REPORT TITLE

Technical Summary Document
For a Multi-Year Pesticide Handler
Worker Exposure Monitoring Program

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SUBMITTED BY

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1 Introduction

1.1 AHETF and AHED™

The Agricultural Handler Exposure Task Force (AHETF) was established in December 2001 to generate exposure data for agricultural pesticide handlers to meet EPA data requirements for registration. Several AHETF member companies had ongoing data requirements resulting from product-specific data call-in notices, reregistration obligations, or prospective registration obligations. These companies agreed to jointly develop generic data in support of their respective registration obligations since existing data are not adequate.

The scientific question AHETF will be addressing is:

> "What is the expected distribution of worker exposures to pesticides during distinct occupational pesticide handling scenarios?"

The primary AHETF goal is the collection of worker exposure monitoring data and its incorporation into a new generic database that will define exposure distributions. The database will be a proprietary product of the task force and will be called AHED™, Agricultural Handlers Exposure Database. AHED™ will be submitted to EPA, and other regulatory agencies, and used by those regulators to conduct detailed quantitative exposure assessments to support safety determinations for occupational pesticide uses.

Generic databases were developed over the last twenty years in response to a regulatory need to assess the occupational risks associated with a wide range of pesticide handling situations. The concept was discussed and its development encouraged by a FIFRA Scientific Advisory Panel in 1986. In 1992, the Pesticide Handlers Exposure Database (PHED) was first released following a joint effort by pesticide manufacturers, the EPA, and Canadian regulators (Honeycutt, 1986; Lunchick, 1994; Reinert, 1986). Since then, PHED has been used extensively in a generic manner and has successfully supported many occupational risk assessments. However, much of the data in PHED are derived from exposure studies that are considered outdated or scientifically inadequate by current standards (Stasikowski, 2001). In addition, many handler scenarios of interest to EPA are absent or under-represented in PHED. Other regulatory agencies have expressed similar dissatisfaction with the limitations of PHED data. A major purpose of the Agricultural Handlers Exposure Database, or AHED™, is to address PHED deficiencies.

Like PHED, AHED™ will be populated with exposure data for workers who handle pesticides as part of their normal job, so their participation does not add appreciably to their typical exposure potential for handling pesticides. All

AHETF studies are designed and conducted in accordance with the latest U.S. EPA guidelines for occupational exposure studies.
The development of AHED™ is funded and directed by the AHETF. However, an AHETF Joint Regulatory Committee (JRC) has been established to promote active participation by interested regulatory agencies. The JRC is comprised of representatives of the U.S. EPA, the Canadian Pest Management Regulatory Agency (PMRA), the California Department of Pesticide Regulation (CDPR), and the United States Department of Agriculture (USDA). This committee meets on a regular basis to review program progress and provide technical and regulatory input to the AHETF.

1.2 Purpose of this Document

This document describes certain technical aspects of the AHETF exposure monitoring program that impact the Science Advisory Panel (SAP) meeting scheduled for January, 2007. It primarily discusses the need for additional human exposure data, the statistical sampling design for exposure data, and the statistical basis for how much exposure data may be needed in a scenario.

1.3 General Purpose and Description of AHETF Monitoring Program

The primary purpose of the AHETF monitoring program is to develop data that will be incorporated into a generic database (Agricultural Handlers Exposure Database, AHED™). These data will consist of dermal and inhalation exposure estimates for workers who handle pesticides under a variety of circumstances, using various pesticides and equipment types. AHETF refers to each unique handling situation as a 'scenario' and anticipates the database will contain sufficient data to support exposure assessments for many distinct scenarios. In general, scenarios are combinations of work task(s), pesticide formulation, equipment, engineering controls, and work practices that are similar. For example, two scenarios of interest are 'mixing/loading dry flowable pesticides using open pouring techniques' and 'applying liquid sprays using airblast equipment with open cabs'.

Within each scenario a number of monitoring units (MUs) will be sampled. Each MU will consist of monitoring dermal and inhalation exposure potential for a single worker for a time period that represents a typical workday. Subjects perform each task as they would during a normal workday. However, scripting of some MUs (i.e., controlling some aspect of the worker activity) may be used to ensure worker safety or introduce diversity among the MUs. Collectively, all of the MUs to be included in AHED™ are referred to as the AHETF monitoring (or testing) program. AHED™ will be used to support North American registrations (i.e., estimate exposure) for existing and new pesticide products as required by FIFRA in the United States and the Pest Control Products Act (PCPA) in Canada.

Regulatory users of the AHED™ database will be able to estimate individual worker exposures for a single workday given only:

- A mixer/loader and/or applicator pesticide handling scenario and
- The amount of active ingredient (ai) to be handled by the worker

Daily exposures are not expected to be identical for all individuals in a given scenario nor would such exposures be identical for the same individual performing the same work on different days. This is true since many factors influence exposure within a scenario in addition to the amount of ai handled. Therefore, specification of a scenario and an amount of ai handled can only determine a distribution of potential exposures; that is, a statistical description of the probability that a given exposure level is attained for a set of monitoring units within a given scenario. It is this distribution, and more often just some characteristic of the distribution, that is needed for regulatory risk assessments. The particular distributional characteristic will depend on the particular type of risk being addressed (e.g., short-term vs. long-term assessments). Examples of commonly used characteristics are the geometric mean, the arithmetic mean, and various upper percentiles.

Consequently, the overall goal of the AHETF monitoring program is to obtain individual exposure data for each scenario sufficient to adequately approximate the distribution of exposures normalized by the amount of ai handled. The predicted distribution of daily exposures can be obtained by simply multiplying this normalized generic exposure distribution by the amount of ai handled for the specific product being evaluated. The desired degree of accuracy of a scenario's exposure distribution may depend, in part, upon the relative importance of the scenario in the regulatory process. For example, great accuracy may not be necessary for scenarios that are less common or that result in very low exposure. In the case of closed loading granules, for example, potential exposure is very low and it may be a better use of resources to more accurately measure the distribution of higher exposure scenarios than pin down exactly how low the exposure potential is for closed loading of granules.

The AHETF monitoring program is designed to answer the scientific question: "What is the expected distribution of worker exposures to pesticides during distinct occupational pesticide handling scenarios?" This information is needed by EPA (and other regulatory agencies) to assess risks to workers who handle pesticides. This safety determination is mandated by FIFRA. The primary goal is to adequately approximate the distribution of exposure so that selected measures (i.e., means and upper percentiles) are accurate to a specified degree for each scenario (e.g., 3-fold, but it could vary by scenario). A secondary goal (for some scenarios) is that the data are adequate to distinguish between complete

proportionality and complete independence between exposure and amount of active handled.

The general approach for scenario-specific sampling designs is to sample a variety of MUs using different workers and a diverse set of common conditions that reflect current agricultural practices in North America. Exposure will usually be monitored at multiple locations and the amount of active ingredient handled will be varied to cover the practical range of product handled for each scenario. However, it should be noted that scenario sampling is not designed to statistically test the impact of location or any other condition on exposure, except for the amount of active ingredient handled.

2 Justification for Human Exposure Data

A necessary condition for scientific acceptability of the AHETF program is that the use of humans to generate these data be justified. This requires that new data are necessary for the regulatory risk assessment process and that adequate alternatives to conducting additional human exposure monitoring are not available.

2.1 Regulatory Need for Generic Exposure Data

FIFRA requires the U.S. Environmental Protection Agency to assure that any pesticide registered in the United States does not have unreasonable adverse effects on workers handling that pesticide. The PCPA requires a similar determination by Health Canada. This safety determination is generally made by means of quantitative risk assessment and risk management procedures. Risk assessments require a detailed evaluation of the toxicity of the pesticide and an estimation or measurement of the exposure potential for workers (and/or amount of pesticide absorbed by the workers as a consequence of its use). Exposure or absorbed dose estimates are quantitatively compared to no-effect exposure levels (often from experimental animals) for hazards identified in standardized toxicology studies. During the risk evaluation, the likelihood of the expression of any toxicological effect on the workers and a comparison of the risks and benefits are considered. This basic paradigm (hazard identification, dose-response assessment, exposure assessment, and risk characterization) was summarized by the National Academy of Sciences and has become the standard for risk assessment by regulatory agencies (NAS, 1983; NAS, 2006).

The AHETF database, AHED™, is intended to provide the North American regulatory agencies with the potential exposure data necessary for them to perform the handler exposure assessment portion of safety determinations.

Toxicology data and benefit information are product-specific and must be provided by individual pesticide product registrants.

When estimating exposure to workers who handle pesticides, a major challenge to overcome is that several parameters contribute to the likelihood and level of exposure. These include factors such as handling liquids versus solids, product packaging, using open versus closed systems, applying with various equipment types, amount of product handled, use of personal protective equipment (PPE), and whether the worker mixes/loads or applies or does both. The number of combinations of these parameters makes it impractical to generate human exposure data for all situations, so a number of simplifying approaches have been adopted. These include:

- Establishing various 'scenarios' that cover common combinations of these parameters and generating data for those scenarios
- Generating data with workers wearing minimum PPE
- Generating data that reflect various upper-end exposure situations
- Using data for one chemical/product as a surrogate for another (similar) product
- Assembling a generic database (e.g., PHED) for use as surrogate data applicable to many products

Since the early 1980's it has been the consensus of the scientific community that the amount of residue that contacts a worker's clothing and skin, and the amount of residue that is available for inhalation, are primarily a function of physical rather than chemical factors. That is, the chemical nature of the active ingredient in a pesticide product has little influence on the extent of exposure compared to physical parameters associated with the use of the product. The physical parameters include formulation type (e.g., liquid or granule product), method of application, and the way in which a person handles the pesticide during mixing, loading and application. Because of this, exposure potential is considered "generic" since it is independent of the specific active ingredient (Hackathorn, 1985; Honeycutt, 1985 and 1986; Reinert, 1985). Generic exposure data may therefore be used in lieu of product-specific data for most safety assessments. One major exception is that exposure to highly volatile compounds, such as fumigants, is not considered to be generic, and so will not be addressed by AHETF.

The use of generic data enhances the efficiency of regulatory agencies in conducting exposure assessments. Rather than relying on individual studies to evaluate case-by-case uses of each pesticide product, a single, comprehensive database of high quality data applicable to most products can be used. The broad

applicability of generic data and the resulting efficiency of their use in regulatory safety assessments led to the widespread acceptance of PHED. PHED components were created by assembling exposure data from studies that had already been conducted and submitted to EPA.

Most of the pesticide exposure data available at that time had been conducted by individual pesticide manufacturers who designed their studies to support the registration of a specific product or a group of similar products. It was very common for these companies to generate a set of exposure data that represented the worst case for exposure potential incorporating design features such as the maximum use rate, minimum PPE, and minimum engineering controls. If a risk assessment was acceptable for such a situation, then it was argued that an assessment involving lower use rates, additional PPE, and additional engineering controls would also be acceptable. However, this meant it was common for a study to involve 15 or more measurements of essentially the same situation where each person handled the same product, in the same packaging, in the same amount, using the same equipment, and for the same amount of time. While these studies are useful for product-specific cases, they are not always generically useful. Nevertheless, many of these types of studies were assembled to form PHED and, collectively, the database did improve the risk assessment process as regulators could often rely on larger data sets to estimate potential exposure.

However, as discussed in detail in Section 5, PHED, in hindsight, was not designed and built to meet the needs of a generic database and has several technical limitations. In addition, it is now an older database and many agricultural practices have changed. Exposure monitoring methods have also changed. The basic passive dosimetry methodology has long been accepted as a standard, reproducible procedure that provides accurate and reliable data that does not underestimate exposure. Even though the passive dosimetry methodology is still a very sound measure of exposure, there have been some improvements. In particular, much of the data in PHED are based on patch dosimetry and exposures were often not measured on all body areas. However, PHED provided reasonable estimates of exposure based on the technology of the 1980's. Today, whole-body garment dosimetry is used instead of patches to improve the ability to estimate the distribution of total body exposure.

There is general consensus among regulatory agencies that the most efficient means of generating handler exposure data is to pool technical resources and assemble a generic database. This consensus, EPA's recognition of the limitations of PHED, and their intention to use proprietary data to augment PHED, led to the formation of the AHETF in December, 2001. The task force database, AHED™, will be designed to reflect a logical set of use scenarios with adequate data in each scenario to provide good estimates of exposure potential and its distribution. Individual measurements will involve separate workers and

more diversity in equipment and conditions than in PHED, especially for the amount of product handled.

2.2 Alternatives to Additional Human Monitoring

Regulatory agencies are charged with assuring that registered uses of a pesticide will not cause unreasonable adverse effects to pesticide handlers. As part of such determinations, regulators and risk assessors must be able to approximate the levels of occupational exposure. Excluding new human monitoring studies, the information available to make reliable approximations currently comes primarily from generic data contained in PHED, but also from pesticide-specific exposure studies, modeling, and published literature. The use of animal data is obviously not an option for studies that monitor the occupational exposure to individuals engaged in their normal work activities.

Therefore, the only alternatives to the conduct of new human monitoring studies appear to be:

- The continued use of the existing information sources (primarily PHED, but also published literature)
- The acquisition of additional handler exposure data from other existing product-specific studies that meet established acceptance criteria and that can be used in a generic fashion

The limitations of PHED have been discussed briefly above and are described in more detail in Section 5.1.

Under the first stage of the AHETF program, and prior to the conduct of any field studies with human volunteers, the AHETF reviewed existing handler exposure data from various sources (primarily from AHETF members, CDPR, and the open literature) and acquired data that met established acceptance criteria. These activities are described in Section 4 below. Although some useful worker exposure studies were acquired by AHETF, most of the existing data were not sufficient to meet the generic data needs identified in advance by the AHETF and the Joint Regulatory Committee. While there may be other data that have been submitted to EPA and may be suitable for a generic database, they are proprietary and AHETF does not have access to them.

Therefore, prior to initiating any studies with human volunteers, AHETF evaluated available exposure studies and acquired the right to use those data that met its acceptance criteria. Consequently, at this point, in order to generate an exposure database, no viable alternatives to performing additional human monitoring studies exist.

It should also be pointed out that pre-requisite studies for AHETF testing do not involve human participants. These pre-requisite studies include analytical method validations, field recovery validations, and toxicity studies that support the registrations of the test materials used. Therefore, the exposure measurements (MUs) proposed by this document reflect the entirety of human participation.

3 Description of and Rationale for Scenarios Considered by AHED™

The handling scenarios selected for inclusion in the AHETF program reflect logical classifications of tasks, equipment, and formulations. Many of these scenarios are similar to those in PHED which have proven to be practical for regulatory use (to support product-specific exposure assessments using a generic database). A few others cover use situations that are not included in PHED. In addition, AHETF has evaluated deficiencies in PHED scenario data to be sure adequate data for exposure assessments do not already exist.

3.1 Limitations of PHED

Since 1992, the EPA has conducted agricultural mixer/loader and applicator exposure and risk assessments relying primarily on the exposure data in PHED. PHED version 1.01 was initially released in February 1992. It was followed by PHED version 1.1 in February 1995. PHED version 1.1 was described by the Agency as an incremental improvement over the 1.01 version (Pesticides Handlers Exposure Database, User's Guide Version 1.1, Health Canada, U.S. Environmental Protection Agency, American Crop Protection Association, February 1995). The forward to Version 1.1 User's Guide cautions the user that the database still has some limitations and should not be considered a panacea in estimating pesticide handler exposure. Noting the limitations, the guide states that a goal was to release a PHED version 2.0 in 1997. However, no subsequent version of PHED has been released.

By 2000, the U.S. Environmental Protection Agency began evaluating alternatives to PHED. On 16 March 2001, the Agency outlined its intentions regarding PHED (Letter from Margaret Stasikowski, Director, Health Effects Division to Daniel Fay, Valent USA Corporation, 16 March 2001). The letter stated EPA's intention to drastically overhaul PHED version 1.1 because many of the existing exposure studies in the database were outdated or scientifically inadequate by "today's standards". In addition, many exposure scenarios that are being assessed by the Agency are under-represented in PHED version 1.1.

In summary, PHED suffers from a number of limitations regarding its use as a generic exposure database, including:

- Inadequate number of measurements for one or more body areas (that reduces the confidence in exposure estimates for those areas)
- Inadequate quality assurance or quality control data (that sheds doubt on the reliability of all measurements)
- Use of patch dosimeters instead of whole-body dosimeters (that don't accurately reflect entire body exposures and requires extrapolations from a small patch area to the entire body area)
- Lack of entire body dermal estimates for workers (i.e., not all body parts monitored for dermal exposure) (that reduces the confidence in exposure estimates for those areas)
- Many non-quantifiable residues on dosimeters (that can lead to overestimates of actual exposure by assuming one-half the limit of quantification is present on all dosimeters with non-quantifiable residues when it may be even lower – this overestimate can also be magnified when patch dosimeters are used when the assumed residue is extrapolated to an entire body area)
- Lack of diversity for test conditions (e.g., same workers used repeatedly or all workers handling the same amount of product) (that reduces the confidence that measurements are reflective of a variety of common practices)
- Lack of 'representativeness' of test conditions (e.g., products or procedures that are no longer in common use) (that sheds doubt on exposures for modern agricultural equipment and practices)

Issues regarding the adequacy of the data in PHED can be illustrated by reviews of the Registration Eligibility Decision (RED) documents issued by EPA as part of the recently completed FQPA reregistration process. These documents have characterized the existing PHED data as low confidence for the following important use patterns. Confidence ratings are based on "number of replicates" (quantity) and "QA/QC Grades" (quality). In general, low confidence scenarios have fewer than 15 replicates and/or barely acceptable laboratory fortification recovery data (or worse).

Low Confidence Scenarios in PHED include:

- Mixing/loading of wettable powder in water soluble packaging (Scenario 5).
- Aerial application of a granular formulation (Scenario 8).
- Application by rotary aircraft (Scenario 9).

- Enclosed cab airblast application without gloves (when inside the cab as allowed by the Worker Protection Standard, WPS) (Scenario 12).
- Application of granular formulation by broadcast spreader (Scenario 15).
- Low pressure hand spray applications for greenhouses (Scenario 18).
- High pressure hand spray applications for greenhouses (Scenario 19).
- Application by backpack sprayer (Scenario 20).
- Application to rights-of-way (Scenario 24).

For reference, PHED confidence ratings can be summarized as:

Confidence Rating	**Number of Measurements**		**QA/QC Grading**
High	>= 15 per body part	And	Good laboratory plus good field fortification data (or better) (Grade AB)
Medium	>= 15 per body part	And	Moderate laboratory fortification data plus either poor field fortification or moderate storage stability data (Grade ABC)
Low	< 15 per body part	Or	Barely acceptable (or unacceptable) laboratory fortification data (Grades D or E = All Grades)

In addition, it should be noted that PHED provides dermal exposure estimates, and confidence ratings, for several distinct clothing situations:

- no clothes (i.e., based on outer dosimeters or clothing)
- single layer of clothing, no gloves
- single layer of clothing, with gloves
- coveralls over single layer of clothing, with gloves (some scenarios)

Therefore, PHED can have low confidence for one clothing/PPE situation and high confidence for another. While protection or penetration factors can be used to estimate protected exposure from non-protected exposure results, or vice versa, this creates additional uncertainty for exposure estimates and may not be appropriate for all risk assessments.

4 Incorporation of Existing Data into AHED™

Following the determination that PHED version 1.1, as a whole, did not meet the current needs for the conduct of handler exposure assessments, the AHETF began a process of evaluating existing handler exposure data available to the task force. Each of the studies considered had the potential to provide exposure data and supporting information from monitoring units (MUs) for a proposed AHED™ scenario. The evaluation process involved the following steps:

- ***Development of data acceptability criteria***: The existing data acceptability criteria addressed general study design and exposure monitoring techniques, including the analytical and quality control aspects of the studies. They are detailed in Appendix A.
- ***Primary review***: A process that involved the screening of handler exposure data from PHED version 1.1, publicly available data, and compensable data owned by AHETF members.
- ***Secondary review***: A detailed evaluation of data that passed the screening process for acceptability under the acceptance criteria with decision records for each study review.
- ***Final review***: A process that involved concurrence by the Joint Regulatory Committee on acceptance of the data for use within AHED™.

A total of 216 existing studies were evaluated from which a total of 105 MUs were deemed to be suitable for the AHETF generic database. It should be pointed out that 19 of these studies reflect data from PHED and only one of these studies met the acceptance criteria. AHETF eventually acquired the rights to use these 105 MUs and they were added to AHED™ under the appropriate scenarios. In most cases, these existing data are not sufficient to satisfy the full MU sampling requirements for the respective scenarios. These scenarios will be supplemented by obtaining new human exposure monitoring data.

Much of the existing data were deemed unsuitable for a generic database (and were not acquired) due to poor QA/QC (generally low or insufficient field fortification results), a preponderance of non-quantifiable residues, or the use of testing conditions that do not represent current agricultural practices in North America. However, the technical issue that eliminated the most existing data was the decision to exclude exposure data for workers who wore more than a single layer of clothing. This decision was discussed with the JRC who agreed that a modern generic database would be most useful if it contained exposure data for minimal clothing and PPE situations. Regulators are generally more comfortable estimating exposures to protected areas (e.g., dermal exposure under coveralls plus normal clothing) using exposure measurements from unprotected areas (e.g., dermal exposure under just one layer of normal clothing) than vice versa.

Therefore, AHED™ has been designed so that clothing/PPE protection factors can be specified by a user in order to estimate protected exposures, but not vice versa.

5 Program Design

5.1 Target Population

To establish the rationale for the AHETF monitoring program it is necessary to first consider the following question: What exposure information would be important in a world where experimental and measurement limitations were absent? This establishes a target to which real world sampling must strive. When such a conceptual goal cannot be envisioned, one might be just 'collecting data for the sake of collecting data'.

Consider the possibility of a worker handling some specified chemical product under one of the possible AHED™ scenarios. Imagine that a risk assessor could specify the set of worker conditions to an infinitely fine detail. This detail is so fine that it includes the particular chemical product tested, identification of a worker, his behavior, and any conceivable environmental conditions. In fact, all worker conditions that would have any impact at all on that worker's exposure are catalogued. For simplicity, denote this set of conditions by C_i, where the subscript "i" just emphasizes that it is just one of many possible worker exposure conditions. Because C_i embodies every possible relevant factor, there is only one possible worker exposure that is possible. Let's assume that the risk assessor can obtain this exposure, E_i, after he specifies C_i.

If this risk assessor knew all possible worker conditions and their corresponding exposures then it would seem he has all that is necessary for a perfect exposure assessment. Unfortunately, this is not the case. He would also need to know the relative likelihood of C_i actually occurring in practice. A high exposure that is very unlikely to occur may not be as important to the risk assessor as a moderate exposure coming from a very common C_i. Therefore, let us allow the risk assessor to also know the probability, P_i, that the set of conditions would actually occur. Armed with this information, this risk assessor can now determine the chance that any exposure might occur. He now knows the distribution of possible exposures within a scenario. He could look for those exposures that are of toxicological concern and then see which conditions are responsible. In this perfect world, the risk assessor would have quite an amazing set of tools for conducting risk assessments.

Actually, the risk assessor can get by with less. Suppose that he does not have knowledge of all parameters described within the C_i but still has all the values for

P_i and the E_i. That is, he just knows the distribution of exposures within the scenario, but not the particular conditions that generated them. With this information, the risk assessor can still evaluate the likelihood that a particular occupational scenario will result in unacceptable worker exposures. Naturally, it would no longer be possible to identify in detail the particular set of conditions that caused the unacceptable exposures.

Although the extensive knowledge described above is impossible to obtain in the real world, it does define the target population for the AHETF monitoring program. This target population consists of all possible C_i in a particular scenario. Here, target population is used in its statistical sense to mean those 'units AHETF would like their data to represent'. It does not mean only the set of workers that could potentially handle the chemical under the scenario. Such workers are only one component of the target population. That is, a particular worker only determines part of what is needed to completely specify C_i.

5.2 AHED™ MU samples in relation to the target population

Obviously, in the real world one will never know E_i and P_i for every possible C_i. But one can always obtain an exposure measurement from a sampled monitoring unit (MU). Each MU is the direct experimental analog to a worker condition, C_i, in the target population. However, there are important issues regarding the correspondence between these experimental MUs and the basic elements of the true target population. These relate to the basic features defined above: i.e., worker conditions (C_i), exposure (E_i), and the likelihood of occurrence (P_i).

5.2.1 Worker monitoring conditions

By definition an MU will have to have been sampled under some set of worker conditions for a particular scenario. However, there is always a question as to whether the conditions of the MU correspond to one of the C_i in the target population. In AHED™, MUs are generally partly scripted. That is, some conditions of the worker's activities are controlled while most are left unspecified. All specified conditions are consistent with the target population by design and most commonly include only the amount of active ingredient handled. The workers selected also always represent the target population since they handle pesticides in the manner being tested as a normal part of their job for that scenario. Consequently, any unspecified conditions (e.g., behaviors) should also be consistent with the set of C_i in the target population. Therefore, AHETF believes that all MU conditions are either identical with or very similar to potential worker conditions in the target population.

For each MU, details of the C_i are not known to the infinite degree discussed in Section 5.1 above. Nevertheless, many factors that make up C_i will be known

since they were recorded as observations. The AHETF program has not been designed to allow inferences regarding most of these factors. That is, the program is not a set of experiments designed to test the impact on exposure for various conditions such as worker, worker behavior, or environmental conditions. For the most part, it is just the distribution of exposure for that particular scenario that is of interest.

For example, in one proposed study to monitor exposure for workers making closed cab airblast applications to orchard crops, pecans were selected as a target crop (in addition to peaches) in part because a higher application rate is allowed by the test material label. Thus, the higher amounts of active ingredient handled were targeted for application to pecans rather than peaches. However, the sampling design for this scenario is not intended to compare worker exposures for pecans versus peaches, but rather to achieve a wide range in amount of active handled and the potential variability in airblast equipment used. This is a fine distinction, but an important one, since the AHETF believes that closed cab, airblast applicator exposure tends to depend on the amount of active handled regardless of the crop treated or specific equipment used.

5.2.2 Exposure measurements

Each MU yields estimates of inhalation and dermal exposure. Total dermal exposure is summed from separate measurements of exposure to various body areas, including summation of multiple hand wash samples. As is true for any exposure study there is no expectation that measured exposures will be exactly equal to E_i. This 'error', if substantial, would increase the apparent variation between MU exposures. However, it is usually the case that true exposure differences between MUs (or between C_i) far outweigh exposure measurement variation. If the MU exposure estimates are unbiased they would show no systematic tendency to be higher or lower than E_i. However, if they are substantially biased with respect to the true variation in exposure, then the mean exposure level obtained from MUs will be different from that in the target population. AHETF believes the passive dosimetry techniques used to measure exposure are unbiased (based on comparisons to biological monitoring) and are suitable for estimating exposure potential to workers.

5.2.3 Purposive sampling of MUs

Lack of knowledge concerning P_i is a major stumbling block in most environmental monitoring studies. It makes strict statistical inference to the target population impossible. Even if E_i were known exactly for an MU, one cannot estimate the distribution of target population exposures without knowing the chance that each set of MU worker conditions will occur in practice.

It is practically impossible to obtain a probability (i.e. 'random') sample of MUs. To do so would require knowledge of P_i for every possible C_i in the target population. (Or, it would be necessary to obtain this information indirectly through a large multistage sampling program.) AHETF would then have to ensure that each C_i has a positive and known chance of being selected as an MU. A simple random sample is even more restrictive. It would require selecting MUs from a set of C_i in exactly the same frequency that they occur in nature (i.e. with probability P_i). This would be extremely difficult even if all P_i were known. Without this knowledge, such random sampling is impossible. Consequently, any MU sampling must be non-random. It is important to note that the situation described above is extremely common for environmental monitoring studies. Unfortunately, researchers often ignore this issue and assume that their non-random sample is random. In some cases, there is an attempt at randomizing some single aspect of the participant selection in the mistaken belief that such partial randomization creates a simple random sample. Here, the AHETF prefers to acknowledge this limitation so it can be accommodated (during study design and analysis).

For each scenario, the AHETF monitoring program will use a purposive non-random sampling approach for selecting MUs. This method is designed to achieve a diversity of major factors that are likely to influence exposure. Such factors include: amount of ai handled, workers, and location. In general, strictly 'worst-case' sampling is avoided since it would reduce diversity. However, the method might occasionally incorporate some bias towards conditions likely to result in higher exposures and would be captured as part of C_i. This sampling approach is described in detail in Appendix B.

As a result of this purposive sampling, the MU exposure values can only be used to establish a surrogate distribution of exposures. This would be true for all studies unable to generate a true probability sample. In such cases one cannot equate the surrogate distribution to the actual distribution in the target population using purely statistical sampling theory. However, this surrogate distribution is felt to be adequate for practical regulatory purposes. While it might not be estimating the exact target population distribution, it is believed to be capturing the major aspects of it. Interested regulatory agencies represented by the JRC are aware of these necessary limitations of the statistical inference and feel this will not be an impediment to the usefulness of AHED™.

In the determination of sample size (Section 7.4) and the statistical analysis of MU data for scenario monograph reports (Section 9), uncertainties for distributional parameter estimates will be based on surrogate simple random sampling or surrogate cluster random sampling models as appropriate.

5.3 Between-worker versus Within-worker distribution

The distribution of exposures within workers is not the focus of the AHETF monitoring program. In fact, the diversity-oriented sampling methodology described in Appendix B was consciously designed to produce MUs that estimate only variation among different workers (i.e., 'total' variation). There is no plan to provide AHED™ users the capability to estimate both the between-worker and the within-worker components of total variation. AHETF has determined this would be of limited regulatory value and an unwarranted drain on limited experimental resources.

Experimental designs to estimate such components of variation are deceptively complex. One primary reason is that there is no single within-worker distribution to estimate. For example:

- Over what period of time should each worker be repeatedly measured?
- Should each worker be repeatedly monitored at the same location or conditions or over different locations or conditions?
- Should each worker handle similar or widely different amounts of ai?

All of these decisions give rise to different types of within-worker distributions that could be estimated. Even if such ambiguity could be resolved, repeated monitoring of many workers would be necessary. Although the exposures might be considered minimal, there would be an added experimental burden on workers who have to participate over longer periods of time. Obviously, the cost of the monitoring would increase considerably. Many more MUs would be necessary to determine both components of variation to the same levels of precision. Such repeated MU studies would also be more complex to manage.

Equally important, the regulatory need for such data is of low priority. Regulatory interest in within-worker exposure is mainly focused on the assessment of cumulative exposures over long periods (e.g., a year or more). In particular, there is a desire to estimate the between-worker distribution of long-term average exposures. If the within-worker correlation, R_{ww}, is at or near zero, the long-term average exposure for all individuals will be near the arithmetic mean of the single-day, between-worker distribution provided by AHED™. At the other extreme, when the within-worker correlation is near one, the long-term average exposures have the same distribution as that of single-day exposures. Again, the AHED™-derived distribution can be used. These two cases bound the

distribution of long-term average exposure since R_{ww} must always be between 0 and 1. Estimates from the literature (e.g., Nigg, et al., 1986; Kromhout and Vermeulen, 2001) and from repeated worker data indicate typical within-worker correlations are around 0.2-0.4 over very short periods of time (2-40 days) at the same location. It would be expected to be even smaller for longer periods or more diverse conditions. Although literature estimates of R_{ww} tend to be quite uncertain, this suggests that an assumption of close-to-zero correlation is reasonable for most regulatory purposes. In practice, most risk assessors will use a different-worker single-exposure distribution (such as that derivable from AHED™) and perhaps make various reasonable assumptions regarding the within-worker correlation, R_{ww}. Thus, the AHED™ database will provide suitable information that will be of use for long-term as well as short-term exposure assessments. Hence, there appears to be little incentive for diverting limited program resources to measure within-worker variation. The logistical difficulties, complexities, costs, and increased days of monitoring exposure to workers outweigh the benefit of pinning down an estimate of any particular within-worker correlation.

5.4 The type and number of MUs needed per scenario

This topic is addressed in a separate technical document titled "Procedures for Determining the Required Number of Clusters and Monitoring Units/Cluster to Achieve Adequacy".

6 Description and Role of GLP Studies under the AHETF Monitoring Program

In the context of the AHETF exposure monitoring program a 'study' takes on a specialized role. It is the component of the program that actually involves sampling MUs in accordance with Good Laboratory Practice (GLP) standards issued by EPA (40 CFR 160). The definition of "study" in the GLPs can be paraphrased as an experiment conducted at one or more test sites in which a test substance is studied in a test system to determine or predict a property of the test substance. Each GLP study may involve sampling MUs under one or a number of scenarios. For example, a study might be designed primarily to monitor rotary-wing pilot exposure, but the mixer/loaders who prepare the spray mixture (and whose exposure measurements will go into a different scenario) will also be monitored. Because it has a very restricted, albeit important, function within the AHETF program, the GLP study protocols need not contain extensive program information that is not relevant to the sampling of particular MUs. However, each study protocol should contain a reference to this program governing document.

6.1 Use of GLP "Study Protocols"

AHETF study timing and location is dictated by the seasonality of the tasks to be performed, pest pressures, and crop growth stages. This often allows a relatively small window of time each year when a study can be conducted. Finding sites and making arrangements for the studies can be challenging, especially when special efforts are made to monitor workers under actual conditions with minimal scripting. For example, a pilot may spray from hundreds, to sometimes over a thousand, acres during a typical workday. The AHETF must identify sufficient crop acreage to allow a full day of application for each worker (i.e., each exposure measurement or MU) while trying to capture the range of potential acres treated. Since data requirements for most use scenarios cannot practically be accomplished in a single study, most individual AHETF study protocols are part of a multi-study and multi-year plan designed to generate a wide range of data for activities associated with that use scenario. An individual protocol typically does not represent a single, stand-alone study; but represents a limited number of MUs that will be monitored at a specific site, generally with one particular pesticide product. Data from several sites and studies will later be combined for most use scenarios.

Each worker exposure field study is performed in accordance with long-standing EPA guidelines for conducting worker exposure studies (Durham, 1962; Wolf, 1967; WHO, 1975 and 1982, OECD, 1981; NACA, 1985; Chester, 1993; Worgan, 1995) as described in Series 875: Occupational and Residential Exposure Test Guidelines (U.S. EPA, 1986 and 1996) and in accordance with U.S. EPA FIFRA Good Laboratory Practice Standards (GLPs), 40 CFR, Part 160 (U.S. EPA, 1989). These guidelines are consistent with guidelines used in other countries such as Canada, Australia, and members of the European Union.

All of the individual study protocols are similar in order to have consistency and uniformity in the data sets. Exposure monitoring protocols differ mainly in the specific product used, equipment used, timing of the study, location and activity performed.

6.1.1 Descriptions of surrogate, locations, number of measurements

Since a major component of quality assurance is to perform field fortifications to test stability of the surrogate chemical (see below), AHETF protocols generally involve just one pesticide product containing one active ingredient. The protocol will generally name the product (since formulation type, container design, and/or product strength may be an important study design factor) and identify the active ingredient. On some occasions, a protocol may identify two potential products which could be used, but the raw data collected during the study would always identify exactly what was used. For example, AHETF has a set of validated

analytical methods which can quantify two organophosphate insecticides, malathion and diazinon, which have many approved uses in common. So, some protocols specify the use of malathion or diazinon.

As described in Appendix B, varying the location of monitoring is an important study design parameter, and some protocols will specify that data be generated in multiple states or provinces. However, since most scenarios consist of multiple studies, perhaps from different sites in different years, there are also situations where a GLP study protocol would reflect just one site. Varying the location of studies is generally done in order to obtain variability in exposure potential that may come from differences in workers, crops, equipment, or environmental conditions. For example, studies involving airblast application to grapes will be conducted in the west and in the east so that any differences in exposure potential that may be caused by weather, grape variety, vine management practices, equipment size, or other conditions will be included in the exposure data for those scenarios.

Each protocol lists a target number of measurements (generally one per worker) that will be generated, often separately for mixing/loading versus application activities. The actual number of MUs completed may be less than the target number due to many factors such as availability of workers and equipment, crop acreage available for treatment, workers who may decide not to participate, and weather conditions.

6.1.2 Documentation procedures

Exposure monitoring studies conducted by the AHETF are designed to measure potential exposure to workers as they perform their normal work functions for a particular handling scenario. As specified in AHETF Standard Operating Procedures and each study protocol (and as required by GLPs), all aspects of study conduct are fully documented. Most of the information collected during each study is entered, by hand by researchers, on standard data forms provided by AHETF. Much of the information that is collected during the study is also entered into the generic database, AHED™, for use in data analysis and for examination by database users in conjunction with data from other AHETF studies.

As required by GLPs, all raw data entries are made in ink and are signed and dated by the person who entered the data. In addition, data corrections must be made by marking a single line through the incorrect information, writing the correct information instead, and entering the reason for the change, typically as one of a set of standard codes that explains why the correction was made. Again, that entry must be initialed and dated by the researcher making the entry.

Raw data are collected in a study notebook which is retained indefinitely in AHETF archives. In addition, a certified copy of the data set is made during report writing and report review so that the original does not have to be shipped between author and Quality Assurance, and in case the original is lost during transit to archives.

6.1.3 GLP quality assurance procedures

A very important aspect of GLPs is the rigorous quality assurance procedures that are designed to assure the quality and integrity of the data that will be relied upon for pesticide handler exposure assessments to support product registrations. All aspects of the studies are monitored by appropriate quality assurance units (QAUs) while studies are in progress to ensure compliance with FIFRA GLP regulations (40 CFR Part 160) and adherence to the protocol and relevant Standard Operating Procedures. This generally involves three different QAUs: 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 from AHETF (the sponsor). For each study, the following specific activities are conducted by these QAUs:

- AHETF QAU inspects all contract research organizations and laboratories prior to use in a study to ensure that those researchers operate in compliance with GLPs
- AHETF QAU reviews protocols prior to finalization
- AHETF QAU observes study conduct in the field
- Field QAU audits the raw data file from the field and Field Report
- Analytical QAU audits the raw analytical data and Analytical Report
- AHETF QAU reviews and audits the final report which includes the Field Report and Analytical Report as appendices

Each QAU submits an inspection report(s) to the Study Director and AHETF Sponsor Representative and any exceptions to full GLP compliance are summarized in the Final Report associated with each protocol.

6.1.4 Quality control procedures

In addition to the formal quality assurance efforts discussed above, there are a number of important quality control procedures which are followed in order to assure that exposure measurements are accurate and precise and to define what those exposure measurements represent. These include complete validation of all analytical methods; extensive documentation of exactly what the participant does

while handling the pesticide product; field fortification and control samples designed to estimate stability of chemical residues during sampling, transit, and storage; laboratory fortification and control samples designed to establish efficiency of the analytical methods on a day-to-day basis; and detailed guidelines on the use of calibration curves to determine chemical residues found on all sample matrices.

In the field during each study, a chemist prepares exposure matrix samples that are fortified with a known amount of active ingredient. These matrices include whole body dosimeters (WBD, cotton long underwear), hand wash detergent solution, face/neck wipes moistened with detergent solution, and inhalation tubes (referred to as OVS tubes which stands for OSHA Versatile Samplers). OVS tubes are fortified in the laboratory by injecting diluted analytical grade active ingredient onto the sorbent in the tube while all other matrices are typically fortified in the field with a suspension of diluted test substance (from individual vials prepared in the laboratory). Each matrix type is generally fortified at three levels of active ingredient designed to span the range of residues anticipated to be collected from workers. At each level, triplicate samples are fortified. In addition, control samples are prepared for each matrix to determine whether background levels of active may be present. Control samples serve as a form of negative control. In general, field control and fortification samples are collected on at least two days during each study and whenever significantly different weather conditions are expected.

Fortified WBD and OVS tubes are "weathered" in the field since these sample types involve collection of residues during the monitoring period. For WBD, this involves laying a fortified section of long underwear onto a table in a sunny location and covering that sample with a single layer of outer shirt material. For OVS tubes, this involves drawing air through the tube in the same manner as done for workers. Fortified hand wash and face/neck wipe samples are not weathered since these samples are collected at specific time points during the monitoring period and immediately placed into frozen storage.

Analysis of field fortification samples provides a "recovery" value which will quantify stability of the active ingredient during sample collection (for weathered samples), storage in the field, shipment to the laboratory, and storage in the laboratory freezer. Therefore, field fortification samples serve as a form of positive controls. Field fortification samples are analyzed along with worker exposure samples and it is assumed that the worker samples experience similar stability as the field fortification samples. Therefore, residues found in worker samples are adjusted by appropriate average field fortification results to estimate the residues actually collected in the field. These practices are standard in pesticide exposure monitoring and are discussed in detail in internationally accepted testing guidelines.

Similar quality control procedures are followed in the laboratory, including control and fortification samples which are designed to detect background residues, monitor the performance of the method, and detect matrix or reagent interferences which may be present. These samples serve as a form of positive and negative controls. In addition to the detailed analytical methods for each surrogate and each matrix, all analyses must follow detailed AHETF analytical guidelines which specify procedures related to standard curves, extract handling, documentation, etc.

6.1.5 Reporting process

Consistent with GLPs and exposure testing guidelines, a detailed report is generated for each study, a "final report" in GLP terminology. AHETF calls these "Summary Reports" which include a text and tabular summary and detailed appendices including a Field Report and an Analytical Report. Summary reports are formally submitted to EPA, California DPR, and PMRA as they are completed. In general, these reports detail exactly what was done in the field, exactly what the results are for analysis of residues, and exactly what information should be entered into AHED™. However, since individual studies do not represent data for a complete scenario, these reports do not include an analysis or interpretation of the exposure data that were generated. Scenario summarization activities are described briefly in Section 7 of this document.

Field reports document the conduct of exposure monitoring, including:

- Identification of the location of the study, and the environmental conditions during the exposure monitoring period(s)
- Descriptions of the participants in the study
- Description of the test substance and packaging
- A record of the mixing, loading, and/or application, including a description of the workers, equipment, and worker activities
- A summary of worker observations identifying any specific occurrences that may contribute to unusual worker exposure
- Descriptions of the work clothing and personal protective equipment worn by each worker
- A detailed summary of the amount of test substance handled or applied for each worker
- A detailed summary of the length of time each worker was monitored
- A complete description of the field recovery evaluation with a summary of specific handling and weathering of all field samples
- A complete description of collection, handling, storage, and shipping of field samples.

Analytical reports document the handling and analysis of residues in all samples collected in the field, including:

- Results of analysis (e.g., µg/sample)
- A detailed description of the analytical instrumentation and methods
- Example calculations
- A summary of field and laboratory fortification recovery data
- Representative chromatograms of control, treated, fortified samples and calibration standards
- A typical standard curve

Summary reports summarize the field and analytical aspects and include calculations of adjusted residues found in all collected samples (i.e., adjusted for field fortification recovery); total dermal exposure for each worker; and the air concentration of active ingredient associated with each worker's monitoring period.

7 Summarization of the AHED™ MU data for each scenario

The ultimate purpose of the monitoring program is to make the individual MU exposure data from all scenarios available to users of AHED™, that is, to develop a generic pesticide handler database. To support AHED™, AHETF will generate scenario monographs for the benefit of regulators and other potential users. Each monograph will include a description of the scenario as well as a standardized statistical analysis of data adequacy within that scenario. Based on this analysis, AHETF may include in the monograph additional recommendations concerning the use of the MU results. Scenario monographs will be formally submitted to the regulatory agencies when AHETF determines the data collection for a particular scenario is complete and suitable for use in exposure assessments.

Monograph reports summarize study design issues as well as data evaluation and analysis, including:

- Representative use information for AHETF member products to define crops, rates, sites, etc.
- Information about the diversity of equipment and procedures currently in use in North America
- Summary of any existing data acquired by AHETF
- Study design summaries for AHETF studies
- Analysis of all relevant MU data to verify that the data quality objectives were met. Such analyses include discussion of the distribution of

exposure, levels of uncertainty, appropriateness of normalization, and statistical estimates describing the exposure distribution.

Scenario monographs will also be formally submitted to the regulatory agencies when AHETF determines the data collection for a particular scenario is complete.

8 Glossary of Terms

Adequacy of AHED™ Data

Each handler scenario within AHED™ will contain sufficient monitoring units to achieve a pre-determined level of accuracy for statistical descriptors (e.g., mean, geometric mean, and 90th percentile) of the distribution of exposure. Generally, AHETF proposes that a scenario data set will be considered accurate if these measures are within approximately 3-fold of the true value; and the number of MUs sampled will be chosen to achieve this level of accuracy.

AHETF = Agricultural Handlers Exposure Task Force, L.L.C.

A consortium of 19 companies that formed a FIFRA joint data development task force to design and develop a database of exposure measurements for agricultural workers during mixing, loading, and/or application of pesticides. The exposure data will cover all important types of mixing/loading systems, application equipment, and formulations. The results will satisfy FIFRA data requirements and be used to assess exposure potential and conduct risk assessments for most pesticide products marketed by AHETF members. AHETF was formed in December, 2001.

CDPR = California Department of Pesticide Regulation

The governmental agency that is responsible for the regulation of pesticide use in California. CDPR participates as a member of the JRC.

Cluster

A set of MUs from the same scenario considered a higher-level sampling unit for the purposes of statistical design and analysis. Usually clusters are comprised of MUs from the same geographic region (e.g. state) within a study. However, studies conducted in the same location, but widely separated in time (e.g., years) could also be considered separate clusters. Exposures between MUs from the same cluster tend to be more similar than those between MUs from different clusters.

Distribution of Exposure

A statistical description of the probability that any given exposure level is attained. For most practical purposes an exposure distribution can be characterized by standard parameters such as the arithmetic mean, geometric mean, and percentiles. Estimates of these distributional parameters are usually obtained from exposures measured on a sample of monitoring units within a given scenario

Exposure Monitoring

Using passive dosimetry techniques to measure dermal and inhalation exposure to professional, occupational pesticide handlers as they perform their typical activities. Researchers will use a variety of pesticide residue collection devices (cloth dosimeters, hand washes, face/neck wipes, and sorbent tubes) and determine the quantity of active ingredient on each device by chemical residue analysis.

FIFRA = Federal Insecticide, Fungicide, and Rodenticide Act

A federal act (7 U.S.C. §136 et seq.) which provided federal control of pesticide distribution, sale, and use. EPA was given authority under FIFRA to study the consequences of pesticide usage and to require registration of pesticides. FIFRA Section 3(c)(2) requires the publication of guidelines specifying data necessary to support registration of pesticides. Guideline 875 Part A is the guideline addressing the development of occupational exposure data such as those being developed by AHETF.

GLP = Good Laboratory Practice Standards

Federal regulations (40 CFR 160) which prescribe good laboratory practices for conducting studies that support pesticide registrations. The standards address the scientific integrity of study conduct and data collection, including specific requirements for study management, equipment calibration, facilities maintenance, record keeping, reporting, and quality assurance. All AHETF studies are conducted in accordance with these standards, both in the field and in the analytical laboratory.

Handling

Generally refers to mixing, loading, transferring, or applying pesticides. However, handling also includes the following common tasks: handling opened containers; disposing of pesticides or pesticide containers; and cleaning, adjusting, handling, or repairing the parts of mixing, loading, or application equipment that may contain pesticide residues.

JRC = Joint Regulatory Committee

A committee comprised of representatives of the U.S. EPA, the Canadian Pest Management Regulatory Agency (PMRA), the California Department of Pesticide Regulation (CDPR), and the U.S. Department of Agriculture (USDA). This committee meets on a regular basis with AHETF to clarify regulatory data requirements, provide technical and regulatory input on study design, and review progress.

Monitoring Program (or Testing Program)

The monitoring program consists of all the MUs from approximately 60 GLP studies which will be conducted by AHETF to monitor exposure to agricultural pesticide handlers and which will be used to develop a generic database to support pesticide registrations. The planned testing program will cover many handling situations, or scenarios.

Monitoring Unit (or MU)

All exposure monitoring activities pertaining to a single worker for a time period that represents a typical workday, including the exposure measurements for the worker involved. (An MU was formerly called a 'replicate'.) A number of monitoring units (MUs) will be sampled for each scenario to adequately define the distribution of exposure expected for that scenario. MUs corresponding to different scenarios may be sampled as part of a single GLP study.

Passive Dosimetry

Techniques for measuring pesticide exposure to humans that do not involve invasive collection techniques such as collecting urine or blood. In particular, AHETF studies involve whole-body garments that serve to collect potential dermal residues, hand washes to collect hand residues, face/neck wipes to collect residues on the face and neck areas, and sorbent tubes which collect air in the breathing zone of a worker. Occasionally, cloth dosimeters will be used to measure exposure to the feet or to the head area with and without headgear.

PMRA = Pest Management Regulatory Agency

The governmental agency that is responsible for the regulation of pesticide use in Canada. PMRA participates as a member of the JRC.

PPE = Personal Protective Equipment

Devices and apparel that are worn to protect the body from contact with pesticides or pesticide residues, including but not limited to coveralls, chemical-resistant suits, chemical-resistant gloves, chemical-resistant footwear, respiratory protection devices, chemical-resistant aprons, chemical-resistant headgear, and protective eyewear (40 CFR 170.240).

Purposive Diversity Sampling

The particular type of non-random MU sampling used in the AHETF monitoring program for each scenario. Sampling is purposive because certain important MU conditions are selectively sampled. Diversity (or heterogeneity) sampling means that the purposive sampling is targeted to achieve a diversity of major factors that are likely to influence exposure including: amount of ai handled, workers, and location.

RED = Reregistration Eligibility Decision Document.

A document produced by the EPA which summarizes the risk assessment conclusions and outlines any risk reduction measures necessary for a pesticide active ingredient to continue to be registered in the U.S.

Scenario

A specific pesticide handling situation that will be represented by data with defined common properties; generally a combination of a work task(s), pesticide formulation, equipment, engineering controls, and work practices. For example, a scenario of interest is 'mixing/loading dry flowable pesticides using open pouring equipment and techniques'.

Scripting, Scripted Study

Scripting is the partial control of the conditions in a particular MU. Workers are asked to conduct their work activities under a set of scripted conditions very similar, but maybe not identical, to those they experience in their normal work activities. Scripted studies must be approved for scientific and ethical validity by EPA and HSRB.

(GLP) Study

A convenient grouping of MUs that will be sampled as one 'study' in accordance with GLPs (including just one protocol and one final report). Generally the field portion of a study will be conducted over a short period of time (1 to 2 weeks), with one surrogate chemical, and may include MUs from one or several handler scenarios.

Surrogate Chemical

A pesticide active ingredient which is present in test materials which are handled during sampling of an MU. AHETF develops validated analytical methods for each surrogate chemical and each exposure matrix so residues collected can be determined. AHETF chooses surrogates which have low volatility and are commercially available in suitable formulations and packaging. Since exposure to handlers is a generic function, exposure measurements from these chemicals are suitable for estimating exposure to other pesticide active ingredients.

Target Population (or Universe)

The target population is a collection of elements representing all possible worker exposures for a scenario. Each element is defined by a set of all conditions that might have any impact at all on that worker's exposure. These conditions include the particular chemical product tested, the worker, his behavior, and all relevant environmental conditions. Each MU is assumed to be a realization of an element from the target population.

USDA = United States Department of Agriculture

A department that provides the federal government with leadership on food, agriculture, natural resources, and related issues based on sound public policy, the best available science, and efficient management. USDA participates as a member of the JRC.

WPS = Worker Protection Standard

A Federal regulation (40 CFR Part 170) which contains a standard designed to reduce the risks of illness or injury resulting from workers' and handlers' occupational exposures to pesticides used in the production of agricultural plants on farms, nurseries, greenhouses, and forests, and also from the accidental exposure of workers and other persons to such pesticides. It requires workplace practices for employers and workers designed to reduce or eliminate exposure to pesticides, and it establishes procedures for responding to exposure-related emergencies.

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Appendix A. AHETF Acceptance Criteria for Existing Studies

General Study Design Criteria

1. All monitored activities and equipment must be well-described and representative of typical agricultural mixing/loading and application practices.
2. It must be clear that the individuals monitored are normally employed in the mixing/loading and/or application of agricultural products.
3. Appropriate supporting information such as the formulation type, mixing and application method, application rate, duration of the work cycle, amount of AI handled/replicate, etc. must be available.
4. The use of personal protective equipment (PPE) is acceptable.
5. The study location and environmental/weather conditions during the monitoring period must be available.
6. All aspects of the study must have been conducted as per GLP regulators or be free of any significant GLP deviations or shortcomings if not conducted under GLP.

Exposure Monitoring Criteria

Field Aspects

1. Field recoveries must have been collected on a site-specific basis for time periods and environmental conditions representative of those during collection of field activity exposure samples.
2. Field fortification data must include at least triplicate samples at 2 rates and duplicate samples of controls.
3. Dermal exposure monitoring techniques must be specified and must include one of the following approaches.
    a. whole-body dosimeters inside of clothing plus hand (gloves cannot substitute for hand exposure) and head/face exposure determinations,
    b. a minimum of 10 patch dosimeters attached inside normal work clothing to the chest, back, both upper arms, both lower arms, both upper legs, both lower legs, plus hand (gloves cannot substitute for hand exposure) and head/face exposure determinations,
    c. combination of patches and clothing that are representative of the whole body, including hand and head/face exposure determinations.

4. Inhalation exposure – Inhalation data are not required. If data were collected, inhalation exposure must have been measured by sampling the person's breathing zone.
5. Exposure monitoring duration – The monitoring period should be at least half of a normal work period duration or half the default acreage.
6. If the exposure monitoring duration does not meet the requirement of item number 5, then the number of non-detects/less than LOQ values should account for less than 20% of the actual dermal exposure.
7. If the exposure monitoring duration and number of non-detects/less than LOQ values do not meet the criteria in items 5 and 6, then the LOQ must be no more than/1.0 ng/cm2 for dermal exposure and no more than 100 ppb for hand exposure.

Analytical Aspects - QA/QC

1. Analytical methods must have been validated for each analyte and substrate by the performing laboratory including establishment of the method's working concentration range to cover values anticipated in the field studies, determination of detector response over a reasonable standard concentration range, and determination of the accuracy and precision of the method within the analytical environment
2. The study must include both field fortification samples and concurrent laboratory spikes.
3. The average recoveries of lab spikes must be between 70-120 percent and the precision value (coefficient of variation) must be less than or equal to 20 percent.
4. Recovery of field fortification samples must be 50-120% with a C.V. ≤25%.
5. Exposure samples must have been analyzed in such a manner that the stability of each analyte in each substrate was assessed for the entire time period from collection to analysis.

Primary Review Process (216 Studies Reviewed)

1. The primary review is conducted by the study submitter (or a designated representative) and provided to AHETF along with a complete copy of the study report at the time the study is submitted to the task force for consideration.
2. The review by the submitter will include all applicable studies, including those that are presently in PHED.

3. The raw data for a study must be available, if requested, in order to be considered for purchase.
4. A list of potential studies must be submitted to the AHETF by March 1 and all primary review forms and reports must be submitted by June 1, 2002.
5. The purpose of the primary review will be to eliminate the submission of studies that clearly do not meet the selection criteria, and to serve as a check on the availability and submission of supporting information.
6. An Excel spreadsheet will be provided to the submitter for use in summarizing the study details and data.
7. A confidentiality agreement will be provided to the submitter to protect the confidential nature of their data.

Secondary Review Process (74 Studies Reviewed)

8. The secondary review will be conducted by a qualified AHETF contractor hired and trained for this purpose.
9. The purpose of the secondary review will be to verify the accuracy of the primary review and, where necessary, provide a more detailed discussion summarizing each specific area of the criteria, including whether each criterion was met and possible deficiencies in the study data.

Final Review Process (6 Studies Acquired)

10. The final review and decision on whether a study is accepted for purchase will be made by the Joint Regulatory/Task Force Technical Committee consisting of representatives from the AHETF, USEPA, PMRA, CDPR, and USDA.
11. The secondary review by the contractor and the regulatory reviews of contributed studies will be made available to the Joint Regulatory/Task Force Technical Committee and will serve as the basis for the final review. The secondary review will be evaluated and a determination made as to whether the study or any of the data could be used in the AHETF database.
12. Studies or portions of studies selected after final review will then be considered for purchase by the AHETF for inclusion in the task force database.
13. Reports for studies that are rejected will be returned to the submitter. Reports of studies that are purchased by AHETF will be placed in the AHETF archives.

Appendix B. Description of Purposive Selection of Monitoring Units

B.1. Background

The theoretical target population for the AHETF program is the set of all possible conditions that could occur under a particular handler exposure scenario (Figure 1). These possible conditions include, but are not restricted to workers, behaviors, chemicals, equipment used, locations, and environmental conditions. Note that conditions and individuals are not synonymous (Figure 2). The same worker could perform his or her job under an infinite variety of conditions.

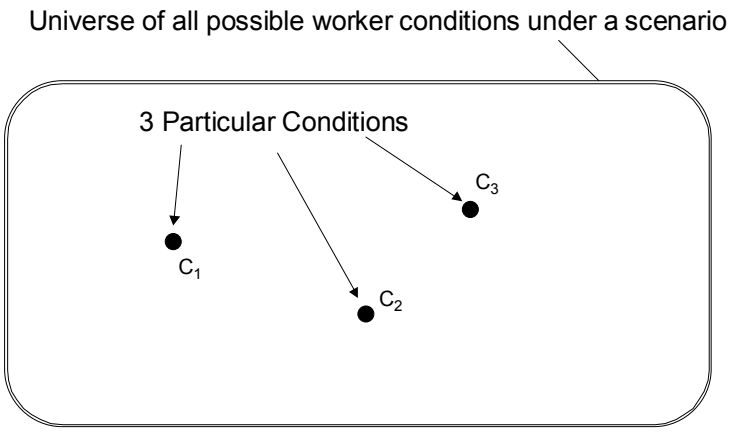

Figure 1. Target population (or 'universe') for the AHETF monitoring program.

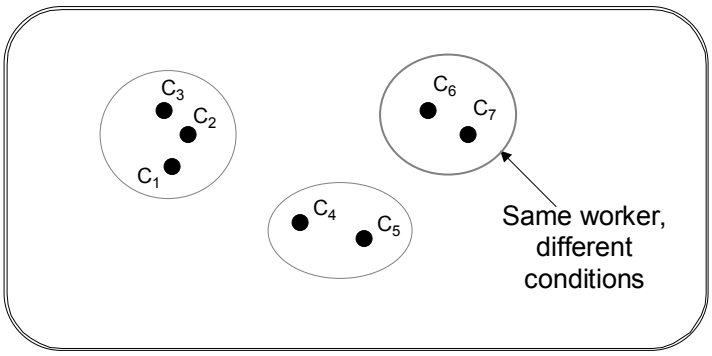

Figure 2. Conditions are not the same as individuals.

As illustrated in Figure 3, each unique combination of conditions (C_i) results in an exposure to the worker (E_i). In addition, each condition has a probability of occurring (P_i). Thus, each element of the target population is really the triplet $T_i = \{C_i, E_i, P_i\}$ representing a particular set of conditions, the resulting exposure, and the chance these conditions will occur in practice. If it were possible to know the exposure and probability of every possible set of worker conditions, risk assessors could isolate and hopefully mitigate conditions that are most likely to result in unacceptable worker exposures.

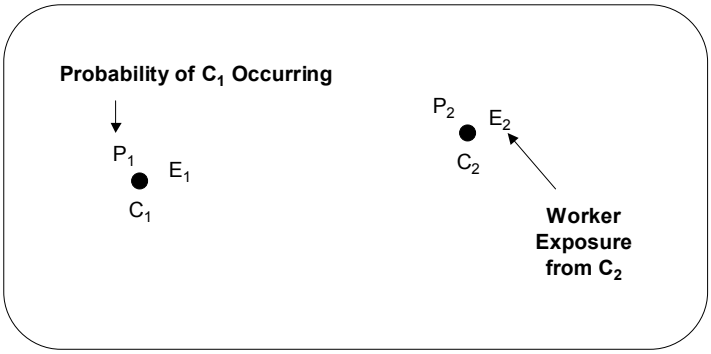

Figure 3. Each possible condition in the target universe has a probability of occurring and results in a particular worker exposure.

One could also use the information from all sets of T_i in the target population to characterize the distribution of exposures in the scenario. In conceptual terms this would mean summing the probabilities for all conditions that result in the same exposure. For each scenario, this would give a distribution of worker exposures, perhaps something like that illustrated in Figure 4 on the following page.

Figure 4. Summing the probabilities for every condition with the same exposure results in a distribution of worker exposures for the scenario

Obviously, such detailed information about all possible conditions could never be acquired in practice. One could, however, sample sets of conditions from the target population and then measure (approximately) the resulting worker exposures from these monitoring units (MUs). If probability (i.e., 'random') sampling is used to select conditions from the target population then each condition will tend to occur in the sample in proportion to its probability, P_i. Hence, the sample would tend to represent exposures with the same frequency as they are likely to occur in practice. (Or those exposures would have larger sampling weights, which amounts to the same thing.) Then, the worker exposure distribution (like in Figure 4) could be estimated from the MU exposure values.

It would be possible to obtain a multistage probability sample (Levy and Lemeshow, 1999) of workers for a particular scenario. It might even be feasible, although quite difficult, to incorporate probability sampling of other conditions into the design as well. However, such a sampling program would be extremely costly and logistically difficult to implement. In addition, it would likely require the participation of large numbers (i.e., hundreds, or even thousands) of individuals per scenario. This is a necessary cost whenever it is desired to statistically incorporate likelihood of occurrence information into the sampling process.

For the AHETF exposure monitoring program, the cost of probability sampling is considered unacceptable. Instead, non-probability methods are used to obtain a sample from the target population of conditions. In particular, the AHETF program uses purposive diversity sampling (e.g., Trochim, 2000). The primary emphasis is to diversify

as much as practical conditions that might affect exposure. As a result, the non-probability sample will tend to be more heterogeneous than an analogous probability sample.

Diversity is achieved through controlling or 'scripting' some aspects of the worker's activities. This scripting will not introduce artificial conditions, but may include normal variations that a particular worker may not have planned to use on a particular day. The bulk of each worker's activity is non-scripted.

As discussed in Section B.3., there are three major factors that will drive the diversity sampling within each scenario: (1) the amount of ai handled, (2) the individual used, and (3) the geographic location. Heterogeneity in these three factors is an integral part of the scenario sampling design. At each location, the AHETF non-probability sampling also attempts to less formally achieve a diversity of other conditions that are felt to affect exposure such as crop conditions, equipment, and procedures used.

When this information is known, the AHETF sampling approach emphasizes coverage of the more commonly occurring conditions over conditions that are rarer. This tends to more closely mimic a random sample. In some cases, however, there is also a bias towards conditions that might yield higher exposure.

B.2. The Role of GLP Studies in MU Sampling

The entire non-probability sample of MU conditions applies to a worker exposure scenario. However, for practical reasons, sets of MUs are sampled in one or more GLP studies. The purpose of each GLP study is to conduct a subset of the scenario's monitoring units, generally in a particular region of the country over a short period of time (e.g., one week). Efficiency requires that some scenarios are jointly addressed by the same GLP study. For example, it is usually more efficient to conduct mixer/loader monitoring and applicator monitoring at the same time. As a result, the general guidelines for diversity sampling described in Section B.1. apply to the scenario and, to some extent, to the GLP study as well. These guidelines need to be somewhat flexible since many MU decisions have to be made or revised in the field (e.g., based on grower needs or weather conditions).

B.3. The Three Primary Factors Controlled in AHED™ Diversity Sampling

For each scenario, the goal of the non-probability sample is to obtain as much diversity as is practical. Although many potential factors are considered, obtaining diversity in three factors is of primary importance. These three are the amount of active ingredient handled, number of unique workers, and number of geographic locations. These conditions are considered the most important based on reviews of existing

pesticide handler exposure data (e.g., in PHED) and have been discussed with the Joint Regulatory Committee.

B.3.1. Amount of Active Ingredient Handled (AaiH)

In the target population for any scenario, there may be a large range in the amount of active ingredient handled by various workers. In different portions of this AaiH range, there could also be differences among many factors that influence exposure. For example, the equipment and handling activities could be quite different for handling small amounts of active ingredient than for handling larger amounts. To capture these sources of variation it is important that a substantial portion of the practical AaiH range be sampled.

In addition, for some scenarios, a secondary objective will be to examine the default assumption that, on the average, exposure is proportional to the amount of ai handled. This will also require obtaining a sufficient number and type of replicates over the practical range of amount of ai handled so that if exposure is truly unrelated to AaiH, a test of consistency with a proportional relationship will be rejected.

AHETF first estimates the practical range of ai likely handled in the target population for each scenario based on information such as current product use rates and assumptions for the amount of crop that can be treated in a day. The upper limit of the practical range (ULPR) might include aerial applications of high use rate products. The lower limit of the practical range (LLPR) reflects handling of very low use rate products. In general, however, the LLPR does not extend below 5 lb. ai since AHETF wants to ensure that quantifiable residues are found for most worker exposure samples and wants to monitor workers for a period of time that is representative of a full workday.

Example B1

When designing studies for the dry flowable, open pour, mixer/loader scenario AHETF established a practical range of ai handled as 5 to 2,000 pounds of active ingredient. The upper limit was based on a high end use rate of 2 lb ai/acre, the assumption that up to 1,200 acres of crop could be treated by air but reduced somewhat since open pouring small containers would probably not be the technique of choice for the very highest use level (i.e., bulk packaging of liquids would be more common).

For practical reasons, the exact mechanism for diversifying this practical ai range will vary. Since each MU involves monitoring an actual commercial work activity, fine control over AaiH is not always possible. The AHETF does, however, follow the same general guidelines for all scenarios:

If the ratio ULPR/LLPR is less than 10 then the practical range is narrow and there is no explicit attempt to diversify AaiH. When the practical range exceeds an order of magnitude, however, one of two general approaches is followed.

An attempt is made to space the AaiH in a scenario more or less evenly along a logarithmic scale. That is, the ratio between successive AaiH levels is approximately the same.

A set of K AaiH target levels are established over the practical ai range and an attempt is made to use an AaiH level for each MU that is close to a target level. The K target levels AaiH1 through AaiHK are given by $AaiH_L = LLPR \times Q^{L-1}$. The factor Q is defined as $(ULPR/LLPR)^{1/(K-1)}$. Thus, $AaiH_K$ is just equal to ULPR. However, these AaiH levels are only approximate targets.

Method 1 is most feasible when it is relatively easy to control the amount of ai handled for different MUs in the same study. It generally achieves the greater diversity of the two methods. Method 2 is often a practical alternative when it is difficult to widely vary the AaiH levels over MU within a study. In this case, different studies could have different AaiH target levels.

Example B1 (continued)

In the dry flowable, open-pour, mixer/loader scenario AHETF defined 5 AaiH categories using method 2. There were 5 MUs used per study and each MU was assigned to only one of the AaiH categories. As a result, each dry flowable M/L study covered the entire practical range of AaiH.

B.3.2. Subjects Monitored

Within each scenario every attempt is made to ensure that each monitoring unit involves a different worker (i.e., different person). It is the intent of the AHETF monitoring program to focus only on the total variation between workers. In some situations, however, such as a subject withdrawing from the study at the last minute, a worker can be used for a second MU. In this case, however, as many other conditions as possible should be varied to reduce any possible correlation due to the repeated use of the same individual. For example, the MU for the same person might use a different AaiH, different equipment, and occur on different days. Regardless, multiple MUs with the same subject should be a rare occurrence for AHETF-conducted studies.

B.3.3. Geographic-Temporal Clusters

It is a common observation in many pesticide worker exposure studies, including many studies conducted by AHETF, that geographic location has a large impact on measured exposure. Varying the location of studies sometimes reflects known or

suspected regional differences in a particular agricultural parameter. More often, however, changing geographic locations merely varies exposure potential that comes from unknown differences in workers, equipment, or environmental conditions. Thus, 'location' is merely a surrogate for a cluster of known and unknown factors that jointly affect exposure. Clusters can also be temporal as well as spatial. Exposure-monitoring studies conducted at the same general location but years apart also differ in many ways and could result in different exposure measures. Usually MUs within the same cluster tend to be slightly more similar than those in different clusters.

To capture this important source of variation, AHETF samples monitoring units for each scenario over several distinct geographic locations. The desired number of clusters and number of monitoring units per cluster are established for each scenario. Studies are then designed to ensure that the complete MU sample includes the desired number of clusters. In some cases, a study protocol will specify that data be generated in multiple states or provinces. However, since most scenarios consist of multiple studies, perhaps from different sites in different years, there are many situations where a GLP study reflects just a single cluster.

Example B2

Studies involving airblast application to grapes will be conducted in the west and in the east so that any differences in exposure potential that may be caused by weather, grape variety, vine management practices, equipment size, or other conditions will be included in the exposure data for the airblast application scenarios.

B.4. Additional Factors

In addition to the three primary factors discussed in Sections B.3.1. through B.3.3, there are many other parameters that can be scripted and might have an impact on dermal and/or inhalation exposure for a particular scenario. These include experimental factors such as equipment used, specific worker techniques, and number of product containers used. There are no strict rules established to diversify these factors within scenarios. However, the AHETF has established a few basic guidelines to be used for each GLP study that help determine the variety of conditions among the monitoring units.

On a scenario-by-scenario basis, AHETF evaluates the equipment and procedures commonly used, often seeking the advice of experts through a variety of sources (see Section B.5. below). Then, the particular conditions are assigned to the MUs in a particular study based upon three considerations:

- Diversity of conditions
- Bias towards more common conditions
- Bias towards higher exposure conditions

B.4.1. Diversity of Conditions

During study design, AHETF attempts to identify typical situations for pesticide handling for each scenario and to identify specific parameters that differ and to evaluate which parameters may have an impact on worker exposure. These factors are varied as much as practical within each study.

Example B1 (continued)

In the open pour mixing/loading of dry flowable studies (5 studies), all of the workers open-poured a dry flowable product, but the 25 total monitoring units (MU) included:

- 24 different workers from 4 different states
- two different products with separate active ingredients
- some workers who measured partial containers and some who didn't
- some workers who used pre-mix (i.e., slurry) tanks and some who didn't
- one worker who used an eductor system
- some workers loading groundboom equipment and some loading aircraft
- workers mixing/loading from 3 to 24 loads
- load sizes that varied from 20 to 1500 gallons
- workers handling from 5 to 2,052 pounds of active ingredient

B.4.2. Bias toward Common Conditions

When planning the scenario MUs, conditions should be biased towards including the commonly occurring conditions as opposed to those that rarely occur. This makes the non-probability sample more representative of the target population.

Example B3

When designing the testing program for open cab groundboom applicator exposures, AHETF purposely included some workers who applied a spray to bare ground along with immediate incorporation into the soil (such as with a disc or tiller pulled behind the spray boom) since this practice is common and

could potentially lead to a slightly different exposure potential than application to a growing crop.

B.4.3. Bias toward Higher Exposures

In an effort to reduce the total number of MUs in the AHETF monitoring program, AHETF will occasionally focus on certain conditions believed to result in slightly higher exposure. For example, mixer/loader MUs will always involve preparation of multiple loads since this probably leads to higher exposure potential than preparing just a single load (involving an equal amount of pesticide). In particular, AHETF has set a minimum of 3 loads as a requirement for mixer/loader MUs.

In some other situations where there is an insufficient number of MUs to obtain wide coverage of conditions, it is acceptable to bias the MUs in a scenario towards conditions likely to give higher exposures. This approach will not be used frequently, but will be considered when practical and only in situations with limited AHETF resources.

Example B2 (continued)

Airblast applications are performed for both dormant and foliar conditions. AHETF believes that foliar applications are more likely to result in slightly higher worker exposures since the applicator is passing between rows of crop that are more dense which will result in slower dissipation of product blasted into the air and a greater likelihood that some spray will reflect off the crop and contact the worker. Spray material also rises to a greater height when applied to a foliated crop than to a dormant crop. Therefore, AHETF is generating all of its airblast applicator exposure data for foliar applications and will use that data to represent (the lower exposure) dormant applications as well.

This approach obviously biases the resulting exposure distribution towards higher exposures and thus is less representative of all airblast applications. However, from a regulatory perspective, overestimation of the exposure distribution is of less concern, especially given that it reduces the total number of human subjects involved in the monitoring program. And as long as workers commonly handle pesticides in the manner prescribed, electing to monitor exposure for these situations only does not trigger ethical concerns about exposing subjects to higher than necessary levels.

B.5. Sources of Expert Information

In order to assess which factors are most relevant for diversity sampling, the AHETF has established several sources of expert information.

B.5.1. Agricultural Handlers Advisory Panel (AHAP)

The AHETF-created Agricultural Handlers Advisory Panel (AHAP) includes experts from grower associations, governmental agencies, and applicator associations. This panel has been convened on an as-needed basis to address specific study design questions from AHETF, generally in reference to a particular crop or crop group (e.g., orchards). The AHAP has been successful in assisting with questions that are largely crop specific (e.g. large acreage aerial applications that are unique to a limited number of crops and airblast applications that are unique to orchards and vineyards). The participants on the panel are committed to provide the most appropriate people for the issues of interest.

B.5.2. Technical Advisory Panel (TAP)

As the AHETF works on scenarios that are specific to equipment rather than crops (e.g. ground boom sprayers, chemigation applications, and hand-held sprayers), there is a need for expert advice from other sources than AHAP. Therefore, AHETF is creating a Technical Advisory Panel (TAP, perhaps as part of the AHAP) that will include various experts who can provide specific information about equipment and procedures currently used in the real world.

Experts will be from various important agricultural regions of the U.S. and Canada. The goal is to have a list of people for each use scenario who can help guide testing design. Participants might include professional crop consultants, grower and applicator organizations, AHETF member company experts, farm equipment manufacturers, USDA Cooperative Extension Service, EPA Benefit and Economic Assessment Division, pesticide dealers and commercial applicators, farm labor organizations, and private research organizations. AHETF would identify specific technical questions related to study design and assemble appropriate experts to help answer those questions. In many cases, this assistance can be obtained via e-mail or conference calls. For example, prior to exposure monitoring for pilots of open cockpit helicopters, AHETF may need assistance with identifying how often this is performed, what types of use sites are commonly treated, and what is commonly the nature of the open cockpit (e.g., are doors simply removed from a typical closed cockpit helicopter).

B.6. References

Levy, P. S. and Lemeshow, S. (1999) Sampling of Populations: Methods and Applications, Third Ed. Wiley, New York.

Trochim, W. (2000). The Research Methods Knowledge Base, 2nd Edition. Atomic Dog Publishing, Cincinnati, OH.