarios	Items	Numbers of MUs		
		Existing	New	Total
CSLL -NR	Clusters	0	7	7
	Workers	0	21	21
	MU	0	21	21
CSLL-R	Clusters	2	5	7
	Workers	9	15	24
	MU	22	15	37

The AHETF suggest that "for the secondary objective the power to detect proportionality between exposure and AaiH also depends on the particular values of AaiH used. For any existing MUs the AaiH levels actually observed were used. However AaiH levels must be simulated for the hypothesized new MUs. Diversity selection for new monitoring areas will require that the AaiH levels for MUs extend over the complete practical range expected for each of the CSLL scenarios. For CSLL-NR, this practical range is 12 to 800 lbs. ai handled per workday. For CSLL-R, the practical range is 60 to 2,400 lbs. ai handled per workday. Diversity in AaiH levels is achieved by first partitioning the appropriate practical range into N_M=3 strata. Then, for each new configuration a single new MU is obtained from within each AaiH stratum. In order to achieve within-monitoring-area diversification of AaiH each of the practical AaiH ranges was partitioned into following three strata:

CSLL-NR:
• From 12 to 30 AaiH
• From 31 to 310 AaiH
• From 311 to 800 AaiH

CSLL-R:
• From 60 to 119 AaiH
• From 120 to 1,200 AaiH
• From 1,201 to 2,400 AaiH "

The AHETF further assert that "within each simulated new configuration, an AaiH level is simulated log-uniformly from within each of the N_M=3 strata. Then exposure data are simulated for both the existing and new MUs assuming proportionality with the AaiH levels. For each simulated set of data, a regression analysis is then performed and the significance of the log-log slope determined (2-sided test). The power is the proportion of the simulated configurations for which the slope was significant at $p<0.05$.

Using the primary benchmark sample sizes in the above table and the AaiH strata, the power was found to exceed 99% for both the CSLL-NR and the CSLL-R scenarios. In other words, the proposed number and configuration of MUs that satisfy the primary benchmark objective also more than satisfy the secondary power objective for both scenarios."

A detailed description of the simulation procedure can be found in section 4 of part A of the AHETF document entitled: "Closed System Loading of Liquids in Returnable and Non-Returnable Containers".

2. **Proposed pattern of exposure:** The proposed minimum exposure duration for each MU was described as being at least 4 hours in duration involving the mixing/loading of at least 3 tank-loads. The 4 hour minimum is considered by the AHETF as a guideline rather than a requirement.

   It should be noted that for both scenarios the subjects will only mix and load the surrogate pesticide. Applying the finished spray solution/suspension will be done by others not participating in the study. Over the course of a day each subject will mix/load the surrogate active ingredient in one of the following three aforementioned strata of AaiH proposed for the CSLL-NR and CSLL-R.

   There are 13 and up to nine surrogate pesticide active ingredients available for the CSLL-NR and CSLL-R, respectively. A cooperating grower may choose to use any of them for a specific MU. The liquid pesticides will be mixed/loaded/transferred via three kinds of closed mixing/loading systems (suction/extraction; direct drop/gravity feed systems; and container breach). The transfer may be to a mixing/holding or application tank.

   The AHETF will attempt to ensure that at least one MU in each cluster will reflect each of the closed mixing/loading systems mentioned above if it is determined that all three categories are possible in a given study area (i.e., cluster).

   For this scenario, the duration of the monitoring period is expected to vary considerably because of the wide range of AI to be handled by the different subjects. Furthermore, some subjects may perform other tasks between episodes of mixing and loading, and others may simply wait at the mixing site between episodes. The AHETF acknowledges that some scripting may be needed for subjects assigned to the lower AI strata to ensure at least 3 mixing/loading events are measured for each worker.

3. **Endpoints and Measures:** The study will measure dermal and inhalation exposure for each MU. These data will contribute to development of Unit Exposures (exposure per unit of pesticide active ingredient applied) or other exposure metrics, and to estimates of dermal and inhalation exposure to other pesticides for workers mixing and loading pesticides formulated as WPs. EPA believes that the proposed measures are appropriate and sound for the study design.

Dermal exposure will be measured by a whole body dosimeter (WBD) worn beneath the subject's outer clothing. After the monitoring event, the inner dosimeter will be removed from the subject and sectioned into two pieces: the upper dosimeter including the torso (above the waist) right and left upper arms (shoulder to elbow); right and left lower arms (elbow to cuff); and the lower dosimeter including right and left upper legs (waist to knee) and the right and left lower legs (knee to cuff).

Before beginning work, subjects will wash their hands in 500 mL of 0.01% Aerosol® OT-75 solution (AOT solution) to remove any source of contamination and to practice the method of hand-washing. These samples will be discarded. Hand wash samples will be collected before toilet and lunch breaks, before water breaks if required by the label or requested by the subject, and at the end of each exposure period.

Before beginning work, each subject's face and neck will be wiped with a cotton gauze swab to remove any contamination not associated with the monitoring event. This wipe sample will be discarded. Subjects will undergo another face/neck wipe sampling prior to the break and again at the end of the exposure period; both these samples will be retained for analysis. As required by AHETF SOP 10.C.4, the study team will record what type of personal protective equipment (PPE), including respirators, was worn at any time during the monitoring event.

Airborne concentrations of the surrogate will be monitored in the subject's breathing zone using an OSHA Versatile Sampler (OVS) tube sample collector connected to a personal sampling pump. The unit will be calibrated prior to the monitoring event using a rotameter. The OVS tube will be clipped to the subject's shirt collar with the intake facing downward. The air sampling pump will be connected to the OVS tube and will be operated for the total monitoring period including any breaks.

Additional measures will record environmental conditions at the time of monitoring. Observers will make field notes of subject activity throughout the monitoring event, and photographs or videos may be taken selectively to illustrate events.

Given the importance in this study of capturing information about observed worker behavior, the AHETF should provide study observers with a list of specific types of behaviors that should be noted in the field log. This guidance could complement the general information provided in SOP AHETF-10.C.5.

4. **QA/QC Plan:** The study will be monitored by three different quality assurance units: one from the exposure monitoring contractor that conducts the study in the field, one from the analytical laboratory that determines the level of pesticide residues in field samples, and one contracted directly by AHETF.

   Analytical and field sampling quality control procedures include complete validation of all analytical methods, field fortification and control samples, laboratory fortification and control samples, and guidelines on the use of calibration curves to determine chemical residues found on all sample matrices.

Field fortifications will be conducted in the field under the same conditions as the field samples. They will be transported and stored in a similar manner as the field samples, and will be analyzed in the laboratory concurrently with the field samples. Samples collected from the subjects will be corrected based on the results of the recovery of the field fortified samples.

5. **Statistical Analysis Plan:** The results of physical sample analysis will be provided in the final report of this field study and in the scenario monograph covering all monitoring conducted under both closed mixing/loading scenarios, and will be posted to the AHED® database, where they will be available to regulatory agencies for later statistical analysis. The documentation will report a confidence-interval-based approach to determine the relative accuracy for the arithmetic mean and 95th percentile of unit exposures. The AHETF will not otherwise statistically analyze the monitoring data.

D. Compliance with Applicable Scientific Standards

EPA agrees that the AHETF collect MUs for CSLL-NR scenario based on participants using a wide range of systems provided that they meet the WPS definition of a closed system – even if this includes the use of custom made systems. EPA also agrees that if recruitment proves difficult, participants may be monitored in a given monitoring area (i.e., cluster) before other participants are recruited.

This protocol itself adequately addresses the following elements according to applicable scientific standards:

- Scientific objective
- Experimental design for achieving objectives
- Quantification of the test materials
- Data collection, compilation and summary of test results
- Justification for selection of test substances
- Justification for sample size
- Fortification levels and number of samples for laboratory, field, and storage stability samples

Additionally, the proposal has addressed the technical aspects provided in the applicable exposure monitoring guidelines (i.e. Series 875 Group A and OECD Applicator Guidelines) as well as Good Laboratory Practices (GLPs).

E. Summary Assessment of Ethical Aspects of the Proposed Research[3]

1. **Societal Value of Proposed Research:** The objective of this study is to develop data to determine the potential exposure for workers who mix and load liquid pesticides using closed systems in the United States. This mixing/loading method is applicable to a large variety of commercially important crops, and the existing exposure data are inadequate. EPA will use the results of this study to estimate the dermal and inhalation exposure likely for a wide range of agricultural pesticides mixed and loaded under this exposure scenario.

2. **Subject Selection:** Subjects will be recruited among the employees of commercial growers who mix and load liquid pesticides using closed loading equipment, who are willing to use at least one of the surrogate active ingredients for this study, and who meet AHETF criteria for participation. Eligible growers will be identified from a complete list of growers in the target area, processed in random sequence. Subjects will be recruited who are employees of eligible growers (or of pesticide application service companies used by eligible growers), with experience within the past year using the piece of closed loading equipment that will be used in the study. If more employees are available and interested than are needed, qualified participants will be selected randomly. Although the design is purposive, and thus participants are not representative in a statistical sense, they are expected to be typical of those who mix and load liquid pesticides with closed systems.

   Subjects will be recruited according to the standard procedures set forth in SOP AHETF-11.B.6. The Study Director or designated researcher will seek permission from the eligible grower to approach his/her employees to recruit volunteers for the study. Depending on the number of employees and size of the grower's facility, the Study Director or researcher may contact employees using an informational recruitment flyer posted in a common work area. Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the grower's employees who express interest in participation. Such recruitment meetings will always occur without the grower or supervisors being present. The Study Director or researcher will describe the AHETF Exposure Monitoring Program, the goals of this specific study, the procedures to be used in exposure monitoring, and the risks and benefits to participants. The subject eligibility factors listed in the consent form and SOP AHETF-11.B.6 are appropriate.

   Candidates who attend an individual interview will be paid $20 whether or not they agree to participate; enrolled subjects who put on the whole-body dosimeter will be paid $80 in addition to their usual pay, whether or not they complete participation.

[3] Supporting details are in Attachment 2.

3. **Risks to Subjects:** Five kinds of risks to subjects are discussed in the protocol, along with specific steps proposed to minimize them:

    - The risk of heat-related illness
    - The risk associated with scripting of field activities
    - Psychological risk
    - The risk of exposure to surfactants
    - The risk of exposure to surrogate chemicals

    In this study, risks to subjects are classified as 'greater than minimal' since the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation. AHETF has adopted an extensive program to minimize these risks. Appropriate provision is made for safety and medical monitoring.

4. **Benefits:** This research offers no direct benefits to the subjects. The principal benefit of this research is likely to be reliable data about the dermal and inhalation exposure of workers mixing/loading pesticides using closed systems, usable by EPA and other regulatory agencies to support exposure assessments for a wide variety of pesticides with similar use patterns.

5. **Risk/Benefit Balance:** Risks to subjects have been minimized in the design of the research. The low residual risk is reasonable in light of the likely benefits to society from new data supporting more accurate handler exposure assessments for a wide range of agricultural pesticides.

6. **Independent Ethics Review:** The proposed research has been reviewed and approved by the Independent Investigational Review Board, Inc., (IIRB, Inc.) of Plantation, Florida. The submitted materials include a record of correspondence between the investigators and IIRB, Inc.

7. **Informed Consent:** Informed consent will be obtained from each prospective subject and appropriately documented. The reading level of the English language consent form is appropriate. Adequate provision is made to meet the needs of subjects who do not read either English or Spanish. EPA assessments of compliance with the requirements of 40 CFR §26.1116 and §26.1117 appear in Attachments 4 and 5 to this review.

8. **Respect for Subjects:** Subject identifying information will be kept strictly confidential. Provision is made for discrete handling of pregnancy testing, required of all female subjects on the day of testing. Candidates and subjects will be repeatedly reminded that they are free to decline to participate or to withdraw at any time for any reason, without penalty.

F. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

A detailed evaluation of how this proposal addresses applicable standards of ethical conduct is included in Attachments 2-5 to this review.

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

> EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

The protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA to rely on a study executed according to this protocol.

If conducted according to the protocol, this research should meet the ethical standards of FIFRA §12(a)(2)(P) and 40 CFR 26 subparts K and L.

Attachments:

1. EPA Scenario Review: AHETF Closed System Liquid Loading (AHE500)
2. EPA Protocol Review: AHETF Closed System Liquid Loading (AHE500)
3. §26.1111 Criteria for IRB approval of research
4. §26.1116 General requirements for informed consent
5. §26.1117 Documentation of informed consent
6. §26.1125 Criteria for Completeness of Proposals for Human Research

EPA Protocol Review: AHETF Closed System Loading of Liquids in Returnable and Non-Returnable Containers (AHE500)

Title: **Monitoring Unit Selection and Construction Plan for Scenarios: Closed System Loading of Liquids (Returnable and Non-Returnable Containers)**

Date: August 2, 2011

Sponsor: Agricultural Handler Exposure Task Force

1. Scope of Scenario Design

"Both closed system loading of liquids scenarios are defined by the formulation type and use of a system designed to safely transfer the pesticide. That is liquid pesticide products that are handled with closed systems to transfer the liquid from commercial packaging into a pre-mix or application tank. Closed systems are defined by the U.S. EPA's Worker Protection Standard (WPS, 40 CFR §170.240 (d)(4)) as those that "enclose the pesticide to prevent it from contacting handlers or other persons". AHETF and the Joint Regulatory Committee (June, 2011) have agreed that the closed loading of liquids handling situation should be addressed by two separate scenarios within AHED: one for non-returnable containers and one for returnable containers (generally 30 gallons or greater). Non-returnable containers are designed to be destroyed or recycled after use, and after rinsing, and are generally 55 gallons or less in capacity. Returnable containers are designed to be returned to the manufacturer or distributor, or refilled on site from a bulk supply such as a tanker truck, and are not rinsed in the field when empty."(p. 15 of 438)

Considering the nine states in the target area for these two scenarios, the following seven states were purposively selected to contain seven monitoring areas. This selection results in no repeats of states involved with existing studies, and no two new states being adjacent to each other.

1. Florida (for CSLL-NR and CSLL-R): Florida reflects a warm and humid climate in the southeastern U.S.

2. Michigan (for CSLL-NR and CSLL-R): Michigan reflects mostly a cool climate in upper Midwestern U.S.

3. Nebraska (for CSLL-NR and CSLL-R): Nebraska reflects a warm and dry climate in central Midwestern U.S.

4. Arizona (for CSLL-NR and CSLL-R): Arizona reflects a hot and dry climate in southwestern U.S.

5. Washington (for CSLL-NR and CSLL-R): Washington reflects both a cool climate (western portion) and a hot and dry climate (eastern portion) in the Pacific Northwest part of U.S.

6. Mississippi (for CSLL-NR only): Mississippi reflects mostly a warm and humid climate in southern U.S.

7. Texas (for CSLL-NR only): Texas reflects a hot and dry climate in the southern U.S. (pp. 42-43 of 438)

(a) Is the scenario adequately defined?

The scenario is clearly and appropriately defined.

(b) Is there a need for the data? Will it fill an important gap in understanding?

"AHETF has identified two closed loading of liquids scenarios as being within the scope of the task force goals and one for which data are lacking. These mixing/loading scenarios are applicable to a wide variety of commercially important crops and application techniques. Therefore, it is necessary to have data in AHED for the mixing/loading technique described by these scenarios." (pp. 22 of 438)

"AHETF (in conjunction with EPA, PMRA, and CDPR, collectively the Joint Regulatory Committee (JRC)) reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that satisfy current acceptability criteria and qualify for inclusion in a generic database. For this particular scenario, the JRC reviewed three studies (AH101, AH301, and AH501) involving closed loading systems. Only one of these studies, AH501 was found to be acceptable, and this study included some monitoring units involving closed system loading of liquids that were deemed appropriate for a generic database. Study AH501 was purchased by AHETF for inclusion into AHED. (p. 23 of 438)

"In addition to previously conducted studies, AHETF collected several MUs for closed loading of liquids in conjunction with study AHE13 that was primarily designed to collect aerial applicator exposure data. This study was conducted in 2004 and involved 15 MUs with large, returnable containers (260-gallons). However, only 7 unique workers were utilized so there is some use of repeated workers as in the purchased study discussed above." (p. 24 of 438)

2. Rationale for Scenario Sampling Design

(a) Are the variables in the scenario design likely to capture diverse exposures at the high-end?

"…exposure experts within the AHETF have identified equipment type as a potentially important parameter that might impact exposure. Factors such as the design of the type of system and the container size could affect the exposure potential of workers using these systems… there are three fundamental types of closed loading systems, plus some other less common system types:

- Suction/Extraction systems
- Direct Drop/Gravity Feed Systems
- Container Breach Systems

- Other systems (e.g., direct injection or gloved boxes)

For all of these system types, the closed transfer might deliver the pesticide to a mixing or holding tank, but not directly to an application tank. In this case, the mixing/loading process must be completed by another closed transfer to and application tank, generally by the use of a pump and flexible hoses with couplings designed to provide a tight fit with minimal liquid leakage upon disconnection… For the purposes of these scenarios, an MU may involve transfer to the mixing tank only, transfer to a mixing tank plus transfer to an application tank, or transfer directly to an application tank." (p. 51 of 438)

"Geographic Stratification: . . . the use of closed systems for loading liquids can be found throughout the nine states comprising the restricted scenario target area and can involve a wide variety of crops, including field crops, trellis crops, orchard crops and greenhouse/nursery crops. Geographic diversity between monitoring areas is expected to provide some variability in agronomic conditions and of other factors, such as equipment type, work practices, weather, etc. That is, it is viewed as a meta-factor that is associated with both known and unknown effects usually classified as simply 'study effects'. . . . A straightforward method for stratifying this area is to define each of the 9 U.S. states as a different geographic stratum. This is also convenient since chemical usage data will be utilized to guide initial monitoring are selection, and these data are available by state." (pp. 41 - 42 of 438)

"Predominant Surrogate Use: AHETF and experts consulted believe that closed systems are probably used in all growing regions of North America. Some product labels require closed systems be utilized, but AHETF also expects that some pesticide handlers will choose to use closed systems because of the added safety involved and to eliminate the need for extra personal protective equipment. For both of these reasons, closed systems will tend to be used with the more toxic chemicals. Some experts also suggest that large growers of commercial applicators are more likely to use closed systems, however this was quite anecdotal. Instead of relying on expert opinion, AHETF decided to begin the monitoring area selection process by listing Restricted Use Products (RUPs) and Toxicity Category I products, and then examining which states or provinces utilize a high quantity of the active ingredients in those products. However, chemical usage dat were not available for all active ingredients or states of for Canada. In the U.s., RUPs require special certifications for handlers and increased use reporting requirements (compared to non-RUP products) since they are generally more acutely toxic products. California has similar requirements "for restricted materials" and also has a database that identifies Toxicity Category I products (the category reflecting the most acutely toxic products). The California Department of Pesticide Regulation "California Product/Label Data Tables" was searched and actives identified: http://www.cdpr.ca.gov/docs/label/prodtables.htm. Another source for identifying RUPs was the USDA publication "Agricultural Chemical Usage 2007 Restricted Use Summary, May, 2008.

. . . .Chemical usage data from the National Agricultural Statistics Service (NASS, 2005, 2006, and 2007) were then examined to determine where most of these more toxic liquid products were used. . . .The results indicate that the following states might be associated with the most use of closed systems for loading liquids:

- Arizona
- California
- Florida
- Idaho
- Michigan
- Mississippi
- Nebraska
- Texas
- Washington

. . . .[and] the following Canadian provinces. . . .

- Manitoba (based on large field crop acerage)
- Ontario (based on large greenhouse/nursery acerage)
- Saskatchewan (based on large field crop acerage)

AHETF then conducted a survey of growers and commercial applicators in the 12 states or provinces listed above. . . .In total a little over 1,400 growers and applicators were interviewed. A little over 350 indicated they used a closed loading system with mini-bulk or bulk containers and almost 175 indicated they used a system with small (5 gallon or less) containers. . . . .follow up calls were made only to the seven states or provinces with the highest positive response rate(AZ, CA, FL, ID, NE, SK, WA). Full results of this survey are presented in Attachment 2; however the following observations were apparent:

- Closes systems are not commonly used, overall about 30% of contacts report using any type of closed system – this means about 70% of those contacted report the never use a closed system with liquids
- Close systems are more commonly used with bulk or mini-bulk systems than with small containers (5 gallons or less); overall about 25% of contacts for large containers vs. about 12% for small containers
- More commercial applicators use closed systems than growers; overall about 30% vs. 20%
- More large growers use closed systems than small growers; average acres grown for growers reporting use of closed systems was about 5,500 versus about 1,900 for all growers contacted
- Based on call cener responses, the prevalence of system types use is: suction/extraction>gravity feed>container breach
- Based onAHETF responses, the prevalence of system types used is: suction/extraction>container breach>gravity feed.

Based on this information, the geographic extent of the CSLL-NR and CSLL-R scenarios will be targeted to only the nine predominant US states listed above. Since more commercial applicators appear to utilize closed systems, the three Canadian provinces will not be included since lists of commercial applicators are not available." (pp. 38-41 of 438)

"**Selection of a Geographically Diverse Set of Monitoring Areas:** Five or seven new monitoring areas need to be selected that are geographically diverse. Such a diverse configuration will be obtained by simply locating each monitoring area in a different geographic stratum (i.e., state). In theory, states could be selected at random and a monitoring area could then be purposively located within each selected state. However, such undirected selection of areas could be quite inefficient. As discussed above, the use of closed systems for liquids is not consistent between growers and commercial applicators.

Considering the nine states in the target area for these two scenarios, the following seven states were purposively selected to contain seven monitoring areas. This selection results in no repeats of states involved with existing studies, and no two new states being adjacent to each other.

1. ***Florida (for CSLL-NR and CSLL-R):*** Florida reflects a warm and humid climate in the southeastern U.S.
2. ***Michigan (for CSLL-NR and CSLL-R):*** Michigan reflects mostly a cool climate in upper Midwestern U.S.
3. ***Nebraska (for CSLL-NR and CSLL-R):*** Nebraska reflects a warm and dry climate in central Midwestern U.S.
4. ***Arizona (for CSLL-NR and CSLL-R):*** Arizona reflects a hot and dry climate in southwestern U.S.
5. ***Washington (for CSLL-NR and CSLL-R):*** Washington reflects both a cool climate (western portion) and a hot and dry climate (eastern portion) in the Pacific Northwest part of U.S.
6. ***Mississippi (for CSLL-NR only):*** Mississippi reflects mostly a warm and humid climate in the southern U.S.
7. ***Texas (for CSLL-NR only):*** Texas reflects a hot and dry climate in the southern U.S. (pp. 42 - 43 of 438)

"**Reduction of Monitoring Areas:** Typically, the final step for selecting monitoring areas would be to restrict the monitoring area to a specific local area within each selected strata identified above where employers (i.e., growers or commercial applicators) and workers can be recruited to conduct the exposure monitoring in a reasonable amount of time. However, in this case each stratum is a state and survey findings indicate the diversity in systems desired might be difficult to find. Therefore, the monitoring areas will not be further restricted within each stratum and the entire state will be considered the monitoring area. (p. 46 of 438)

(b) How have random elements been incorporated into the scenario sampling design?

All choices in the first stage of the proposed diversity selection process, and stratification by AaiH in the second stage, are purposive choices.

"AHETF has determined that a method of identifying an essentially unbiased working pool of employers (i.e., growers or commercial applicators) is practical for each monitoring area of each scenario. Each pool of employers will provide the workers and mixing/loading conditions needed to construct the configuration of MUs. This is desirable, when feasible, to reduce the possibility of selection bias that might arise from a local agricultural researcher purposively choosing specific employers to contact, for example. Therefore, a procedure for generating a comprehensive list of available growers and commercial applicators associated with each local monitoring area, and identifying a pool of potentially eligible employers from that list, will be established in the protocol. The general procedure to be followed for each monitoring area is described in the following steps:

1. Contact resources such as those listed below to obtain a list of growers for crops expected to use closed systems within the identified state/province (these crops will be listed in the study protocol):
   - Farm Market ID, and/or
   - Meister Media Worldwide.

2. Assemble a list of growers and eliminate any duplicates. If the list is large, it may be limited by eliminating smaller growers if farm size information is available.

3. Assemble a list of commercial applicators in the state from:
   - Government agencies that issue applicator licenses, and
   - The National Agricultural Aviators Association.

4. Combine the grower and commercial applicator lists into a single randomized list of employers.
5. Contact a random subsample of the employers on the list (or the entire list if needed) and determine whether the employer is qualified and willing to participate. If so, the employer will be considered potentially eligible, which generally means all of the following are true:
   - The employer is willing to cooperate with AHETF, including the ethical aspects of the research
   - The employer has the necessary closed loading equipment for liquids
   - The employer has at least one worker with experience in loading liquid products with that closed system
   - The employer is willing to allow AHETF to recruit his/her workers(s)
   - The employer plans to treat sufficient acerage with a liquid product so that the minimum AaiH can reasonably be handled by a worker in one day

- The employer is willing to use at least one of the surrogate active ingredients listed in the study protocol

6. Each employer identified as potentially eligible (sometimes along with an associated commercial pesticide application company) is placed into a working pool along with information on:
   - Specific location of mixing/loading areas
   - Description of closed loading equipment available (e.g., number, type, and size)
   - Type of containers handled, i.e., returnable and/or non-returnable
   - Surrogate chemical(s) that might be utilized
   - Approximate timing of surrogate applications
   - Number of workers available
   - AiaH those works might be able to handle in a day (pp. 53-54 of 438)

(c) What feasible opportunities to incorporate random elements in the design—if any—have been overlooked?

If more handlers and growers are in the recruiting pool in a given state, it is likely that the opportunity will arise to select randomly from among interested workers.

(d) What typical patterns of exposure will likely be included by the sampling design?

"The workers will be allowed to follow their normal procedures as long as they fit the scenario definition and do not conflict with EPA's Worker Protection Standard (WPS) regulations. The duration of the work activity will be partially determined by the amount of AaiH but will involve the mixing/loading of at least three loads. In addition, efforts will be made to keep a minimum duration of four hours for exposure monitoring, however it is recognized that the low levels of AaiH might not require this much time and so this 4-hour minimum is only a guideline and not a requirement."

"The number of loads prepared by a worker is considered by AHETF to be a parameter that might impact exposure since each mixing/loading event will require transferring undiluted product from a container to a tank and potential contact with contaminated surfaces (e.g., containers, probes, tanks, hoses, etc.). In addition, preparing a new load using non-returnable containers and closed systems will often involve a new container which leads to connecting and disconnecting the closed system from the container which again increases the chances of worker exposure." (pp. 57 of 438)

(e) What typical patterns of exposure will likely be excluded by the sampling design?

"While other factors were considered that might potentially affect exposure potential, see Section 2.2, they will not be purposively diversified. For example, the concentration of the product might possible impact exposure. However, AHETF believes the differences

are small enough that they could not be measured with the sample sizes proposed in this plan." (p. 58 of 438)

3. Are the proposed test materials appropriate surrogates?

"The following table identifies current active ingredients that are available as a liquid formulation(s) and whether they are currently available in returnable and/or non-returnable commercial packaging. Any of these surrogates would be acceptable for use in the appropriate scenario.

Surrogate Active Ingredient	Available as Liquid In Non-Returnable Containers	Available as Liquid In Returnable Containers?
Carbaryl	Yes	No
Chlorothalonil	Yes	Possibly*
Dacthal (DCPA)	Yes	No
Fosamine	Yes	Yes
Glyphosate	Yes	Yes
Imazapyr	Yes	Yes
Imidacloprid	Yes	Limited
Malathion	Yes	Yes
Simazine	Yes	Possibly*
Sulfur	Yes	Unknown
Thiophanate-Methyl	Yes	Unknown
2,4-D	Yes	Yes
2,4-DB	Yes	yes

* Some products are sold in bulk, so refilling into refillable containers is possible (by distributors, for example)

Some of these surrogate active ingredients also have relatively high application rates for a variety of crops which enables measurements at the high end of AaiH per day. Additional, these active ingredients have been used as surrogates in other studies and are known to have the required stability under field study conditions." (pp. 58 - 59 of 438)

4. What is the rationale for the proposed cluster design and sample size?

"Appendix C of the Governing Document describes the simulation methodology to calculate sample sizes when the reference model used is cluster sampling from a lognormal distribution. These simulations determine either accuracy or power given the number and configuration of MUs. When there are no existing data, the simulations only consider new MU configurations. However, for this scenario, the simulations require that the structure of the existing MUs be held constant and only the number of new MUs is varied. Regardless, it is still the combination of existing and new MUs that must satisfy the benchmark objectives:

1. **Primary Objective**: Estimates of the geometric mean, the arithmetic mean, and the 95th percentile of normalized dermal exposure generally need to be accurate to

within 3-fold of their actual population value assuming the reference random sampling model applies.

2. **Secondary Objective**: There should be at least 80% statistical power to distinguish complete proportionality from complete independence between dermal exposure and AaiH (the normalizing factor for this scenario)." (pp. 32 of 438)

4.5.1. GSD and ICC

"To determine sample sizes, reasonable values for variation parameters are needed. Based on analysis of exposure from a number of available monitoring studies, Appendix C of the AHETF Governing Document derived a default relative variation structure consisting of geometric standard deviation (GSD) of 4 and an intra-cluster correlation (ICC) of 03. Unless there is other evidence or expert opinion to the contrary, sample sizes are determined for all scenarios using these default values. The AHETF and the Joint Regulatory Committee agreed there is no additional evidence to suggest otherwise and no other strong opinion to the contrary (meeting June, 2011). Therefore, GSD=4 and ICC=0.3 will be used for both the CSLL-NR and CSLL-R.

In general, for the purpose of sampling size determination AHETF avoids assuming that the variation among any existing MUs chosen for the scenario is the true variation. These data are unreliable and would introduce a degree of circularity into the sample size process. However it seems prudent to verify that the existing MU data for the CSLL-R scenario are not grossly inconsistent with the above assumptions of GSD=4 and ICC=0.3.

The existing data for CSLL-R consist of a cluster of 7 MUs from one purchased study and a second cluster of 15 MUs from an (pre-rule) AHETF study. Both of these studies involved workers conducting Multiple MUs. In addition, the purchased study involved workers conduction two MUs on the same day.

The Consistency of these existing data with the assumption of GSD=4 and ICC=0.3) was verified using a likelihood ration test (West et al, 2007). The lognormal reference model described above was used to compare an unrestricted variance component reference model with one conditional on GSD=4 and ICC=0.3. These results are summarized in the following table:

CSLL-R Reference Model Variation Parameter		Value
Restricted parameters	GSD	4
	ICC	0.3
Estimated parameters	IWC	0.63
	IDC	0.00
	p-value	0.6106

The limited existing CSLL-R data are not significantly inconsistent (i.e., at $p<0.05$) with GSD=4 and ICC=0.3. The same-worker correlation is large (0.63) but there is no apparent same-worker and day correlation. These data are too limited to trust the IWC and IDC estimates to any degree. However, new monitoring studies are not permitted to have the same worker generate multiple MUS so the only estimates for IWC and IDC will come from these data. Therefore, it seems reasonable to use the above values for IWC and IDC in the CSLL-R reference model when determining sample size. (pp. 26 -27 of 438)

4.5.2. Required Number and Configuration of New MUs

In addition to the benchmark objectives described above, a critical issue for these CSLL scenarios is the likelihood of obtaining a sufficient number of eligible MUs in a monitoring area. Based on interviews with growers and commercial application companies, there are several factors that make obtaining Jus especiall difficult for these scenarios:

- Suitable closed systems are not commonly in use.
- Commercially available systems are not readily available for some system types.
- Handlers that do use appropriate systems sometimes wear additional PPE that are contrary to the design criteria for these scenarios, such as chemical-resistant clothing or aprons.
- Diversity in system type is desirable within each monitoring area.

In general it is less costly to keep the number of monitoring areas as small as possible. Because of the above complication, however, designs with a small number of MUs per monitoring area are more likely to be attainable for all the areas selected. Therefore, the configuration size is restricted to $N_M=3$ for all new MUs. This restriction will necessarily result in the need for a larger number of monitoring areas than would be typical. Although it might be more costly, AHETF believes that configurations with more monitoring areas with fewer MUs per area will be more successful in obtaining the planned number of MUs than configurations with more MUs per monitoring area.

As noted above, Appendix C of the AHETF Governing Document describes simulation methods that can be used to determine reasonable sample sizes for new clusters of MUs. In principle, these methods are easily extended to accommodate existing MUs as well. In brief, the simulation procedure consists of the following steps for each scenario independently:

1. Using the structure of the **existing data** (e.g., number of clusters, number of MUs per cluster, AaiH levels for each MU, etc.) simulate normalized exposures, and exposures derived from AaiH levels assuming proportionality, from the multistage lognormal reference model.
2. Given candidate values for numbers of **new monitoring areas** (N_C) numbers of MUs per configuration ($N_M=3$), and AaiH strata, simulate

normalized exposures, and exposures derived from AaiH levels assuming proportionality, from the two-stage lognormal reference model.

3. Combine any 'existing' and 'new' simulated data together and estimate the geometric mean, arithmetic mean, and 95th percentile of normalized exposure. Calculate the fold relative accuracy of these estimates compared to their true values.
4. In addition, from the combined 'new' and 'existing' exposure data, determine if the slope from a mixed model regression of log exposure of AaiH is significantly different from zero.
5. Repeat steps 1 through 4 10,000 times and calculate the 95th percentile of fold relative accuracy for each normalized exposure statistic and determine if it satisfies the primary benchmark objective. Also compute the percentage of simulations yielding a statistically significant slope. The percentage is the power needed to evaluate the secondary benchmark objective.

Using this simulation approach, it was found the the primary objective cen be met for the CSLL-NR scenario with 7 newly obtained monitoring areas of 3 MUs each. This would provide a total of 21 MUs.

For the CSLL-R scenario, the primary objective is satisfied if the two existing clusters of 22 MUs are augmented with 5 new monitoring areas of 3 MUs each. If each new monitoring area provides only a single cluster this would result in a combined set of 37 total MUs in 7 clusters.

Assuming each new monitoring area provides only a single cluster. These primary benchmark sample sizes are summarized below:

Scenarios	Items	Numbers of MUs		
		Existing	New	Total
CSLL -NR	Clusters	0	7	7
	Workers	0	21	21
	MU	0	21	21
CSLL-R	Clusters	2	5	7
	Workers	9	15	24
	MU	22	15	37

(pp. 27-29 of 438)

EPA Protocol Review: AHETF Closed System Loading of Liquids in Returnable and Non-Returnable Containers (AHE500)

Title: Determination of Dermal and Inhalation Exposure to Workers during Closed System Loading of Liquids in Returnable and Non-Returnable Containers

Revision Date: July 8, 2011

Study Director and Sub-Investigators:
Eric D. Bruce
Aaron Rotondaro
Brian Lange

Field Facility: Multiple outdoor agricultural locations; each principal field investigator utilizes a mobile laboratory

Analytical Facility: TBD

Sponsor: Agricultural Handler Exposure Task Force, LLC
c/o David R. Johnson, Ph.D.
1720 Prospect Drive
Macon MO 63552

Reviewing IRB: Independent Investigational Review Board, Inc.
6738 West Sunrise Blvd Suite 102
Plantation FL 33313

1. Societal Value of Proposed Research

(a) What is the stated purpose of the proposed research?

"The objective of this study is to develop data to characterize the potential exposure for workers using closed systems to load liquids products from returnable (R) or non-returnable (NR) containers into mix or spray tanks. … Exposure monitoring will be conducted at five (R) or seven (NR) monitoring areas representing a variety of geographical regions of the United States." (pp. 311 of 438)

(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?

This study will provide a partial answer to the question of what dermal and inhalation exposures are likely for workers who mix and load liquid pesticide products using closed loading systems. This is a critical method of mixing and loading liquid pesticide products used to mitigate handler risks and for which existing data are inadequate.

(c) How would the study be used by EPA?

EPA will use the results of this study to estimate the dermal and inhalation exposure likely for handlers using closed mixing and loading techniques for agricultural pesticides formulated as liquids.

(d) Could the research question be answered with existing data? If so, how?

"AHETF (in conjunction with EPA, PMRA, and CDPR, collectively the Joint Regulatory Committee (JRC)) reviewed handler exposure measurements in existing studies (mostly not included in PHED) to identify those that satisfy current acceptability criteria and qualify for inclusion in a generic database. For this particular scenario, the JRC reviewed three studies (AH101, AH301, and AH501) involving closed loading systems. Only one of these studies, AH501 was found to be acceptable, and this study included some monitoring units involving closed system loading of liquids that were deemed appropriate for a generic database. Study AH501 was purchased by AHETF for inclusion into AHED.

This study included two MUS that utilized a container breach system to open, drain and rinse 5-gallon non-returnable cans of pesticide. These two MUs involved the same worker on the same day, so they do not represent distinctly different measurements. This study also included six MUs that utilized a suction/extraction system with non-returnable 30 gallon drums. These MUs involved only two workers, so again the measurements are not distinctly different. AHETF has concerns about the suitability of these MUs for a generic database since several observations were found in the report and raw data indicating that subjects performed some activities that are not normally associated with mixing/loading. In particular, workers were observed to make repairs of ground sprayers in the field (possibly entering a treated area), changed/checked/adjusted nozzles (with latex gloves on), and stood behind spray rigs and/or leaned on spray booms when sprayers were turned on. These activities are not considered part of the normal duties associated with mixing/loading and make it difficult to judge whether the resulting exposure can be attributed entirely to mixing/loading with a closed system. There, AHETF prefers to exclude the few MUs from AHE 501 in the XSLL-NR scenario.

The existing study also included seven MUs involving 500-gallon returnable containers and a suction/extraction system that again involved the use of repeated workers. These MUs were associated with aerial applications in a different location and did not have the concerns mentioned above, so these MUs are suitable for the generic database for data involving liquids in returnable containers and closed systems.

AHETF also conducted a detailed review of the data in PHED for this scenario to determine if any of the data were suitable for a modern generic database. . . . 15 MUs from one study were found that met the acceptance criteria established by AHETF. This study is the same study referenced above that AHETF purchased from one of its members, therefore, there are no additional data for these scenarios in PHED that are useful for a modern generic database. In addition to previously conducted studies,

AHETF collected several MUs for closed loading of liquids in conjunction with study AHE13 that was primarily designed to collect aerial applicator exposure data. This study was conducted in 2004 and involved 15 MUs with large, returnable containers (260-gallons). However, only 7 unique workers were utilized so there is some use of repeated workers as in the purchased study discussed above. Liquid was either extracted from the top of the container with a suction robe or flowed from the bottom by gravity and/or with the assistance of a pump. The pesticide was transferred directly into spray tanks on fixed-wing aircraft.

Finally, EPA examined data from existing exposure studies or exposure assessments that were not available to the AHETF and concluded that none of the exposure data should be included in the AHETF database (June 2010). (pp. 23-24 of 438)

(e) Could the question be answered without newly exposing human subjects? If so how? If not, why not?

There is no alternative to monitoring handlers as they mix/load pesticides for measuring their dermal and inhalation exposure.

2. Study Design

(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?

"The goal of conducting MUs for the CSLL-NR and CSLL-R scenarios is to develop a set of generic dermal and inhalation exposure data which regulators and other potential users of the generic database can utilize to characterize the magnitude and likely range of future exposures, and to perform exposure assessments for these two related scenarios." (pp. 60 of 403)

1. **Primary Objective**: Estimates of the geometric mean, the arithmetic mean, and the 95th percentile of normalized dermal exposure generally need to be accurate to within approximately 3-fold of their actual population value assuming the reference random sampling model applies.

2. **Secondary Objective**: If the reference model were true, there should be at least 80% statistical power to distinguish complete proportionality from complete independence between dermal exposure and AaiH (the normalizing factor for this scenario)." (pp. 32 of 438)

No explicit hypothesis is stated, nor is the study explicitly designed to test one.

(b) Can the study as proposed achieve that objective or test this hypothesis?

It is likely that the objective can be achieved by the proposed study.

2.1 Statistical Design

(a) What is the rationale for the choice of sample size?

"To determine sample sizes, reasonable values for reference model variation parameters are needed. Based on analysis of exposure from a number of available monitoring studies, Appendix C of the AHETF Governing Document derived a default relative variation structure consisting of a geometric standard deviation (GSD) of 4 and an intra-cluster correlation (ICC) of 03. Unless there is other evidence or expert opinion to the contrary, sample sizes are determined for all scenarios using these default values. The AHETF and the Joint Regulatory Committee agreed there is o additional evidence to suggest otherwise and no other strong opinion to the contrary (meeting June, 2011). Therefore, GSD=4 and ICC=0.3 will be used for both the CSLL-NR and CSLL-R scenarios to determine sample sizes.

In general, for the purpose of sample size determination, AHETF avoids assuming that the variation among any existing MUs chosen for the scenario is the true variation. These data are unreliable and would introduce a degree of circularity into the sample size process. However, it seems prudent to verify that the existing MU data for the CSLL-R scenario are not grossly inconsistent with the above assumptions of GSD=4 and ICC=0.3.

The existing data for CLSS-R consist of a cluster of 7 MUs from one purchased study and a second cluster of 15 MUs from an ('pre-rule') AHETF study. Bothe of these studies involved workers conducting multiple MUs. In addition, the purchased study involved workers conduction two MUs on the same day.

The consistency of these existing data with the assumption of GSD=4 and ICC=0.3 was verified using a likelihood ration test (West et al, 2007). The lognormal reference model described above was used to compare an unrestricted variance component reference model with one conditional on GSD=4 and ICC=0.3. These results are summarized in the following table:

CSLL-R Reference Model Variation Parameter		Value
Restricted parameters	GSD	4
	ICC	0.3
Estimated parameters	IWC	0.63
	IDC	0.00
	p-value	0.6106

The limited existing CSLL-R data are not significantly inconsistent (i.e., at $p<0.05$) with GSD=4 and ICC=0.3. The same-worker correlation is large (0.63) but there is no apparent same-worker and day correlation. These data are too limited to trust the IWC

and IDC estimates to any great degree. However, new monitoring studies are not permitted to have the same worker generate multiple MUs so the only estimates for IWC and IDC will come from these data. Therefore, it seems reasonable to use the above values for IWC and IDC in the CSLL-R reference model when determining sample size." (pp. 33-34 of 438)

4.5.2. Required Number and Configuration of New MUs

As noted above, Appendix C of the AHETF Governing Document describes simulation methods that can be used to determine reasonable sample sizes for new configurations of MUs. In principle, these methods are easily extended to accommodate existing MUs as well. In brief, the simulation procedure consists of the following steps for each scenario independently:

1. Using the structure of the **existing data** (e.g., number of clusters, number of MUs per cluster, AaiH levels for each MU, etc.) simulate normalized exposures, and exposures derived from AaiH levels assuming proportionality, from the multistage lognormal reference model.
2. Given candidate values for numbers of **new monitoring areas** (N_C), numbers of MUs per configuration (N_M=3), and AaiH strata, simulate normalized exposures, AaiH levels, and exposures derived from AaiH levels assuming proportionality, from the two-stage lognormal reference model
3. Combine the any 'existing' and 'new' simulated data together and estimate the geometric mean, arithmetic mean, and 95th percentile of normalized exposure. Calculate the fold relative accuracy of these estimates compared to their true values.
4. In addition, from the combined 'new' and 'existing' exposure data, determine if the slope from a mixed model regression of log exposure of AaiH is significantly different from zero.
5. Repeat steps 1 through 4 10,000 times and calculate the 95th percentile of fold relative accuracy for each normalized exposure statistic and determine if it satisfies the primary benchmark objective. Also compute the percentage of simulations yielding a statistically significant slope. The percentage is the power needed to evaluate the secondary benchmark objective.

Using this simulation approach, it was found that the primary objective can be met for the CSLL-NR scenario with 7 newly obtained monitoring areas of 3 MUs each. This would provide a total of 21 MUs.

For the CSLL-R scenario, the primary objective is satisfied if the two existing clusters of 22 MUs are augmented with 5 new monitoring areas of 3 MUs each. If each new monitoring area provides only a single cluster this would result in a combined set of 37 total MUs in 7 clusters.

Assuming each new monitoring area provides only a single cluster, these primary benchmark samples sizes are summarized below:

Scenarios	Items	Numbers of MUs		
		Existing	New	Total
CSLL -NR	Clusters	0	7	7
	Workers	0	21	21
	MU	0	21	21
CSLL-R	Clusters	2	5	7
	Workers	9	15	24
	MU	22	15	37

For the secondary objective the power to detect proportionality between exposure and AaiH also depends on the particular set of AaiH used. For any existing MUs the AaiH levels actually observed were used. But and noted in step 4 above, the AaiH levels must be simulated for the hypothesized new MUs. As described in Section 5.2.1 below, diversity selection for new monitoring areas will require that the AaiH levels for MUs extend over the complete practical range expected for each of the CSLL scenarios. For CSLL-NR, this practical range is 12 to 800 lbs. ai handled per workday. Diversity in AaiH levels is achieved by first partitioning the appropriate practical range into N_M=3 strata. Then for each new configuration a single new MU is obtained from within each AaiH stratum. The AaiH strata are each designed so the middle stratum is an order of magnitude wide while the two end strata have approximately the same upper-to-lower bound ratio.

An analogous procedure is followed in step 2. Above when simulating AaiH levels for new MUs: within each simulated new configuration, an AaiH level is simulated log-uniformly from within each of the N_M=3 strata. Then exposure data are simulated for both the existing and new MUs assuming proportionality with the AaiH levels. For each simulated set of data, a regression analysis is then performed and the significance of thelog-log slope determined (2-sided test). The power is the proportion of the time that the slope was significant at $p<0.05$.

Using the primary benchmark sample sizes in the above table and the AaiH strata given in Section 5.2.1., the power was found to exceed 99% for both the CSLL-NR and the CSLL-R scenarios. In other words, the proposed number and configuration of MUs that satisfy the primary benchmark objective also more than satisfy the secondary power objective for both scenarios. (pp. 23-26 of 403)

(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

No positive or negative controls are proposed. This is appropriate for the study design and statistical analysis plan.

(c) How is the study blinded?

The study is not blinded, nor could it be.

(d) What is the plan for allocating individuals to treatment or control groups?

"As the pool of potentially eligible growers and commercial applicators is assembled, researchers (e.g, the Study Director) will examine the details of potential MUs and attempt to identify a diverse configuration of MUs (i.e., growers, companies, chemicals, workers, AaiH, closed system, application equipment, and timing) that might be cost-effective. Such an efficient configuration would ideally involve a group of employers that: are in the same geographical area, can provide separate workers for all the strata of AaiH, involve the required diversity in equipment, and are expected to make applications within a narrow time frame. This configuration might also include more employers and workers than are needed since employers could change their mind about cooperating; workers might not volunteer to participate; the mixing/loading event might not take place due to lack of pest pressure; and various employers have different application timing, etc." (p. 55 of 438)

"For both scenarios, the following similarity restrictions are used when selecting the three MUs within any monitoring area:

- No two MUs obtained for the same scenario can utilize the same worker.
- No two workers in the same monitoring area used for the same scenario can have the same employer.
- If an employer has previously contributed a worker to an MU in a different monitoring area for the same scenario, then it is preferable that this same employer not contribute a worker to another monitoring area.
- It is preferable that no two MUs obtained for the same scenario in the same monitoring area be in the same AaiH stratum.
- Each MU in a monitoring area must differ with respect to at least one of the following characteristics: type of closed system, container size, and transfer set-up (i.e., transfer directly to a spray tank or transfer to a mix tank and then to a spray tank). Ideally, each MU will utilize a different system type, but it is likely that it will be difficult to locate all systems in all monitoring areas. In addition, completely closed systems are most desirable. (pp. 50-51 of 438)

(e) Can the data be statistically analyzed?

"As has always been the case, any statistical conclusions based on such data imply the qualification: 'to the extent that the data can be viewed as deriving from a true random sample.'" (p. 61 of 438)

(f) What is the plan for statistical analysis of the data?

"As discussed in the Governing Document, the two categories of benchmark data adequacy considered are:

1. The relative accuracy of selected statistics characterizing the distribution of exposure normalized by amount of active ingredient handled (AaiH).

2. How well the data can be expected to describe a relationship between exposure and AaiH, if one existed." (pp. 60-61 of 438)

"The primary benchmark objective is that selected lognormal-based estimates of normalized dermal exposure distribution be accurate to within 3-fold, at least 95% of the time. The benchmark estimates specified are those for the geometric mean, arithmetic mean, and the 95th percentile.

To evaluate how well the collected data conform to this benchmark, the 95 percent bound on relative accuracy will be calculated from the confidence interval for each of the three parameters given above."

"This secondary benchmark objective [Adequacy of the Data for Distinguishing a Proportional from an Independent Relationship between Exposure and AaiH] applies to each of the closed loading of liquids scenarios because the practical range in the amount of active ingredient handled (AaiH) exceeds an order of magnitude. In this case it is reasonable to consider the linear regression of log dermal exposure on log AaiH. Such a regression would use a mixed model formulation in order to incorporate random cluster effects." (p. 61 of 438)

(g) Are proposed statistical methods appropriate to answer the research question?

Yes.

(h) Does the proposed design have adequate statistical power to definitively answer the research question?

Since the primary objective of the research is to characterize the distribution of exposure normalized by the amount of active ingredient handled (AaiH), statistical power does not relate to this objective. However, EPA believes the resulting data will reliably characterize the distribution of exposures for the individuals monitored during closed system liquid loading in this study, and that these exposures can inform assessments of the likely exposures for individuals in similar future situations.

Regarding the secondary objective, distinguishing a proportional from an independent relationship between exposure and AaiH, statistical power is relevant.

"This secondary benchmark objective applies to each of the closed loading of liquids scenarios because the practical range in the amount of active ingredient handled (AaiH) exceeds an order of magnitude. In this case it is reasonable to consider the linear regression of log dermal exposure on log AaiH. Such a regression would use a mixed model formulation in order to incorporate random cluster effects due to monitoring area 'clusters'. As described in the Governing Document, in such a model the true slope, β, would be equal to one if dermal exposure were directly proportional to AaiH. If exposure were independent of AaiH, then β=0. This benchmark objective requires that the number of clusters and the allocation of AaiH levels to MUs should be adequate to ensure that the regression analysis has at least 80% power to reject the hypothesis that β=0 when β is actually equal to one. By symmetry, the mixed model linear regression would also have the same power to reject the hypothesis that β=1 when β=0. This is the precise meaning of being able to 'discriminate between proportionality and independence'." (pp. 62 of 438)

2.2 How and to what will human subjects be exposed?

"The scenario program for closed loading of liquids in non-returnable and returnable containers will monitor instances of worker exposure resulting from the mixing/loading of liquid and using closed systems." (p. 26 of 438)

"The following table identifies current active ingredients that are available as a liquid formulation(s) and whether they are currently available in returnable and/or non-returnable commercial packaging. Any of these surrogates would be acceptable for use in the appropriate scenario."

Surrogate Active Ingredient	Available as Liquid In Non-Returnable Containers	Available as Liquid In Returnable Containers?
Carbaryl	Yes	No
Chlorothalonil	Yes	Possibly*
Dacthal (DCPA)	Yes	No
Fosamine	Yes	Yes
Glyphosate	Yes	Yes
Imazapyr	Yes	Yes
Imidacloprid	Yes	Limited
Malathion	Yes	Yes
Simazine	Yes	Possibly*
Sulfur	Yes	Unknown
Thiophanate-Methyl	Yes	Unknown
2,4-D	Yes	Yes
2,4-DB	Yes	yes

* Some products are sold in bulk, so refilling into refillable containers is possible (by distributors, for example) (pp. 58-59 of 438)

(a) What is the rationale for the choice of test material and formulation?

"The AHETF has developed several pesticide active ingredient compounds for use as surrogates . . . . Since the AHETF is developing a generic database that will be applicable to nearly all pesticide products and uses, any of the AHETF surrogates can be used for generating exposure data for this scenario. The choice of surrogate at each location will depend largely upon the preference of the grower and pest pressure on his crop at that time… (p. 51 of 438)

(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?

"In addition to its potential direct relationship to exposure, the amount of active ingredient handled is also viewed as a meta-factor affecting parameters such as the number of connect/disconnect cycles, number of containers used, tank size, number of loads prepared etc. Thus diversification of AaiH induces diversification of such associated factors as well. Therefore, in addition to having a wide range, no two MUs within the same monitoring area should have similar AaiH levels.

AHETF has calculated a practical range in AaiH for this scenario taking into account the typical concentration of liquid products packaged in non-returnable or returnable containers and the number of containers a pesticide handler is expected to use in a single day." (p. 47 of 438)

As previously noted, it is desirable that the AaiH levels have a wide range within each monitoring area. Preferably, the AaiH levels within each monitoring area should be all different and span at least an order of magnitude. This increases the likelihood that the data for this scenario can be used to discriminate a completely proportional relationship from a completely independent relationship between exposure and AaiH (if one of these two relationships were true). The proposed ranges are each more than one order-of-magnitude, and should be adequate for this purpose (se Appendix C of the Governing Document). Within-monitoring-area diversification of AaiH will be accomplished by partitioning each of the practical AaiH ranges into three strata:

CSLL-NR

- From 12 to 30 lbs.
- From 31 to 310 lbs.
- From 311 to 800 lbs.

CSLL-R

- From 60 to 119 lbs
- From 120 to 1,200 lbs.
- From 1,201 to 2,400 lbs." (p. 49 of 438)

(c) What duration of exposure is proposed?

"Duration of monitoring is another parameter that could vary between MUs, especially since the AaiH will be varied by more than two orders of magnitude. Mixer/loaders might spend several hours per day at the mixing area but can also spend long intervals performing other tasks (or just sitting around) between actual mix/load events (i.e., while the applicator is making the application). So MUs will be monitored during their entire work day since many other unknown factors might contribute to exposure. All monitoring periods for this scenario must meet the general rule of being at least 4 hours. This is designed to overcome the criticism of early exposure studies where many of the sampling regimes monitored workers for only a few minutes. Avoiding very short monitoring intervals will ensure that daily exposure estimates are not biased by unusual conditions during that short interval. If practical, some minor scripting of worker activities will be done to ensure the lowest levels of AaiH are handled and/or to increase monitoring time to four hours. For example, a worker might be asked to use a smaller tank, or decrease load size, etc., in order to mix 3 or more loads in at least four hours." (pp. 43-44 of 403)

2.3 Endpoints and Measures

(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?

"At the completion of the monitoring period, exposure samples will be taken in the following order to minimize cross contamination: inhalation samples (discussed in the next section), then hand washes, then face/neck wipes, and finally inner dosimeters as described in SOP AHETF-10.E.2." (p. 344 of 438)

For this study, inner dosimeters will be cut into two sections after collection.

"Full details for sampling air with OSHA Versatile Sampler (OVS) tubes and personal air-sampling pumps are given in the most recent versions of SOP AHETF-8.D and 10.G." (p. 344 of 438)

(b) What steps are proposed to ensure measurements are accurate and reliable?

"Field fortification samples are exposure matrix samples that are fortified (or spiked), generally in the field, with known amounts of active ingredient and subsequently analyzed to determine the amount of active ingredient recovered. Field fortification samples are subjected to the same environmental, handling, shipping and storage conditions as worker samples. Because these conditions are similar, and because field fortification samples are analyzed along with worker samples, recovery values calculated from analysis of fortification samples are applicable to worker exposure samples. Field fortification recoveries are therefore used to adjust residue levels found in worker samples for residue losses that might have occurred during collection, handling, shipping and storage." (p. 169 of 438)

(c) What QA methods are proposed?

"AHETF intends that all regulatory studies are conducted in accordance with the FIFRA GLP Standards (40 CFR part 160). Field and analytical aspects of this study will be monitored by the relevant quality assurance units(s) (QAU) while this study is in progress to ensure compliance with the FIFRA GLP regulation and adherence to this protocol and relevant SOPs. The QAU(s) will submit copies of its/their inspection reports to the Study Director and AHETF Sponsor Representative (40 CFR part 160.35(4)). Field portions of the Study Report will be audited by the QAU specified in Section 1.15 to ensure that the contents of the report accurately describe the conduct and findings of the study.

The Study Report will contain a Quality Assurance Statement from the QAU of each contributing facility conducting QA audits, and from the QAU specified in Section 1.14." (pp. 354-355 of 438)

(d) How will uncertainty be addressed? Will reported point values be accompanied by measures of uncertainty?

Uncertainty in field measurements will be addressed via fortification samples.

"Sample matrix fortifications designed to assess the stability of the active ingredient during field, transit and storage conditions in or on the sampling materials (inner dosimeters, hand wash solutions, face/neck wipes, and air sampling matrices) will be conducted on a minimum of one day of exposure monitoring at each monitoring area, or more days as appropriate for environmental conditions. . . .

For each fortification event, two untreated control samples of each matrix will be processed similar to the field fortification samples (i.e., some are weathered). Packaging, storage and shipment of the field fortification samples will be the same as for the worker exposure samples." (pp. 345-346 of 438)

In general, field measurements are adjusted based on the recovery from the fortification sample. For example, a field measurement for an inner dosimeter of 300 ug would be adjusted based on the applicable fortification sample for the inner dosimeter matrix. If the recovery from that matrix was 80%, the reported measurement for that sample would be 300 ug/80% = 375 ug.

3. Subject Selection

3.1 Representativeness of Sample

(a) What is the population of concern? How was it identified?

"The scenario programs for closed loading of liquids in non-returnable and returnable containers will monitor instances of worker exposure resulting from the mixing/loading of liquid and using closed systems. Each instance of exposure monitoring is termed a monitoring unit (MU). Each MU consists of a set of mixing/loading conditions (including the particular worker) that are intended to represent the scenario activities for a single workday. Therefore each MU is an experimental realization of a 'mixer/loader-day' (or ML-day) from the scenario population of all possible ML-days. However, the selected mixing loading conditions are sometimes modified or scripted slightly to ensure that the sample of MUs reflects the expected diversity in the entire population of future closed system mixer/loader-days. . . .Thus, MUs are technically not 'sampled' from an existing population as would be the case say, with a statistical survey. More correctly, they should be viewed as synthetic closed system mixing/loading-days derived from both selected and constructed conditions." (pp. 26-27 of 438)

(b) From what populations will subjects be recruited?

"As the pool of potential eligible growers and commercial applicators is assembled, researchers (e.g., the Study Director) will examine the details of potential MUs and attempt to identify a diverse configuration of MUs (i.e., growers, companies, chemicals, workers, AaiH, closes system, application equipment and timing) that might be cost – effective. Such an efficient configuration would ideally involve a group of employers that: are in the same geographical area, can provide separate workers for all the strata of AaiH, involve the required diversity in equipment, and are expected to make applications within a narrow time frame…. As this (ideally cost-effective) pool of eligible employers is identified, workers will be recruited as described in the Governing Document and the study protocol." (p. 55 of 438)

(c) Are expected participants representative of the population of concern? If not, why not?

"AHETF has determined that a method of identifying an essentially unbiased working pool of employers (i.e., growers or commercial applicators) is practical for each monitoring area of each scenario. Each pool of employers will provide the workers and mixing/loading conditions needed to construct the configuration of MUs. This is desirable, when feasible, to reduce the possibility of selection bias that might arise from a local agricultural researcher purposively choosing specific employers to contact, for example. Therefore, a procedure for generating a comprehensive list of available growers and commercial applicators associated with each local monitoring area, and indentifying a pool of potentially eligible employers from that list, will be

established in the protocol. The general procedure to be followed for each monitoring area is described in the following steps:

1. Contact resources such as those listed below to obtain a list of growers for crops expected to use closed systems within the identified state/province (these crops will be listed in the study protocol):
    - Farm Market ID, and/or
    - Meister Media Worldwide
2. Assemble a list of growers and eliminate any duplicates. If the list is large, it may be limited by eliminating smaller growers if farm size information is available.
3. Assemble a list of commercial applicators in the state from:
    - Government agencies that issue applicator licenses, and
    - The National Agricultural Aviation Association
4. Combine the grower and commercial applicator lists into a single randomized list of employers.
5. Contact a random subsample of the employers on the list (or the entire list if needed) and determine whether the employer is qualified and willing to participate. If so, the employer will be considered potentially eligible, which generally means all of the following are true:
    - The employer is willing to cooperate with AHETF, including the ethical aspects of the research
    - The employer has the necessary closed loading equipment for liquids
    - The employer has at least one worker with experience in loading liquid products with that closes system
    - The employer is willing to allow AHETF to recruit his/her worker(s)
    - The employer plans to treat sufficient acerage with a liquid product so that the minimum AaiH can reasonably be handled by a worker in one day
    - The employer is willing to use at least one of the surrogate active ingredients listed in the study protocol
6. Each employer identified as potentially eligible (sometimes along with an associated commercial pesticide application company) is placed into a working pool along with information on:
    - Specific location of mixing/loading areas
    - Description of closed loading equipment available (e.g., number, type and size)
    - Type of containers handled, i.e., returnable and/or non-returnable
    - Surrogate chemical(s) that might be utilized
    - Approximate timing of surrogate applications
    - Number of workers available
    - AaiH those workers might be able to handle in a day

This process results in a minimally biased sample of potentially eligible employers and, by association, a pool of potential workers associated with potentially eligible growers. The recruitment of growers and/or commercial

pesticide application companies from the list will be made by a task force contractor as specified in the study protocol. All discussions and decisions made during this eligibility screening will be documented (e.g., as phone logs and/or in Excel spreadsheets) and retained as raw data for the study. This process is conducted independently for each monitoring area." (pp. 52-54 of 438)

(d) Can the findings from the proposed study be generalized beyond the study sample?

Yes, within the limits imposed by the purposive design of the study.

3.2 Equitable Selection of Subjects

(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?

"[A]ll AHETF Study participants must meet these inclusion criteria:

- Have experience within the past year with the work activity being monitored in the study (including the particular equipment to be used during mixing/loading or application)
- Handle pesticides as part of their job
- Be trained in safe pesticide handling practices in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training
- Provide proof of being at least 18 years old with a government-issued photo ID
- Confirm they do not work for a pesticide company or a contractor of the AHETF
- Consider their general health status to be good and tell researchers they have no medical conditions that affect their ability to participate in the study (See SOP AHETF-11.C for health status determination)
- Not be pregnant or nursing (See SOP AHETF-11.D)
- Confirm they do normally wear personal protective equipment that is required by the label. If the worker indicates that they may wear additional PPE not required by the product label, and that additional PPE might impact the objectives of the study, such as chemical-resistant clothing, then the Study Director should be notified to determine if the worker shall be included iin the study. Confirm they will follow label directions. The research staff shall not influence nor ask in a manner to influence the worker to wear less PPE than they normally wear.
- Have a private meeting with a researcher to review and discuss the consent form
- Understand English or Spanish (See SOP AHETF-11.I for a detailed discussion of this topic)

- Understand and sign the consent form, and if in California, the California Experimental Research Subject's Bill of Rights" (SOP AHETF-11.B.6) (pp. 213-214 of 438)

"For this closed loading of liquids study, the following inclusion criterion also applies:

- Have experience within the past year with closed loading of liquids in returnable containers (CSLL-R) or with closed loading of liquids in non-returnable containers (CSLL-NR) including the type of equipment to be used." (p. 315 of 438)

(b) What, if any, is the relationship between the investigator and the subjects?

None

(c) If any potential subjects are likely to be especially vulnerable to coercion or undue influence, what is the justification for including them?

Potential subjects are of necessity agricultural workers, and could potentially be subjected to undue influence either to participate or not to participate by their employers. This possibility is minimized through methods of recruiting growers and by requiring growers to promise in writing not to influence their employee's decisions.

(d) What process is proposed for recruiting and informing potential subjects?

"For each eligible employer identified, AHETF will follow standard procedures (see SOP AHETF-11.B.6; pp. 210-215 of 438) to recruit potential participants for this study. Individual workers will be recruited during an initial interview with (or visit to) a potentially eligible employer once eligibility has been established. Alternatively, recruitment can occur on subsequent interviews with or visit(s) to an eligible employer.

"The Study Director or designated researcher will seek permission from the eligible grower to approach his/her employees to recruit workers for the study. Depending on the number of employees and size of the employer's facility the Study Director or researcher may contact employees using an informational recruitment flyer posted in a common work area. Such a flyer will briefly describe the research study and provide a toll-free phone number for employees to express an interest in participating in the study. The flyer shall have been previously reviewed and approved by an IRB.

"Alternatively, or subsequent to the use of a flyer, the Study Director or researcher will arrange a meeting with the employer's employees who express an interest in participation. Such recruitment meetings will always occur without the grower or supervisors being present (SOP AHETF-11.B). The Study Director or researcher shall make a presentation describing the AHETF Exposure Monitoring Program, the goals

of the research study, the procedures used in exposure monitoring, and the risks and benefits to participants. A toll-free phone number will be provided, and individuals will be encouraged to contact AHETF if they desire additional information about the study or are interested in participating in the study. All presentation materials, such as handouts or visual aids, shall be reviewed and approved by an IRB prior to use in recruiting subjects." (pp. 336 of 438)

(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?

"In accordance with SOP AHETF-11.B, employers will be asked to sign a non-coercion statement (Employer Cooperation Statement) affirming to their workers and AHETF that they will not coerce or unduly influence their workers to either participate or not participate in the study. Employers must also certify that alternate work will be provided on study days for workers who choose not to volunteer; and that the employee's decision to participate or not will have no impact on their employment." (p. 335 of 438)

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for the subjects?

"During recruitment, workers will be offered an opportunity to take part in a recruitment meeting with the Study Director or other designated member of the study team (but without the workers' supervisors) to learn about participating in this study. (Section 5.2) No remuneration is offered for this introductory meeting. Workers who are still interested in participating in the study will attend a private meeting with a researcher who will obtain the informed consent of the worker (Section 2.7). Workers will be paid $20 for their attendance right after the consent meeting, whether or not they decide to participate in the study. Workers who decide to participate in the study will be paid an additional $80 each time they suit up (i.e., put on the long underwear) to participate in the study. Usually, workers will participate in the study on only one day unless their participation is terminated due to weather or other unexpected occurrences. The additional $80 is provided in cash at the end of the monitoring period or at the time the worker withdraws from the study. All workers who participate will receive the payment, even if they withdraw or their participation is terminated by the study team." (pp. 315-316 of 438)

(b) Is proposed remuneration so high as to be an undue inducement? No.

(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects? No.

(d) How and when would subjects be paid?

In cash, immediately after their participation.

4. Risks to Subjects

4.1 Risk Characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?

The potential surrogate materials are registered with EPA, are well understood, and have been fully tested.

This study could involve any of thirteen active ingredients: carbaryl, chlorothalonil, dacthal (DCPA), fosamine, glyphosate, imazapyr, imidacloprid, malathion, simazine, sulfur, thiophanate-methyl, 2,4-D, and 2,4-DB. "Pesticide products containing these active ingredients and potentially used in this study are currently registered for agricultural use and the specific application planned by the employer. AHETF will only monitor workers loading products in accordance with all label requirements." (p. 319 of 438)

For all thirteen of the possible active ingredients for this study, the Margins of Exposure (MOEs) calculated for the highest level of exposure in this protocol meet or exceed the minimum required MOE, or level of concern (generally 100), for the individual dermal and inhalation routes of exposure, as well as for the combined exposure.

(b) What is the nature of the risks to subjects of the proposed research?

The protocol and consent form currently lists five kinds of risks:

- The risk of heat-related illness
- The risk associated with scripting of field activities
- Psychological risks
- The risk of exposure to surfactants
- The risk of exposure to surrogate chemicals

"In this study risks to subjects are classified as 'greater than minimal' since the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation. AHETF has adopted an extensive program to minimize these risks." (p. 316 of 438)

(c) What is the probability of each risk associated with the research? How was this probability estimated?

Quantitative probabilities are not estimated.

4.2 Risk Minimization

(a) What specific steps are proposed to minimize risks to subjects?

"The following practices, designed to minimize these risks and respond to injuries, will be followed during this study (see AHETF SOPS 11.C, 11.E, 11.G and 11.H):

- Selecting only experienced pesticide handlers who consider themselves to be in good health
- Requiring experience with the type of closed loading system to be used
- Reminding workers of safe chemical handling practices
- Practicing the face wipe and hand wash procedures with each participant before pesticide handling begins
- Identifying nearby medical treatment facilities in case of emergency
- Monitoring the heat index and stopping the study if conditions warrant
- Providing transportation to medical treatment and covering the costs of treatment, if needed
- Having a medical professional at each MU site to observe the worker, provide urgent care, and decide whether the subject is too sick to make a decision about refusing medical treatment
- Observing study participants throughout the monitoring period
- Ensuring that all tank mix products are used according to approved label(s) and state regulations, and do not require any additional PPE that could adversely affect the study objectives (for example, chemical-resistant coveralls or aprons)." (p. 321of 438)

Risk reduction actions specific to the identified kinds of risk are discussed in the protocol (pp. 316-321 of 438).

(b) How do proposed dose/exposure levels compare to established NOELs/NOAELs for the test materials?

For all thirteen of the possible active ingredients for this study, the Margins of Exposure (MOEs) calculated for the highest level of exposure in this protocol meet or exceed the minimum required MOE, or level of concern (generally 100), for the individual dermal and inhalation routes of exposure, as well as for the combined exposure.

(c) What stopping rules are proposed in the protocol?

"AHETF will monitor environmental conditions to determine the heat index near the closed loading activities. Exposure monitoring will be discontinued if the heat index cutoff of 105^{o} F (adjusted for direct sun, if applicable) is reached or exceeded. The Study Director or other researcher shall stop the monitoring and/or move the worker to a cooler environment until monitoring can be resumed." (p. 317 of 438)

(d) How does the protocol provide for medical management of potential illness or injury to subjects?

"As a safety measure, AHETF will have a medical professional on site during the study. This may be a paramedic, physician's assistant, nurse, or emergency medical technician. This professional will also watch you for signs of illness. They will provide medical attention as needed." (p. 363 of 438)

SOP AHETF-11.H.3 (pp. 238-241 of 438) defines procedures to be followed if a subject in an AHETF study requires emergency medical attention.

(e) How does the protocol provide for safety monitoring?

The protocol refers to various SOPs which define procedures for safety monitoring:

- SOP AHETF-11.E.3 (pp. 221-222 of 438) calls for researchers to monitor worker compliance with label and Worker Protection Standard requirements and labeling, and permits the Study Director to remove from the study a worker who engages in unsafe work practices.
- SOP AHETF-11.G (pp. 225-237 of 438) calls for the Study Director, the on-site medical professional, and all researchers and observers to monitor subjects for any indication of heat-related illness.
- SOP AHETF-11.H (pp. 238-241 of 438) defines procedures to be followed if a subject in an AHETF study requires emergency medical attention.

(f) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

"During the consenting process each volunteer will be provided the opportunity to request a summary of their personal results from the study. This will require the worker to provide a name and address (mail or e-mail). The results will include a distribution of chemical exposure among the various body parts and a comparison of results from other workers performing the same task. Results are typically available 9-12 months after all monitoring is completed. The personal information related to this follow-up will be retained as described in SOP AHETF-6.D.

"Just prior to the completion of the volunteer's participation in the study, a researcher will remind the volunteer he/she should bathe or shower as soon as practical and that they have received a copy of the signed consent form with phone numbers for reporting any health changes they think might be related to participation in the study. Post-study inquiries will be forwarded to the Study Director who will deal with the situation as appropriate and notify AHETF management (SOP AHETF-11.J)." (pp. 325-6 of 438)

(g) How and by whom will medical care for research-related injuries to subjects be paid for?

"If you are injured or get sick because of your participation in this study, medical treatment will be available at your workplace and at a nearby health care facility. If necessary, AHETF will arrange to have you taken to receive medical attention. You may refuse medical treatment unless the medical professional decides you are too sick to make a decision about getting medical treatment."

"AHETF will cover the cost of reasonable and appropriate medical attention for a study-related injury or illness that is not covered by your own insurance or insurance provided through your employer. This includes deductible costs and any out-of-pocket expenses, including co-payments, you might have. The Study Director, in consultation with the on-site medical professional, will decide if you have an illness or injury that is due to your participation in this study." (p. 363 of 438)

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

"There are no personal benefits to the study participants." (p. 322 of 438)

(b) What benefits to society are anticipated from the information likely to be gained through the research?

"Data from the AHETF exposure monitoring program has the potential to improve the ability of EPA and other regulatory agencies to accurately assess occupational risks associated with closed loading of pesticides from returnable and non-returnable containers. The knowledge likely to be obtained from this study is generalizable and will contribute to assessments of the risks of both new and existing pesticides.

"Since there are insufficient existing data suitable for use in a generic database describing the exposure to workers from closed loading of liquids, society will likely benefit from data generated by this study through the improved risk assessments by EPA and other regulatory agencies." (p. 322 of 403)

(c) How would societal benefits be distributed? Who would benefit from the proposed research?

"Growers who allow the study to be conducted using their equipment, crops and facilities will be reimbursed for the pesticides used for the study. While this is beneficial to the grower, it is considered a minor benefit when compared to the costs of running their businesses. The AHETF member companies will likely realize a benefit by addressing regulatory data requirements generically, at lower cost (and using fewer human subjects), than if they conducted similar studies for individual pesticide ingredients." (p. 112 of 403)

(d) What is the likelihood that each identified societal benefits would be realized?

Identified societal benefits are likely to be realized.

6. Risk/Benefit Balance: How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

"By monitoring exposure to professional agricultural handlers who follow their normal practices, but wear an additional layer of clothing (as an inner dosimeter which traps chemical that penetrates the work clothing), this study presents a greater than minimal risk to participants. Participating in this study increases the risk of heat-related illness, but this risk is mitigated by a medical management program which emphasizes prevention measures and guidelines for stopping participation when warranted based on environmental conditions.

"The likely benefit to agricultural workers as a whole and to society in general, in the form of more accurate measurements of potential exposure to pesticides, must be weighed against the risks to participants. Closed systems for loading liquids is an engineering control designed to reduce handler exposure and requiring the use of closed systems is a common mitigation technique for reducing handler exposure. Therefore, exposure data for these scenarios meeting contemporary standards of reliability and quality will likely provide a significant benefit to society. Because margins of exposure are acceptable for the products proposed for use in this research study, subjects are very unlikely to experience acute toxic effects, and because extensive procedures will be in place to minimize these and other risks to participants, the likelihood of serious adverse effects is very small. In summary, AHETF believes the risks to study participants from participating in this study are reasonable in light of the likely benefit to society of the knowledge to be gained. (p 322 of 438)

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Independent Investigational Review Board, Inc., of Plantation FL

(b) Is this IRB independent of the investigators and sponsors of the research? Yes

(c) Is this IRB registered with OHRP? Yes

(d) Is this IRB accredited?

IIRB, Inc. earned "Full Accreditation" from the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) in December of 2009.

(e) Are complete records of the IRB review provided as required by 40 CFR 26.1125? Yes.

(f) What standard(s) of ethical conduct would govern the work?

"This study will be conducted in accordance with EPA's final regulation published at 40 CFR Part 26 that establishes requirements for the protection of subjects in human research (see SOP AHETF-11.A). The protocol, informed consent form(s), and other required documentation for this study will be approved by an institutional review board (IRB) and submitted to the EPA as required by 40 CFR 26.1125. The report of the completed research is subject to 40 CFR 26.1303 requirements to document its ethical conduct.

"The IRB for the proposed research shall be the Independent Investigational Review Board Inc. (IIRB) of Plantation, Florida. Complete records of the IIRB review as required by 40 CFR 26.1125 will be submitted to EPA for review along with this protocol and other documents.

"Researchers that participate in the study and interact with study participants must undergo ethics training (SOP AHETF-1.B). The training shall include successful completion of the course from the National Institutes of Health (Protecting Human Research Participants (PHRP)) and/or the Basic Collaborative IRB Training Initiative Course (CITI; The Protection of Human Research Subjects). Copies of the certificates of completion for the ethics courses will be submitted to the IRB and stored in the respective personnel files (maintained by the AHETF and all contract facilities.)" (pp. 314-15 of 438)

8. Informed Consent

(a) Will informed consent be obtained from each prospective subject? Yes

(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR §26.1117? Yes

(c) Do the informed consent materials meet the requirements of 40 CFR §26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research? Yes

(d) What is the literacy rate in English or other languages among the intended research subjects?

The literacy rate of intended subjects is not addressed in the protocol. Procedures for accommodating English- or Spanish-speaking candidates of low or limited literacy are explained in SOP AHETF-11.I.3. (pp. 242-247 of 438)

(e) What measures are proposed to overcome language differences, if any, between investigators and subjects?

See SOP AHETF-11.I.3 (pp. 242-247 of 438)

(f) What measures are proposed to ensure subject comprehension of risks and discomforts?

"In all situations, the person obtaining consent will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential workers that would require a response that indicates understanding of key issues. The form in Attachment 11-J-1 will be used to ascertain general understanding. (SOP AHETF-11.J.1 §3.10.a) (p. 250, 252-4 of 438)

(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

"The SD (or designee) will be responsible for obtaining informed consent from all study workers prior to their participation in the study. Any materials used during the consent meeting will be approved by the IRB before use.

"Informed consent will be sought in an individual meeting with each worker. The worker may have a friend, family member, or advisor with them during the meeting. Witnesses may also be present as described in SOP AHETF-11.I.

"The person conducting the consent meeting will inform the worker that he/she will receive $20 (or another amount specified in the protocol) for participation in the meeting, whether or not he/she volunteers to participate in the research.

"During the private consent meeting the person conducting the consent meeting will provide each worker with a full explanation of the study, its requirements, any potential risks, its benefits, alternatives to participation, etc. Workers will be advised of their right to withdraw from the study at any time and for any reason without jeopardizing their normal position with their employers or their daily wages. Workers will be told they will receive an additional $80 (or another amount specified in the protocol) if they decide to participate and put on the dosimeters, whether or not they complete the monitoring period.

"The person obtaining consent will provide information about the risk of the surrogate chemical in the study, including signs and symptoms of acute overexposure. This information will be presented in the product label and/or the MSDS. Refer to SOP AHETF-11.E for details.

"Information will be provided about the risk of heat stress, including signs and symptoms, and ways to prevent it. Information will also be provided about the

availability of medical attention during the study. Details on heat stress and its presentation are outlined in SOP AHETF-11.G, while details on emergency medical procedures are outlined in SOP AHETF-11.H.

"During the discussions between potential participants and the person obtaining consent, ample time will be provided for questions and the person obtaining consent will provide any additional information or clarification that is requested.

"The IRB-approved Consent Form (and all supporting documents, except the product labels and MSDS forms) will be presented in the preferred language (English or Spanish) of the worker. All sections of the Consent Form will be explained in detail. When the person obtaining consent is satisfied that the worker understands the requirements and risks of the study, and if the worker still wants to participate, he/she will be asked to sign and date the Consent Form and the person obtaining consent will provide a copy of the signed form to the worker.

"If the study is conducted in California, the IRB-approved "California Experimental Research Subject's Bill of Rights" will also be attached. These documents (in the appropriate language) will be reviewed, signed and dated by the worker, and copies will be provided.

"In all situations, the person obtaining consent will not sign the Consent Form unless he/she believes the candidate fully understands the information presented. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential workers that would require a response that indicates understanding of key issues. The form in Attachment 11-J-1 will be used to ascertain general understanding.

"The person obtaining consent will not sign the Consent Form unless he/she believes that the process has been free of any element of coercion or undue influence and the witness (when required) has signed the consent form." (SOP AHETF-11.J.1 §3.2-3.11) (pp. 249-250 of 438)

(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

"In accordance with SOP AHETF-11.B, growers will be asked to sign a non-coercion statement (Employer Cooperation Statement) affirming to their workers and AHETF that they will not coerce or unduly influence their workers to either participate or not participate in the study. Employers must also certify that alternate work will be provided on study days for workers who choose not to volunteer; and that the employee's decision to participate or not will have no impact on their employment." (p. 335 of 438)

9. Respect for Subjects

(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?

"The AHETF employs many procedures to protect subject privacy during recruitment, consent, study conduct, and maintenance of study records. The consent form also summarizes important confidentiality issues for subjects. These procedures are described in SOPs AHETF-6.B, 6.D, 11.B, 11.D, and 11-J." (p. 323 of 438)

"Your name will only appear on the consent form, an optional form for you to request your personal study results. In all other parts of the study you will be identified by a code. Records with your name will be stored in a secure place with limited access.

"Information we collect while you take part in this study will not be given to your employer.

"A study report will be written by AHETF and will be available to member companies. It will be sent to the US Environmental Protection Agency (EPA). It may also be sent to state government agencies and to governments in other countries. Your name will not be in the study report.

"We cannot promise you total confidentiality. There may be a need to give information to some organizations or to parties in legal actions, as required by law. Records which identify you may be looked at or copied by the AHETF and any consultants working with the AHETF, by EPA or other government agencies, and by the Independent Investigational Review Board, Inc., (IIRB). IIRB is a group of people who review and monitor research to make sure the people who take part are protected.

"You may ask the Study Director for a copy of your personal results from this study. You will need to provide your name and a mail or e-mail address." (p. 364 of 438)

(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

"The absolute right for subjects to withdraw from the research is the cornerstone of protection of human subjects. Prospective and enrolled subjects will be informed of their right to withdraw without consequence prior to and during the conduct of the research.

"Any subject expressing a need or desire to withdraw from the research after exposure monitoring begins will be paid $80 and allowed to return to their normal work duties for their employer. If a subject withdraws while being monitored, the long underwear and air sampling pump will be removed, and the hand and face/neck samples will be collected with the worker's consent. The Study Director will decide whether these samples will be analyzed." (SOP AHETF-8.K). (p. 323 of 438)

"Your employer has agreed to let us do the research and has confirmed that he/she does not mind if you do or do not take part in this study. Your decision to be in this study is voluntary. This decision is entirely up to you. If you decide to take part, you may change your mind and drop out of the study at any time and for any reason. A decision not to take part, or to withdraw from the study after it starts, will not affect your job or pay or include any penalty or loss of benefits you are owed." (p. 365 of 438)

(c) How will subjects who decline to participate or who withdraw from the research be dealt with?

"If you decide to take part, you may change your mind and drop out of the study at any time and for any reason. A decision not to take part, or to withdraw from the study after it starts, will not affect your job or pay or include any penalty or any loss of benefits you are owed.

"If you withdraw, the long underwear and air sampling pump will be removed. The hand and face/neck samples may be collected if you agree.

"Your part in this study may be stopped at any time by the researchers or the AHETF. The long underwear and air sampling pump will be removed. The hand and face/neck samples may be collected if you agree.

"If you withdraw or are removed from the study, you can go back to your usual work activities. If the study does not last an entire workday, you can go back to your usual work activities.

"No one can force you to take part in this study. Taking part is totally voluntary. If you choose not to take part in this study you will perform your ordinary activities on the day of the study. Your alternative is to not take part." (pp. 365 of 438)

§ 26.1111 Criteria for IRB approval of research
AHETF Protocol: Closed System Liquid Loading (AHE500)

Criterion	Y/N	Comment/Page Reference
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	n/a	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	Y	
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	Y	

§26.1116 General requirements for informed consent
AHETF Protocol: Closed System Liquid Loading (AHE500)

Criterion		Y/N	Comment/Page Reference
No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative		OK	
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		OK	
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		OK	
No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence		OK	
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	OK	
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	OK	
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	OK	
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	n/a	
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	OK	
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	OK	
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	OK	
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	OK	
(b) When appropriate, one or more of the following elements of information shall also be provided to each subject	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	OK	
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	OK	
	(3) Any additional costs to the subject that may result from participation in the research	OK	
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	OK	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	n/a	
	(6) The approximate number of subjects involved in the study	OK	
(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		OK	

§26.1117 Documentation of informed consent
AHETF Protocol: Closed System Liquid Loading (AHE500)

Criterion	Y/N	Comment/Page Reference
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.	OK	
(b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or	OK	
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	n/a	

40 CFR 26.1125 Prior submission of proposed human research for EPA review
AHETF Protocol: Closed System Liquid Loading (AHE500)

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

	Requirement		Y/N	Comments/Page Refs
All information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	pp 287-383 pp. 388, 419
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		n/a n/a	pp 436 No controverted issues
	(3) Records of continuing review activities.		n/a	
	(4) Copies of all correspondence between the IRB and the investigators.		Y	pp. 287, 371, 372, 384, 385, 399, 400, 414-416, 433-435
	(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y	IIRB roster and credentials on file with EPA.
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		Y	Separately submitted to EPA under confidentiality claim
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	
The following Information, to the extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 316-321
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 316-321
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 322
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	pp. 22-26
		(5) The balance of risks and benefits of the proposed research.	Y	p. 322
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Original pp. 358, 401 Approved pp. 388, 419
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 52-54, 315, 327-344, 387, 417
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	pp. 323-326
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 287, 371, 372, 384, 385, 399, 400, 414-416, 433-435
	§1125(f): Official notification to the sponsor or investigator…that research involving human subjects has been reviewed and approved by an IRB.		Y	pp. 385, 416