Review Of Worker Exposure Assessment Methods

Presented Jointly To The FIFRA Scientific Advisory Panel By:

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1. Introduction

In this meeting of the Scientific Advisory Panel (SAP) the Agency is seeking review and comments on its evaluation of currently available exposure data and on proposed exposure measurement techniques to collect data that will be used in the future to assess the exposure to those involved in pesticide application activities. The data under consideration include the data available in the Pesticide Handlers Exposure Database (PHED). PHED is a database consisting of dermal and inhalation exposure measurements from a wide variety of scenario specific pesticide handler exposure studies (e.g., mixing and loading liquid formulations of pesticides into tractor mounted spray tanks). While this database has been a valuable tool used by North American regulatory agencies since the early 1990s, it is not without limitations. Therefore, over the years there has been an increased desire by various stakeholders to replace it. In 2001, a group of pesticide industry companies formed the Agricultural Handlers Exposure Task Force (AHETF) to develop a new database; the Agricultural Handlers Exposure Database (AHED).

In June 2006, the AHETF submitted 5 protocols for field trials for an ethics review by the Human Subjects Review Board (HSRB) pursuant to 40 CFR 26, subpart K. The protocols described 5 field trials that were part of their 2006 data collection efforts. These trials are part of a multi-year effort to develop data to populate AHED. In their review of the five protocols, the HSRB identified a number of issues including dermal exposure collection methodologies proposed by the AHETF and a lack of information on how an adequate sample size was derived. In addition, the HSRB asserted that the Agency had not demonstrated the need for these data in light of the current PHED database and consequently questioned whether additional testing involving intentional exposure to workers was justified. The HSRB report from that meeting is available at (http://www.epa.gov/osa/hsrb/files/june2006mtgreportfinal100606.pdf). Since the HSRB identified key scientific issues impacting many data generating efforts outside of the AHETF, such as the Antimicrobial Task Force (AEATF) which is planning to update exposure data to individuals involved in the handling of antimicrobial pesticides, the Agency believes the timing is appropriate for a scientific review of the methods and data analysis approaches that are to be used for the next generation of exposure data.

The broad purposes of this SAP review are:

1) To obtain comments on the adequacy of existing data (the PHED dataset) to support more refined worker exposure assessments (there is a case study of six example scenarios presented in the background document);

2) To obtain advice on how best to ensure that when new data are generated (whether for AHED or other efforts), such data are collected in manner that produces accurate information, to the extent reasonably possible, without, resulting in systematic underestimation of exposure; and

3) To obtain comment on the AHETF and AEATF documents: *Agricultural Handlers Exposure Task Force (AHETF) Technical Summary Document For a Multi-Year Pesticide Handler Worker Exposure Monitoring Program* (AHETFa, 2006)*, Procedures for Determining the Required Number of Clusters and Monitoring Units per Cluster to Achieve Benchmark Adequacy* (AHETFb, 2006) and *American Chemistry Council-Antimicrobials Exposure Assessment Task Force II (AEATF II) Background and Scoping Summary* (ACCa, 2006). To obtain comment on the AHETF

document: Procedures for Determining the Required Number of Clusters and Monitoring Units per Cluster to Achieve Benchmark Adequacy.

The Agency has collaborated very closely with the Pest Management Regulatory Agency of Health Canada (PMRA) as well as the Worker Health and Safety Branch of the California Department of Pesticide Regulation (DPR) in preparing for this meeting and, in general, over several years regarding occupational exposure assessment issues. This meeting represents a joint effort by all three agencies. In addition, these agencies have worked closely with the regulated industry (mainly through task forces) to ensure that the study designs and methodologies collected comprehensive, reliable data on exposures to workers.

The current state of the science as well as the development of more refined analytical tools necessitates the need to obtain more refined data with which to conduct occupational exposure assessments. Recognizing this and the Agency's desire to conduct more refined occupational handler exposure assessments, the affected industry has also pursued development of monitoring data that could be used for these purposes (Stasikowski, 2001). This industry effort essentially mirrors the development of the Pesticide Handlers Exposure Database (PHED) in which the industry collaborated with the Agency as well as PMRA, DPR and various European entities (e.g., Pesticide Safety Directorate in the UK). The ongoing development and implementation of the research by AHETF and AEATF have been closely monitored by the Agency, PMRA and DPR.

In 2006, the Agency established the Human Studies Review Board (herein referred to as the HSRB) that is charged with the evaluation of studies that involve intentional exposure of human subjects, from both a scientific and ethical perspective. HSRB review of new data is required prior to the Agency relying on the information in its regulatory decisions under current pesticide laws. More information regarding the HSRB is available at the following website (http://www.epa.gov/OSA/hsrb/index.htm). The AHETF has conducted a number of worker exposure field studies to date and had proposed several more for the 2006 growing season and beyond. The protocols for the studies to be conducted in 2006 were reviewed in June by the HSRB. Some of the major issues identified by the HSRB included:

- Study design issues
    - Limitations and utility of existing data need clarification;
    - Use of new data needs clarification (e.g., as a replacement or combined with existing data);
    - Statistical considerations of the research plan for conducting new studies needs further development;
    - Sample size issues related to the utility of the data need explored/clarified;
    - Baseline biomedical and/or biological monitoring data need to be considered.
- Methodological issues
    - Systematic bias in the sampling methods should be clarified;
    - Hand sampling methods (gloves or washes) need examination;
    - Dermal sampling methods (swiping, patch, or whole-body dosimeter) need examination;
    - Dosimeter performance under field conditions needs examination (e.g., losses, breakthrough, etc.).

The HSRB established criteria that it will use as the basis for the scientific evaluation of data. The Agency has attempted to address these scientific review criteria in this document in order to ensure that the SAP review of the occupational exposure assessment methods can also be used in any upcoming meetings of the HSRB. Because the issues to be considered in this meeting are interconnected to and associated with the research plans of the AHETF and AEATF, many analyses completed by these groups will be referenced in this document along with a discussion of the Agency's consideration of those analyses.

In addition to the AHETF which was formed to generate exposure data for conventional agricultural pesticides, a task force (the AEATF) was also formed to generate exposure data for antimicrobial pesticides. Many of the same issues and concerns regarding the methodologies and data generation that the HSRB raised in its review of the AHETF protocols also are relevant for the AEATF. The Agency believes the timing is appropriate for a scientific review of the methods and data analysis approaches that are to be used for the next generation of exposure data. Specifically, the exigencies giving rise to this effort include:

- the Agency's desire to develop a broader and more current database of occupational exposure data for completing risk assessments, formation of the AHETF and AEATF, and the scientific issues and concerns expressed by the HSRB in its review of the proposed 2007 AHETF protocols;

- the Agency's desire to incorporate more sophisticated data analysis tools such as distributional and probabilistic treatments into occupational exposure assessments for both agricultural and antimicrobial pesticides;

- to address the HSRB's questions pertaining to the need for additional data which would require developing and implementing an approach for examining the currently available data and then providing a justification for collecting additional information in a robust manner to estimate occupational exposures;

- the completion of the Food Quality Protection Act analysis of all food tolerance chemicals and an Agency emphasis on refining its tools (e.g., exposure assessment guidelines such as Series 875, Group B described below) for analyses related to occupational handler exposure assessment that are to be completed under PRIA (Pesticide Registration Improvement Act) registration and reregistration review;

- the development of updated requirements for occupational handler exposure monitoring data as illustrated in proposed updates to 40CFR158 which include codified requirements for occupational handler exposure data; and

- additional programmatic emphasis on worker exposure issues related to the results of studies such as the Agricultural Health Study and surveillance monitoring programs such as that conducted by the Washington state government.

The purpose of this document is to provide general background information for the SAP pertaining to how the Agency completes exposure assessments for occupationally exposed agricultural or antimicrobial pesticide handlers and to present the scientific issues to be

considered in that context. The issues which have been addressed in this document are described in the following sections:

- ***Section 2: Background Information -*** An overview of the data and methodologies typically used by the Agency for completing occupational handler risk assessments is contained in this section to provide context for the deliberations of the panel. Information includes a history of critical events that pertain to occupational handler exposure assessment by the Agency, and identification of the types of exposure scenarios considered by the Agency and the calculations used. Finally, this section contains a case study that presents the data and detailed methods used in PHED to calculate exposures for 6 common occupational pesticide handler tasks. [Note: Information pertaining to the data used to assess antimicrobial chemicals has also been included in this section. However, the detailed case study and follow-up analyses have been developed using only the agriculturally-based data.] The case study has been used as the basis for the analyses presented below in order to illustrate the approaches used by the Agency to examine the need for additional data and the potential refinements that such data could support.

- ***Section 3: Monitoring Methods*** - The performance of current recommended passive dosimetry exposure monitoring methods will be examined with a focus on the potential for inherent bias compared to biological monitoring estimates. The possibility of bias associated with hand monitoring techniques will also be examined since hands tend to be a large contributor during many activities. Other issues will also be addressed including the possibility for breakthrough of residues in dosimeters and dermal absorption when using removal methods such as hand washing. The information presented herein will also provide additional context to the analyses presented below.

- ***Section 4: Unit Exposure & Applicability Across Anticipated Working Conditions*** – Unit exposures, as currently used by the Agency, represent exposure normalized by the amount of active ingredient handled (e.g., mg/lb ai) that is based on the assumption that the two variables are proportional (i.e., if one doubles the amount of pesticide handled or applied, the resultant exposure will be doubled as well). The case study data has been analyzed to evaluate the extent to that the underlying default assumption of proportionality between exposure and amount of active ingredient handled for the Agency's unit exposure estimates is demonstrated and applicable across anticipated working conditions within our current database. Other possible normalization factors and the applicability of this approach for other possible use practices are discussed to the extent possible. The limitations of the existing data, as they pertain to this analysis, have been described as well as how additional data could be used to refine the Agency's understanding of the normalization issue.

- ***Section 5: Scope of Research Plan*** – The intent of this section is to describe/summarize the basic research plans that have been developed by both the AHETF and AEATF, as well as to provide the Agency's thoughts on the nature of these plans. Additionally, the methods that have been used by these groups to define the scope of their approaches (e.g., numbers of measurements) will be addressed. The size of the exposed population is an integral part of these analyses, especially related to the number of required datapoints. The Agency has provided background information of this issue as well in this section in order to provide a context for the analysis on the AHETF and AEATF proposals.

In addition, ***Section 6: Bibliography*** provides the citations used in the development of this document.

2. Background Information

This section provides the general background information on how the Agency currently conducts its occupational exposure assessments that will be helpful to the SAP as it considers the issues raised by the charge questions. The processes that lead to the development of current Agency guidance on exposure monitoring have been described below in ***Section 2.1: Historical Perspective***. Additionally, ***Section 2.2: Exposure Assessment Approach*** provides a brief overview of how exposures are calculated in order to provide context for the deliberations of the panel. In order to illustrate the concepts associated with the data currently used in typical Agency exposure assessments and the issues and limitations those data, a case study has been developed that is presented in ***Section 2.3: Occupational Handler Unit Exposure Case Study***.

The Agency has been actively involved over a number of years in the development and upgrading of testing guidelines which inform the development of the current protocols used for exposure monitoring purposes. Sound risk assessment practice dictates that appropriate scientific developments be integrated into the Agency's risk assessment process to ensure that the best available, sound science forms the basis of its regulatory decisions. Additionally, a case study has been developed that describes the available information which the Agency currently uses to develop its assessments and to illustrate why the Agency would like additional data. The considerations regarding how that data might be used in the regulatory process is also presented. In practical terms, this will allow the Agency to refine its standard exposure and risk assessment methods for use in the future.

2.1 Historical Perspective

Throughout the last 25 or so years, the Agency has been very actively engaged in attempting to refine the methodologies for completing occupational exposure and risk assessments. There have been many milestones but some of the more critical events are identified below:

- **The 1974 President's Council On Environmental Quality (CEQ) Task Group** This group focused on occupational exposure to pesticides and identified a need to evaluate exposures from plant surfaces with a focus on heavy contact field operations (e.g., picking, thinning) in order to establish restricted entry intervals. Key recommendations included requiring monitoring data, evaluating geographical and other factors which influence exposures, establishment of a surveillance system, and to develop lower risk alternatives. The general guidance from this working group stimulated Agency activity in the area of occupational exposure assessment over the next decade or so, which lead to the development of the Agency's first guidelines related to the assessment of occupational exposures.

- **1984 Pesticide Assessment Guidelines, Subdivision K – Exposure: Reentry Protection** [NTIS Document Number PB85-120962 (October, 1984).] Much of the seminal research related to exposure monitoring was conducted between 1974 and 1984. The Agency synthesized this information (a summary of key studies is included in preamble) and established the testing guidelines for monitoring post-application worker exposures based on this information (USEPA, 1984).

- **1986 Pesticide Assessment Guidelines, Subdivision U – Applicator Exposure Monitoring** [NTIS Document Number PB87-133286 (October, 1986).] When first engaged in developing occupational testing guidelines the Agency focused on post-application worker exposure issues and after completion of Subdivision K, completed similar guidelines for occupational handlers of pesticides (USEPA, 1986b).

- **1986 FIFRA Science Advisory Panel (SAP) Review Of Subdivision U** This effort represents the first SAP review of the Agency's exposure monitoring guidelines. Key recommendations from this review that are germane to the current SAP evaluation include: the use of concurrent dosimetry and biological monitoring should be encouraged; the use of either handwashes or lightweight gloves was recommended for monitoring hand exposures with some chemicals needing special consideration because of rapid absorption, persistence in the skin, etc.; and the utility of exposure monitoring data in a generic sense was agreed upon although factors that affect bioavailability should be considered when the approach is used (USEPA, 1986a)

- **1989 Good Laboratory Practices (40CFR160)** This document provides generalized guidance related to ensuring the quality control and quality assurance elements of data generated for pesticide registration purposes. Key elements related to exposure monitoring include recordkeeping, field calibration, laboratory quality control, and sample integrity (USEPA, 1989).

- **1992 Pesticide Handlers Exposure Database (PHED)** This database assembled the available data for pesticide handlers into a system that is still used today to generically address the exposures of that population (Hackathorn and Eberhart, 1985). This system established many precedents related to the use of data in a generic manner (e.g., correction for quality control, data grouping based on exposures, and monitoring refinements). Many of the studies conducted by the pesticide registrants were generated during the 1986 through 1992 timeframe which necessitated that Agency resources be devoted to protocol development and data review activities. PHED is an important tool because it allowed the Agency to begin to compile data for similar scenarios and to begin to elucidate trends in the data as well as limitations. The case study to be presented in this document is based on PHED data. [Note: The case study data are provided in Exhibit A. Also see *Reference Manual* and *Surrogate Guide* below – USEPA 1995a & USEPA, 1998b, respectively.]

- **1992 Chemical Manufacturers Association (CMA) Exposure Study** On 4 March 1987, a Data Call-In Notice was issued for submission of data for antimicrobial pesticide active ingredients. In response, the Chemical Manufacturers Association (CMA) developed a

generic biocide exposure assessment study, *Chemical Manufacturers Association Antimicrobial Exposure Assessment Study*. In total, 88 separate samples were obtained for six end-use settings and nine application methods to assess both dermal and inhalation exposures. Based on the considerable limitations of this study, industry has formed the AEATF to replace these data.

- **1993 Pesticide Rejection Rate Analysis: Occupational and Residential Exposure:** [EPA Document 738-R-93-008, September, 1993] In many scientific disciplines, there was a high rejection rate among studies submitted to the Agency for pesticide registration purposes. Therefore, in 1991 the Agency decided to evaluate the factors that most frequently caused studies to be rejected in order to assess the adequacy of EPA's guidance documents and to determine if rejection issues were avoidable. The key factors related to worker exposure monitoring were identified as inadequate quality assurance/quality control and inadequate sampling for residue decay studies (USEPA, 1993).

- **1994 & 1997 Workshops On Revisions To Agency Guidelines For Exposure Assessment:** After the release of the rejection rate analysis for exposure data and the experience gained during the development and review of many studies, it was clear that the current Agency guidelines for worker exposure required updating and that additional data were required to address various exposure issues. As such, the Agency along with other regulatory bodies (i.e., Health Canada, California Department Of Pesticide Regulation, and the Organization For Economic Cooperation and Development) sponsored workshops to determine how the current guidelines could be refined. Both whole-body dosimetry and various hand exposure monitoring methods were considered as appropriate at those meetings (PMRA, 1994 & USEPA, 1997).

- **1995 Pesticide Handlers Exposure Database (PHED) V1.1** The second release of PHED occurred in February 1995. PHED V1.1 is the current version in use today. Updates to the original release from 1992 included additional field exposure studies, additional application method codes, and additional studies with whole body dosimeters (USEPA 1995a).

- **1995 Data Call-In For Post-Application Worker Exposure Data:** This action by the Agency required pesticide registrants with the potential for post-application worker exposure associated with it (e.g., pickers, thinners) to generate data which could be used to quantify these exposures. This effort initiated the current model for developing large datasets of non-dietary exposure data in a systematic manner (USEPA, 1995b). [Note: The results of this group are undergoing Agency review and revised policies related to its efforts will be developed thereafter. More information can be found about this group at the following website (http://www.exposuretf.com/artf/index.htm).]

- **1997 Organization for Economic Co-operation and Development (OECD) Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application** The origin of this document was conceived at the International Workshop on Risk Assessment for Worker Exposure to Agricultural Pesticides held in the Hague, The Netherlands, in 1992, and was the focus of the Workshop on Methods of Pesticide Exposure Assessment held in Ottawa, Canada, in 1993. The OECD document

was developed by Health Canada and the North Atlantic Treaty Organization (NATO) and supported by USEPA. This document was developed to review and standardize the available exposure monitoring methodologies. The document also provides a detailed outline of the tier approach to pesticide risk assessments (OECD 1997).

- **1998 Draft Series 875 – Occupational and Residential Exposure Test Guidelines, Group B – Postapplication Exposure Monitoring Test Guidelines:** This draft guideline document reflected the state of the science for conducting exposure monitoring studies at that time. This document also describes the uncertainties associated with monitoring approaches as well as issues that should be considered by investigators related to logistics and data quality (USEPA, 1998a). These guidelines were taken to the SAP in 1998 and are available at http://www.epa.gov/scipoly/sap/1998/march/contents.htm . [Note: This document will also undergo final review in the next year or so and will incorporate many of the results of this SAP meeting since the charge for this meeting addresses generally applicable sampling methods issues and study/research plan design issues.]

- **2001 Formation of Agricultural Handlers Exposure Task Force (AHETF):** The AHETF was formed to address industry concerns over the nature of the data being used in Agency assessments for occupational handlers of pesticides. [Note: See the following website for more information: http://www.exposuretf.com/ahetf/index.htm .] The Agency expects this effort will improve the breadth, depth, and quality of the data currently in use for these purposes. Therefore; the AHETF will be an integral part of the discussions at the upcoming SAP meeting. The preparatory materials for SAP review related to each of the charge questions have referenced AHETF produced materials as appropriate. Agency responses to the content of these materials have also been provided as appropriate.

- **2003 Formation of Antimicrobial Exposure Assessment Task Force (AEATF):** The AEATF was formed to address industry concerns regarding the data being used in Agency assessments for occupational handlers of antimicrobial products. The Agency expects this effort will improve the breadth, depth, and quality of the data currently in use for these purposes. The AEATF will be an integral part of the discussions at the upcoming SAP meeting. The preparatory materials for SAP review related to each of the charge questions have referenced AEATF produced materials as appropriate (ACCa, 2006 & ACCb, 2006). Agency responses to the content of these materials have also been provided as appropriate. [Note: The case study included in this background document and much of the discussions are focused on the AHETF since it is further along with the development of protocols and a research plan than AEATF. However, many of the issues to be discussed are also applicable to the goals of AEATF. Specific references to AEATF are included in this document to delineate differences as appropriate. Additionally, separate presentation materials during the meeting will also be developed related to AEATF as appropriate to address the scope of the effort and any substantive differences with AHETF.]

The above information has attempted to summarize much of the level of effort by the Agency related to worker exposure and risk assessment over the last 25 years in order to provide a level of background knowledge for the panel discussions. Much of this effort has been focused on two areas including (1) conducting exposure and risk assessments under the timelines specified by the reregistration process and the tolerance reassessment timelines in the Food Quality Protection Act and (2) coordination with Health Canada and the California Department of Pesticide Regulation related to the data development efforts of the ARTF, AHETF, and AEATF. At this point in time, many of these efforts are either nearing completion (e.g., ARTF) or are formative (e.g., AHETF) and the Agency desires to move forward by again evaluating the current state of the science with regard to exposure monitoring methodologies. Since the AHETF and AEATF are in their formative stages of development of its research goals and objectives the Agency believes that the timing of this SAP review is appropriate.

2.2 Exposure Assessment Approach

The Agency uses the term "Handlers" to describe those individuals who are involved in the pesticide application process. The Agency believes that there are distinct job functions or tasks related to applications and that exposures can vary depending on the specifics of each task. Job requirements (e.g., amount of chemical to be used in an application), the kinds of equipment used, the crop or target being treated, and the circumstances of the user (e.g., the level of protection used by a handler) can cause exposure levels to differ in a manner specific to each application event. The scenarios that serve as the basis for the risk assessment are described in *Section 2.2.1: Handler Exposure Scenarios*. *Section 2.2.2: Algorithms Used For Risk Calculations* describes the actual mathematical procedures used to calculate exposures for toxicological endpoints that are based on both non-cancer and cancer effects.

2.2.1 Handler Exposure Scenarios

Exposure scenarios have been developed to categorize and group the kinds of exposures that occur related to the use of a chemical. The use of scenarios in exposure assessment is very common as described in the *U.S. EPA Guidelines For Exposure Assessment* (U.S. EPA; FR Vol. 57, No. 104; May 29, 1992; http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=15263). The purpose of this section is to describe the exposure scenarios that are typically used by the Agency in occupational handler exposure assessments and to explain how the scenarios were defined.

The first step in the handler exposure assessment process is to identify the kinds of workers that are likely to be exposed during the application process. In order to do this in a consistent manner, the Agency has developed a series of general descriptions for tasks that are associated with pesticide applications. Common tasks (as an example) can include: preparation of dilute, water-based spray solutions for application; transferring or loading dilute spray solutions into sprayers for application; and making applications with specific types of equipment such as a groundboom or airblast sprayer. Tasks associated with occupational pesticide use (i.e., for "handlers") can generally be categorized using one of the following terms:

- **Occupational Mixer/loaders:** these individuals perform tasks in preparation for an application using concentrated end-use products. For example, they would prepare dilute spray solutions and/or load/transfer solid materials (e.g., granulars) or dilute spray solutions into application equipment such as a groundboom tractor or planter prior to application.

- **Occupational Applicators:** these individuals operate application equipment during the release of a pesticide product into the environment. These individuals can make applications using equipment such as groundboom sprayers with dilute sprays or tractor-drawn spreaders for concentrated granular materials.

- **Occupational Mixer/loader/applicators:** these individuals are involved in the entire pesticide application process (i.e., they do all job functions related to a pesticide application event). These individuals would use concentrate materials to prepare a dilute spray solution and then also apply the solution or use concentrate solids. The Agency always considers some exposures to be mixer/loader/applicator exposures because of the equipment used and the logistics associated with such applications. For example, if one uses a small handheld device such as a 1 gallon low pressure handwand sprayer it is anticipated that one individual will mix a spray solution and then apply the solution because of labor and logistical considerations.

- **Occupational Flaggers:** these individuals guide aerial applicators during the release of a pesticide product onto an intended target. Most flaggers are primarily exposed to dilute sprays.

Next, assessors must understand how exposures occur (i.e., frequency and duration) and how the patterns of these occurrences can cause result in different toxicological effects. Wherever possible, use and usage data determine the appropriateness of certain types of risk assessments (e.g., a chronic risk assessment for occupational handlers is generally not warranted for many pesticide uses because chronic duration exposure patterns do not generally occur due to the seasonal uses of most pesticides). Other parameters are also determined from use and usage data such as application rates and application frequency. The Agency always conducts risk assessments using maximum application rates for each scenario because what is possible under the label (the legal means of controlling pesticide use) must be evaluated, for complete stewardship, in order to ensure there are no concerns for each specific use. Additionally, whenever the Agency has additional information such as typical application rates for some crops, it uses the information to evaluate the overall risks associated with the use of the chemical in order to allow for a more informed risk management decision.

A chemical can produce different toxic effects based on the duration of a person's exposure, how frequently exposures occur, and the intensity of exposure. It is likely that exposures for most chemicals can occur in a variety of patterns. The Agency believes that occupational exposures for most chemicals can occur over a single day or up to weeks at a time even though each crop or application target is generally treated only a few times per season. Intermittent exposures over several weeks are also anticipated. Some applicators may apply pesticides over a period of weeks because they need to cover large acreages. They may be custom or professional applicators who are completing a number of applications within a region, or they may be applying over a period of several days. In order to better describe different exposure patterns, a series of generalized time-based categories have been developed. For example, the Agency classifies exposures up to 30 days as short-term and exposures greater than 30 days up to several months as intermediate-term. The Agency completes both short- and intermediate-term assessments for occupational scenarios in essentially all cases because these kinds of exposures are likely and acceptable use and usage data are not available to justify omitting intermediate-term scenarios.

The toxicity of chemicals can also vary based on the route of exposure or how a chemical enters the body. For example, exposures via the skin can result in a different toxic effect and/or severity of reaction than exposures via inhalation. The effects of a chemical can also vary for different durations of exposure. The toxicology database for many chemicals indicates that the Agency consider exposures to the skin combined with exposures via inhalation because the effects which occur are the same regardless of whether it is deposited on the skin or it is inhaled (e.g., cholinesterase inhibition is an example of a common effect where this type of analysis is completed).

EPA's Occupational handler exposure assessments also reflect that a worker may use different levels of personal protection. The Agency typically evaluates all exposures with a tiered approach. The lowest tier is represented by the baseline exposure scenario followed by increasing levels of personal protective equipment (PPE) such as gloves, extra clothing, and respirators or the use of engineering controls (e.g., closed cabs and closed loading systems). The Agency conducts assessments of exposure with differing levels of PPE in order to be able to define label language using a risk-based approach and not based on generic requirements for label language as outlined in the Agency's Worker Protection Standard (40CFR170). [Note: All AHETF protocols at this point require single layer clothing, chemical-resistant gloves, and no respirator. This represents the current labels for the chemicals which have been selected for use by AHETF.] In addition, the minimal level of adequate protection for a chemical is generally considered by the Agency to be the most practical option for risk reduction (i.e., over-burdensome risk mitigation measures are not considered a practical alternative). The levels of protection described below form the basis for calculations completed in most Agency assessments and they include:

- **Baseline:** Represents typical work clothing or a long-sleeved shirt and long pants with no respiratory protection. No chemical-resistant gloves are included in this scenario.

- **Minimum Personal Protective Equipment (PPE):** Represents the baseline scenario with the use of chemical-resistant gloves and a dust/mist respirator with a protection factor of 5 which is commonly used for exposure assessment purposes in different settings (NIOSH, 2004).

- **Maximum Personal Protective Equipment (PPE):** Represents the baseline scenario with the use of an additional layer of clothing (e.g., a pair of coveralls), chemical-resistant gloves, and an air purifying respirator with a protection factor of 10 which is commonly used for exposure assessment purposes in different settings (NIOSH, 2004).

- **Engineering Controls:** Represents the use of an appropriate engineering control such as a closed tractor cab or closed loading system for granulars or liquids. Engineering controls are generally not applicable to handheld application methods which have no known devices that can be used to routinely lower the exposures for these methods.

It has been determined that exposure to pesticide handlers is likely during the occupational use of various pesticides. These uses can occur in a variety of environments including agriculture, commercial/industrial premises, and in residential environments. After examining the anticipated use patterns and current labeling for many pesticides, EPA identified 37 major agricultural exposure scenarios for workers. These scenarios reflect different activities and the types of equipment and techniques used in agriculture. Quantitative exposure assessments are typically developed for occupational handlers based on these scenarios but not limited by them (e.g., seed treatment is addressed using a different source of data but with a similar analytical approach). [Note: The scenario numbers correspond to the PHED surrogate exposure guide that is used by the Agency. The results and values which are applicable to these scenarios are summarized in the *PHED Surrogate Exposure Guide* (USEPA, 1998b). It should also be noted there are exposure estimates for differing levels of PPE associated with each scenario.] The scenarios in this guide include:

Mixing/Loading
(1) Dry Flowable mixing & loading;
(2) Granular mixing & loading;
(3) Liquids mixing & loading;
(4) Wettable Powder;
(5) Wettable Powder (or any formulation) in water soluble packets; and
(6) Liquids in closed loading systems.

Applicator:
(7) Aerial fixed wing aircraft liquid applications;
(8) Aerial fixed wing aircraft granular applications;
(9) Helicopter closed cockpit applications;
(10) Aerosol can applications;
(11) Airblast open cab tractor applications;
(12) Airblast closed cab tractor applications;
(13) Groundboom open cab applications;
(14) Groundboom closed cab applications;
(15) Solid broadcast spreader open cab applications for agricultural settings;
(16) Solid broadcast spreader closed cab applications for agricultural settings;
(17) Granular bait dispersed by hand;
(18) Low pressure handwand applications;
(19) High pressure handwand applications;
(20) Backpack applications;
(21) Handgun (i.e., turfgun) applications;
(22) Paintbrush applications;
(23) Airless sprayer applications; and
(24) Rights-of-way sprayer application.

Flaggers:
(25) Flagging for liquid spray applications; and
(26) Flagging for granular applications.

Mixer/Loader/Applicators:
(27) Wettable powder/liquid open mixing/loading with open cab tractor applications;
(28) Groundboom liquid open mixing/loading with open cab tractor applications;
(29) Groundboom liquid open mixing/loading with closed cab tractor applications;
(30) Belly grinder applications;
(31) Push-type granular spreader applications;
(32) Liquid open mixing/loading low pressure handwand applications;
(33) Wettable powder open mixing/loading low pressure handwand applications;
(34) Liquid open mixing/loading backpack sprayer applications;
(35) Liquid open mixing/loading high pressure handwand applications;
(36) Liquid open mixing/loading garden hose-end sprayer applications; and
(37) Liquid open mixing/loading termiticide injection applications.

The scenarios from the *PHED Surrogate Exposure Guide* presented above represent those commonly used in Agency assessments. The case study the Agency is using in its analyses is a subset of these scenarios as described below. The same methods could be applied to each scenario to examine the entire database if so desired. The AHETF research plan will address some, but not all, of these scenarios for a variety of reasons which are discussed in Section 6 below as well as the research plan itself.

The above are scenarios mostly for conventional agricultural pesticides. Similar types of scenarios would apply to the use of antimicrobial chemicals. The antimicrobial scenarios used by the Agency include data from both PHED and the CMA study (i.e., CMA = Chemical Manufacturers Association). The common handler exposure scenarios used in antimicrobial assessments have been organized in a slightly different manner by *Use Site Categories* and *Application Methods*. These are presented below:

(1) Agricultural Premises and Equipment (pump, pour liquid, aerosol spray, spray, mop, wipe, fog, soak/immerse);
(2) Food Handling/Storage Establishments Premises and Equipment (pump, pour liquid, aerosol spray, spray, mop, wipe, fog, soak/immerse);
(3) Commercial, Institutional & Industrial Premises and Equipment (pump, pour liquid, aerosol spray, spray, mop, wipe, fog, soak/immerse);
(4) Residential and Public Access Premises (pump, pour liquid, aerosol spray, spray, mop, wipe, fog, soak/immerse);
(5) Medical Premises and Equipment (aerosol spray, spray, mop, wipe, fog, soak/immerse);
(6) Human Drinking Water Systems (pump);
(7) Industrial Process Water Systems (pump, pour liquid);
(8) Material Preservatives (pump, pour liquid, pour solid, place solid, spray, soak/immersion, airless spray, brush/roll);
(9) Antifoulant Coatings (airless spray, brush/roll);
(10) Wood Preservatives (pressure treatment, soak/immersion, brush/roll, spray);
(11) Swimming Pools (pump, pour liquid, pour solid, place solid); and
(12) Aquatic Areas (pump, pour liquid, pour solid, place solid).

2.1.2 Algorithms Used For Risk Calculations

The occupational handler exposure and risk calculations are presented in this section. Noncancer risks are calculated using the Margin of Exposure (MOE) which is a ratio of the toxicological endpoint of concern to dose. Dose values are calculated by first calculating exposures by considering application parameters (i.e., rate and area treated) along with unit exposure levels (i.e., the amount of exposure per pound of active ingredient handled for a specific job task using specific equipment types and personal protective equipment). Exposure is normalized by body weight and adjusted for absorption factors as appropriate to calculate dose (i.e., body burden). Finally, MOE values are calculated to represent the magnitude of the risk. For cancer risk calculations, the next step is to develop lifetime average daily dose estimates (LADD) which are then compared to a cancer slope factor (i.e., Q_1*) in order to calculate population-based risk estimates.

Daily Exposure: The daily exposure, daily dose and hence the risks, to handlers are calculated as described below. The first step is to calculate daily exposure (dermal or inhalation) using the following formula:

Daily Exposure (mg ai/day) =

Unit Exposure (mg ai/lb ai) x Application Rate (lb ai/A) x Daily Area Treated (A/day)

Where:

Daily Exposure = Amount deposited on the surface of the skin that is available for dermal absorption or amount that is inhaled, also referred to as potential dose (mg ai/day);

Unit Exposure = Normalized exposure value derived from August 1998 PHED Surrogate Exposure Guide and various referenced exposure studies noted above (mg ai/lb ai);

Application Rate = Normalized application rate based on a logical unit treatment such as acres or gallons, maximum and typical values are generally used (lb ai/A); and

Daily Area Treated = Normalized application area based on a logical unit treatment such as acres (A/day) or gallons per day can be substituted (gal/day), such as common with antimicrobials.

The Agency uses a concept known as *unit exposure* as the basis for the scenarios used to assess handler exposures to pesticides (Hackathorn and Eberhart, 1985). *Unit exposures* numerically represent the exposures one would receive related to an application. They are generally presented as (mg active ingredient exposure/pounds of active ingredient handled). The Agency has developed unique unit exposures for each scenario typically considered in our assessments (i.e., there are different unit exposures for different types of application equipment; formulation type, job functions; and levels of protection). These are considered generic and used regardless of chemical identity. The Agency only uses these to address exposures to pesticides which are considered semi-volatile or non-volatile. More volatile materials such as fumigants are not addressed with generic data. Typically, chemical-specific data are required for these assessments. Chemical-specific and/or scenario-specific data can also be used if available for any assessment if it is determined that the specific data are more applicable to the scenario being evaluated.

The generic *unit exposure* concept is generally accepted in the scientific literature (Hackathorn and Eberhart, 1985) and also through various exposure monitoring guidelines published by the U.S. EPA and international organizations such as Health Canada and OECD (Organization For Economic Cooperation and Development). The concept of generic unit exposures can be illustrated by the following example. If an individual makes an application using a groundboom sprayer with either 10 pounds of chemical A or 10 pounds of chemical B using the same application equipment and protective measures, the exposures to chemicals A and B would be similar. The unit exposure in both cases would be 1/10th of the total exposure (measured in milligrams) received during the application of either chemical A or chemical B (i.e., milligrams on the skin after applying 10 pounds of active ingredient divided by 10 pounds of active ingredient applied). Likewise, if 5 pounds of chemical were applied, instead of 10 pounds, then the unit exposures would be 1/5th of the total exposure received. [Note: The underlying premise for unit exposures is examined below.]

PHED is the source of the generic unit exposure estimates that are used by the Agency as the basis for its exposure assessments for conventional pesticides and some antimicrobial pesticide uses. PHED was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to segment and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored events. Once the data for a given exposure scenario have been selected, the data are typically normalized (i.e., divided by) by the amount of pesticide handled then adjusted by the dermal surface area for the region of the body resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following this, the data from various body parts are summarized. The distribution of exposure values for each body part (e.g., chest upper arm) is categorized as normal, log-normal, or “other” (i.e., neither normal nor log-normal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for log-normal distributions, and the median for all “other” distributions. Once selected, the central tendency values for each body part are summed into a "central tendency" value representing the entire body. A complete description of the system is included in the *PHED Reference Manual* (USEPA, 1995a). This document describes all algorithms and analysis approaches included in PHED. It also contains an explanation of the data coding system that is included in PHED that is critical to the interpretation of the raw data as presented. [**Note:** As indicated above, the Agency is seeking guidance on many factors related to occupational exposure monitoring, study design, and the analysis of data. It was also noted that the industry groups AHETF and AEATF are in the formative stages of generating substantive databases that will likely be used for a number of years in order to address occupational exposures. ***The specific product of AHETF and AEATF will be databases of generic unit exposure estimates for a variety of agricultural and biocidal use patterns.*** How these data will be used in Agency assessments is pending but likely scenarios include replacing PHED estimates because they are of better quality, being combined with PHED estimates in order to enhance the number of available measurements, or addressing scenarios not adequately determined in PHED and/or CMA. Since the AHETF and AEATF products are integral to the Agency’s plan for refining its assessments over the next several years, many AHETF and AEATF produced analyses have been referenced in this document. Similar findings

of the SAP that pertain to AHETF will be considered in the process for evaluating AEATF progress.]

Daily Dose: After daily exposure is calculated, daily dose (inhalation or dermal) is calculated by normalizing the daily dermal exposure value by body weight and accounting for dermal absorption if appropriate. If a dermal administration toxicity study is used to calculate risks for dermal exposure, the term to adjust for dermal absorption is dropped from the calculation. It should also be noted that there are generally no specific inhalation absorption factors available so a factor of 100 percent is typically used for all calculations. Daily dose is calculated using the following formula:

$$Average\ Daily\ Dose\left(\frac{mg\ ai}{kg/day}\right) = Daily\ Exposure\left(\frac{mg\ ai}{day}\right) x \left(\frac{AbsorptionFactor(\%/100)}{Body\ Weight\ (kg)}\right)$$

Where:

Average Daily Dose = the amount as absorbed dose received from exposure to a pesticide in a given scenario (mg pesticide active ingredient/kg body weight/day, also referred to as ADD);

Daily Exposure = Amount deposited on the surface of the skin that is available for dermal absorption or amount that is inhaled, also referred to as potential dose (mg ai/day);

Absorption Factor = A measure of the flux or amount of chemical that crosses a biological boundary such as the skin (% of the total available absorbed); and

Body Weight = Body weight determined to represent the population of interest in a risk assessment (kg).

Margins of Exposure: Once daily dose estimates are defined, they are compared to the appropriate point of departure (i.e., NOAEL or LOAEL) to assess noncancer risks (or threshold cancer effects) to handlers for each exposure route within each scenario and suite of personal protective equipment. MOEs for all applicable exposure durations are also calculated for each of the scenarios. MOEs are calculated using the formula below:

$$MOE = \frac{NOAELorLOAEL\left(\frac{mg\ ai}{kg/day}\right)}{Average\ Daily\ Dose\left(\frac{mg\ ai}{kg/day}\right)}$$

Where:

MOE = Margin of exposure, value used by the Agency to represent risk or how close a chemical exposure is to being a concern (unitless);

ADD = (Average Daily Dose) or the amount as absorbed dose received from exposure to a pesticide in a given scenario (mg pesticide active ingredient/kg body weight/day); and

NOAEL or LOAEL = Dose level in a toxicity study, where no observed adverse effects occurred (NOAEL) in the study or the lowest dose level where an adverse effect occurred (LOAEL) in the study (mg pesticide active ingredient/kg body weight/day).

[Note: A risk is typically considered a concern if the MOE is <100 for occupational populations (10x for intraspecies variation and 10x for interspecies extrapolation). This can vary based on different factors related to the breadth and quality of the hazard database upon which the assessment is based.]

It is important to present risk values for each route of exposure (i.e., dermal or inhalation) in each scenario because it makes determining appropriate risk mitigation measures easier. For example, if overall risks are driven by dermal exposures and not inhalation, it would not be advisable to require respirators as they may marginally reduce overall risks. It is also important to present overall risk estimates for each scenario considered by calculating total MOEs. Total MOEs can be calculated if toxicity endpoints are similar between routes of exposure (e.g., cholinesterase inhibition associated with carbamate pesticides). The following formula is used to calculate total MOE values by combining the route-specific MOEs:

$$\mathbf{MOE_{total} = 1/((1/MOE_{dermal}) + (1/MOE_{inhalation}))}$$

Cancer Risks: Cancer risk calculations build on the above daily dose estimates which are used to calculate a lifetime average daily dose (LADD). LADD values are multiplied by an estimate of the carcinogenic potency (cancer slope factor or Q1*) to calculate a population-based cancer risk. LADD values are calculated by amortizing Average Daily Dose estimates based on the amount of years worked over a lifetime (i.e., typically 30 out of an average 70 year lifetime) and also the annual frequency of use (e.g., in many cases 30 working days per year with a particular chemical). To calculate a population-based cancer risk estimate, LADD values are multiplied by the slope factor.

The algorithms that are typically used by the Agency for exposure assessment purposes have been presented above in order to put the theme of this SAP meeting into context (i.e., how unit exposure estimates are generated including the factors that should be considered and the methods used). Other factors of equal import in the calculation of risks include inputs such as acres treated, application rates, or the selection of toxicological endpoints and associated dose estimates for risk assessment. These additional factors have not been included in the charge to the panel for this meeting as the Agency desires to focus on the issues related to the generation of unit exposure estimates.

2.3 Occupational Handler Unit Exposure Case Study

The intent of this section is to describe the data and methods the Agency uses to conduct its occupational pesticide handler exposure assessments and to discuss, in general terms, the limitations that are associated with the Agency's current data and approaches. This has been done in order to provide context to the analyses of the case study data below. PHED is a database system that the Agency uses to store occupational handler exposure data and also develop exposure estimates essentially from skin loading rates presented as either ($\mu g/cm^2$ of skin surface area or residue loading across an entire body). For convenience, a subset of the entire PHED database (i.e., approximately 25 % of all PHED data) was selected that reflects very common job tasks that occur in agriculture. The analyses of the data also illustrates why the Agency needs additional occupational exposure monitoring data if EPA is to be able to perform more refined assessments. For example, EPA would like to describe what “more refined” assessments could

include probabilistic treatments of data and the ability to define higher percentiles of exposure from a distribution.

Exhibit A provides the detailed data from the scenarios selected for the case study. The *PHED Reference Manual* and the *PHED Surrogate Exposure Guide* include the approaches used to calculate unit exposure estimates from these data (and also specifies the coding processes for the data) and the unit exposures which have been calculated by the Agency based on these data which are commonly used. [Note: The report of the June 2006 HSRB indicated that the Agency modify its nomenclature with regard to individuals who participate in exposure monitoring studies. The surrogate guide and reference manual documents were developed approximately 10 years ago and have been in constant use since then. In these documents, the term "replicate" has been used to represent a dataset generated by collecting dosimeters from an individual after one monitoring event. The Agency will modify this nomenclature (the term monitoring unit is under consideration). It should also be noted that the term "replicate" has not been revised in the historical documents. This issue will be addressed in the future, especially related to the development of any new databases and guidance documents.]

As described above in *Section 2.2.1: Handler Exposure Scenarios,* unit exposure estimates have been developed for a total of 37 agricultural pesticide handler scenarios as described in the *PHED Surrogate Exposure Guide*. This case study presents the data from 6 of these scenarios. The data contained in the selected scenarios range from extremely sparse (yet the best available information for the particular scenarios) to more complete datasets that tend to be of higher quality. The scenarios upon which the case study is based include:

Mixing/Loading
(1) Dry Flowable mixing & loading
(2) Granular mixing & loading
(3) Liquids mixing & loading

Applicator:
(11) Airblast open cab tractor applications
(12) Airblast closed cab tractor applications
(15) Solid broadcast spreader open cab applications for agricultural settings

More specifics regarding the data used to develop each scenario are included in Table 2-1.

Table 2-1: Summary of Studies And Monitoring Events Used In PHED Case Study

#	Scenario Description	# Studies	Timespan For Data Collection	Locations Where Collected	# Subjects	# Monitoring Events	# Subjects With >1 Event (range of events per each of these subjects)
1	Dry Flowable Mixer/Loader	6	1985 to 1991	CA, GA, IN, ND, MO, TX Canada, Australia	28	50	9 (2 to 5)
2	Granular Mixer/Loader	8	1977 to 1993	Il, MN, ND, AK, MO, NE, IA, NC, GA, Canada	48	96	15 (2 to 5)
3	Liquid Mixer/Loader	43	1977 to 1994	SC, IA, WI, FL, CA, NJ, IL, NE, MN, CO, ND, PA, VA, NC, OH, IN, AK, OR, MISS, AZ, MD, GA, MI, England, Sri Lanka, Malaysia	146	271	54 (2 to 15)
11	Airblast Open Cab	14	1977 to 1992	CA, NC, NY, OH, PA, VA, WA	39	91	19 (2 to 7)

	Application						
12	Airblast Closed Application	4	1987 TO 1991	CA, OR, GA	19	32	3 (4 to 7)
15	Solid Broadcast Spreader Open Cab Application	2	1979 & 1990	ND & Manitoba	2	5	1 (4)

Based on the information presented in Table 2-1 it is clear that there are great differences in the amount of data which are available for varying scenarios. Other differences exist with respect to the quality and the manner in which the data were collected (e.g., measurements of intra- and inter-personal variability within each set of data).

Additionally, the types of collection media used to generate these data need to be considered. As described in the Agency guidelines for conducting exposure studies (USEPA 1984; USEPA, 1986 and http://www.epa.gov/scipoly/sap/1998/march/contents.htm) there are varying media and approaches that can be used to collect similar types of information. For example, dermal exposure data (not on the hands) have typically been collected using either patches, made of alpha-cellulose or gauze, or whole body dosimeters (Durham & Wolfe, 1962 and WHO 1985). Other devices have sometimes been used such as cotton socks covering the forearm or swabbing methods. Additionally, differences exist in the configurations of the monitors (e.g., different investigators could place patches at different body locations). Hand exposures have also been collected using a variety of media and approaches but generally involve the use of cotton gloves or some type of hand washing method. In this case study, 8 different media were used to quantify hand exposures (i.e., ethanol, acetone, methanol, cotton gloves, Tyvek© gloves, isopropanol, gauze patches, soapy water). Figures 2-1 through 2-3 depict the variety of sampling methods used to generate the data for three of the scenarios in the case study.

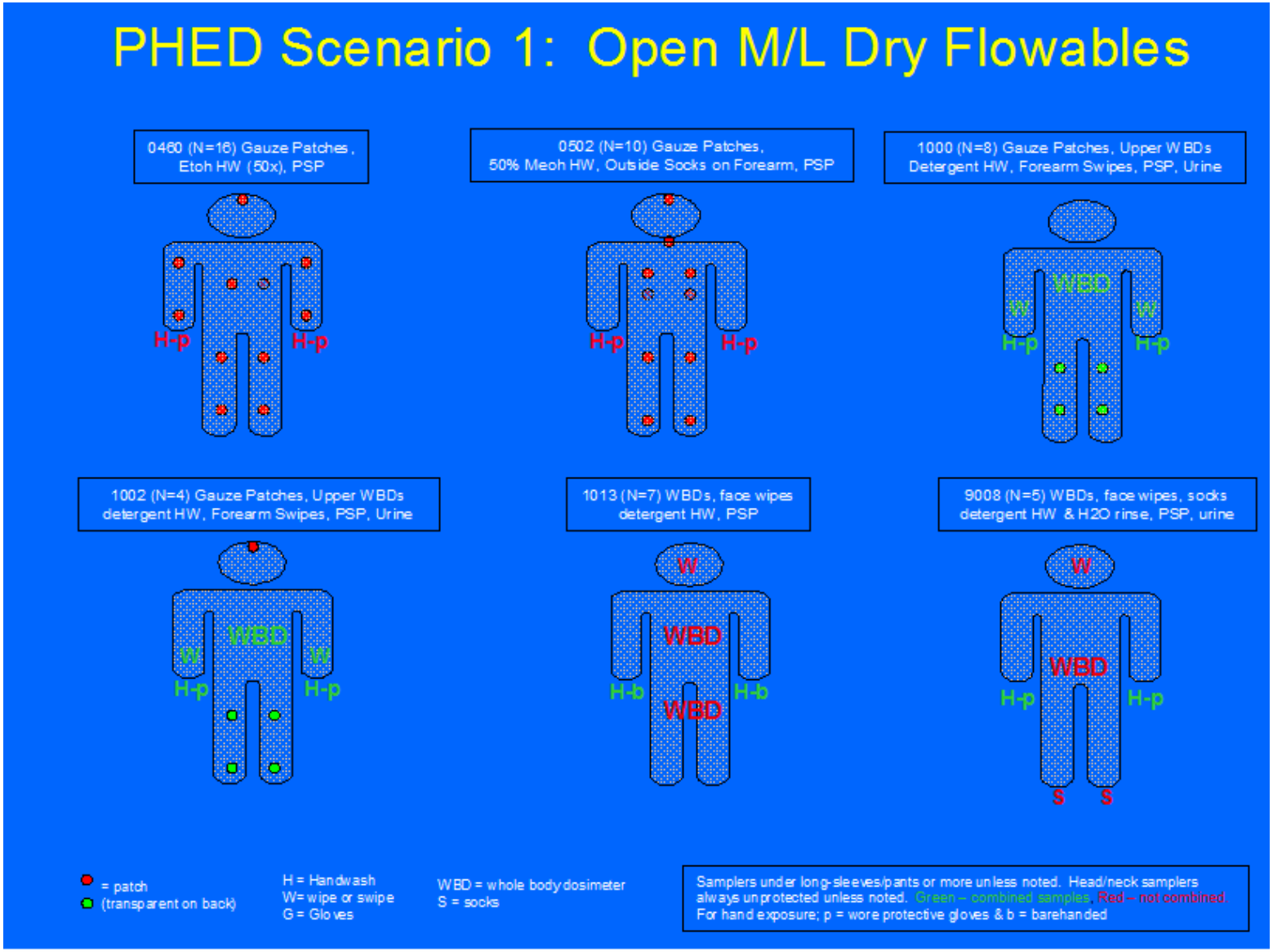


Figure 2-1: Sampling Regimen Associated With Data From PHED Scenario 1.

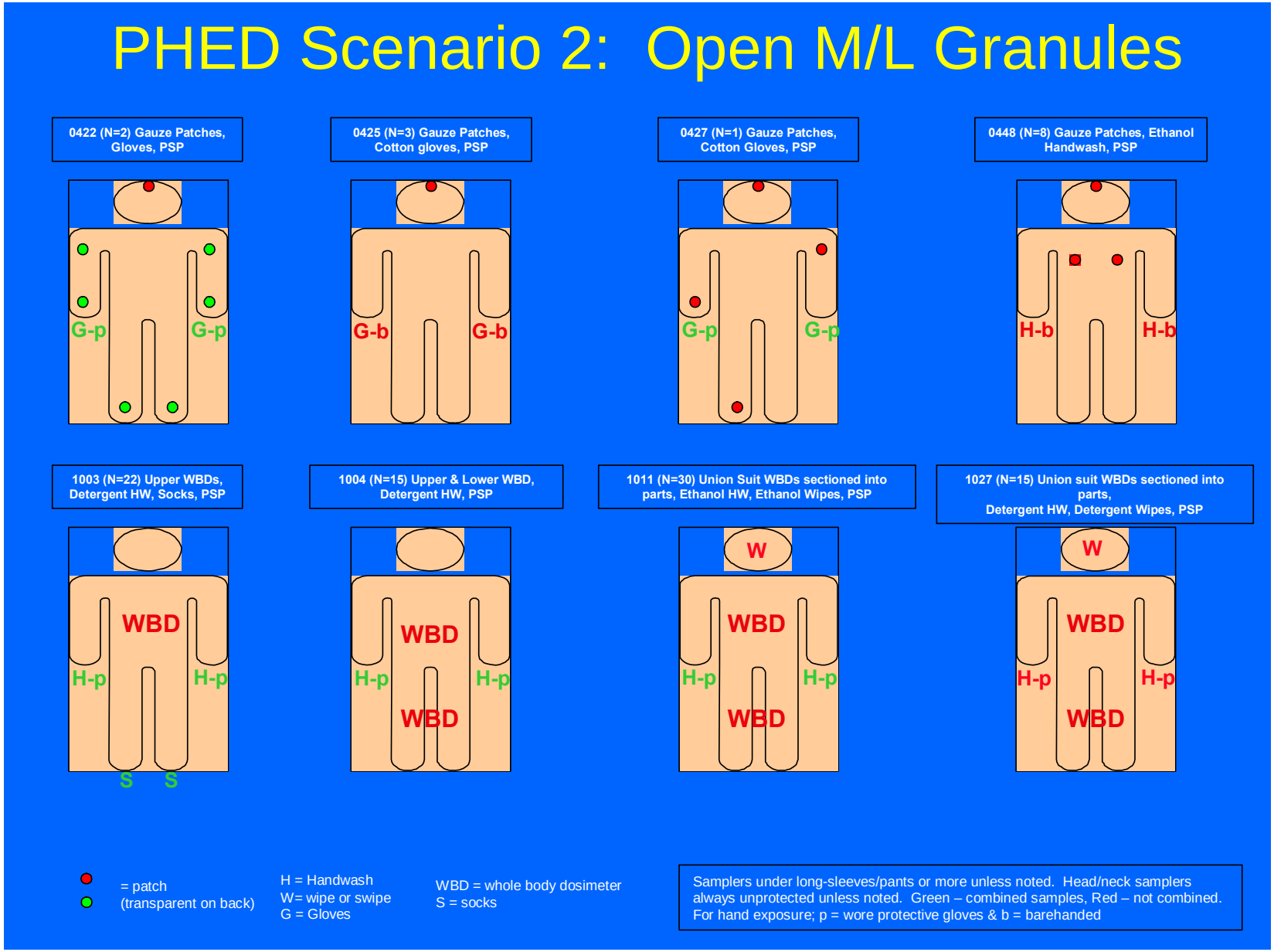


Figure 2-2: Sampling Regimen Associated With Data From PHED Scenario 2.

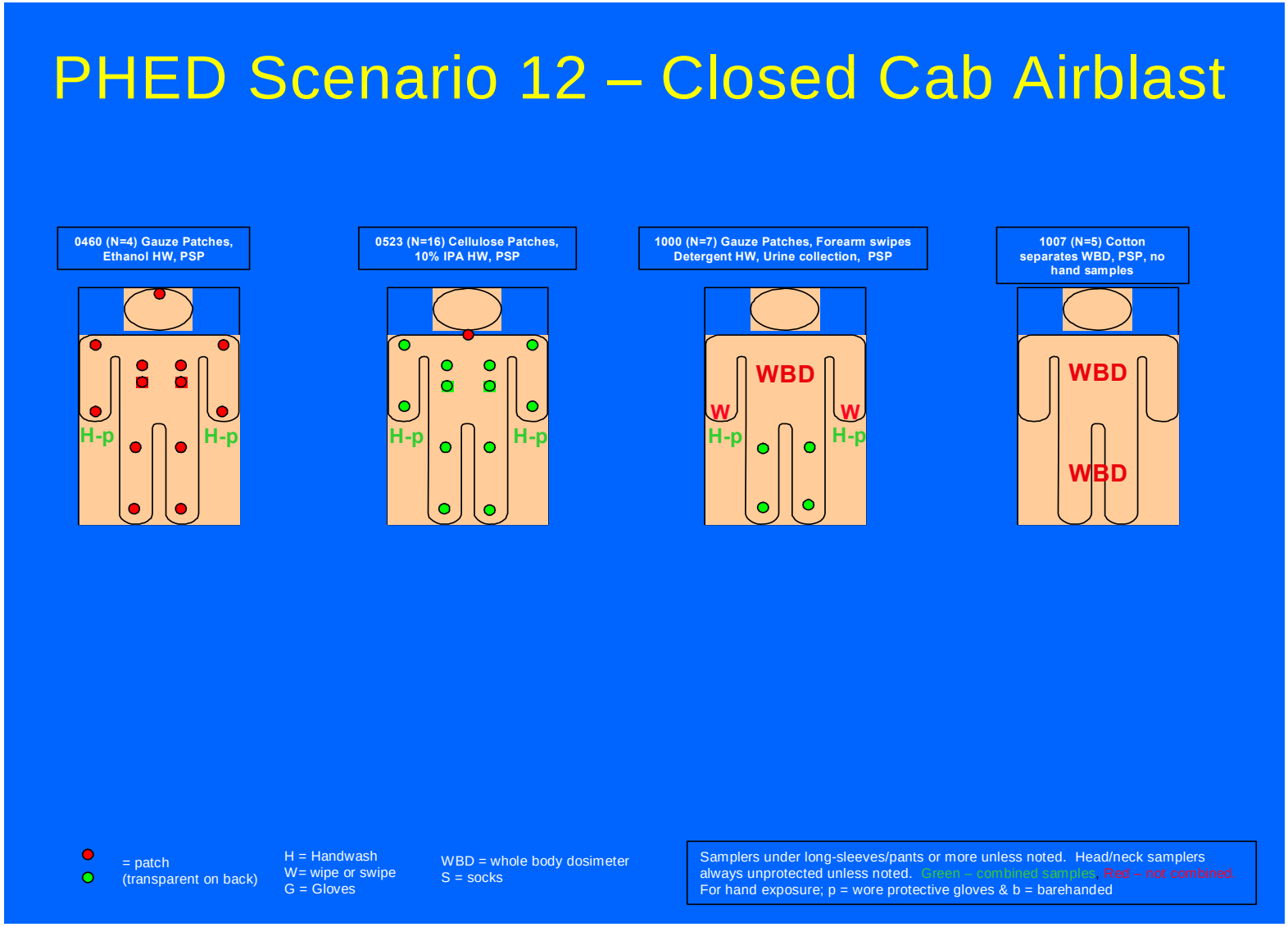


Figure 2-3: Sampling Regimen Associated With Data From PHED Scenario 12

PHED contains a large amount of information about each monitoring event used to develop exposure estimates (these are referred to as a "replicate" in PHED). The *PHED Reference Manual* (USEPA, 1995a) describes all of the different data fields in detail captured in PHED. Figure 2-4 reproduces a form on which EPA recorded some of the data which were collected for applicators when developing the system (i.e., it is an image of an actual data entry sheet). Similar data would be collected under current Agency guidelines. [See the reference manual appendices for complete data entry forms (U.S. EPA, 1995a).]

Worker I.D. | Work Cycle Number
Do Not Leave Blank

Study Code No.:_____
(EPA Use Only)

APPLICATOR EXPOSURE SURVEY FORM

(ONE FORM PER REPLICATE)

Location of * Data:
Worker I.D. | Work Cycle Number
See Instructions

Sampling Date _____

Time of Day Monitoring Took Place (use military time):

From _____ To _____

COMPOUND IDENTIFICATION *Action of Pesticide: 1) Fungicide;

2) Herbicide; 3) Insecticide; 4) Fumigant; 5) Plant Growth Regulator

*Formulation: Liquid (lb ai/gal)_____ OR Solid (% ai by weight)_____

1) Emulsifiable Concentrate
2) Suspension (aqueous)
3) Microencapsulated
4) Solution
5) Liquid (undiluted; e.g., fumigant)

1) Wettable-powder
2) Dry-flowable
3) Dust
4) Granule

SITE DATA *Location (State/Province and Country)_____

*(check one)____ Indoor or____ Outdoor *Crop_____

*Crop Height (feet)_____ *Row Spacing (feet)_____

APPLICATION INFORMATION *Method of Application:

1) Airblast
2) Groundboom Tractor
3) Groundboom Truck
4) Groundboom Rail Car
5) Aerial - Fixed Wing
6) Aerial - Rotary Wing
7) Low Pressure Hand Wand
8) High Pressure Hand Wand (attached to truck)
9) Backpack
10) Shank Injection
11) Fumigation
12) Solid Broadcast Spreader
13) Liquid Broadcast Spreader
14) Other (describe)

If 14, describe_____

_____

_____

Rate: (lb ai/acre) _____ and (gal/acre) _____ Total lb ai Applied _____

Total # Acres Treated _____ Final Mix Concentration (lb ai/gal Diluent)_____

Total # Gallons Sprayed _____ # Tank Applications Monitored _____

*Vehicle Make and Model: _____

_____

*Cab Type:
1) Open Cab (Cockpit)
2) Closed Cab (Cockpit)/Window Open
3) Closed Cab (Cockpit)/Window Closed
4) Closed Cab (Cockpit)/Window Closed/Filtered Air

The Agency has characterized estimates calculated using PHED by considering associated exposure factor information such as the amounts handled, field conditions and various sampling parameters such as the limit of quantification for specific sampling media. These factors help determine the applicability of exposure data for relating to various agricultural use patterns where they could be used to calculate exposures. They also help in determining how skin loading and other exposure information can be segregated based on application techniques and other factors. Exhibit A contains all of the raw data fields that represent the 6 scenarios selected for the case study including various exposure factors data. An example of the type of information that can be identified from the data within this case study is presented in Table 2-2 for PHED Scenario 1 – Open Mixing/Loading of Dry Flowables. For example, note that in 45 monitoring events the container size ranged from 1 to 5 pounds and that the overall mean was approximately 2.1 pounds. This indicates that the use of mini-bulk or bulk packaging systems (which contain larger quantities of materials) containing dry flowable formulations was not evaluated in the monitoring data available for this scenario. The meteorological data, likewise, indicate that conditions were typical for agricultural pesticide applications particularly since temperatures were not extremely low during the monitoring events.

Table 2-2: Example Summary Of Exposure Factors For PHED Scenario 1 – Open Mixing/Loading Of Dry Flowables

Mixing/Loading Parameters						
	Container Size (lb)	% AI	[mix conc. (lb/gal)]	Total Gal. Mixed	# Tank loads	Total ai Mixed
N	45	50	49	49	45	50
Average	2.133	55.900	0.046	1594.255	3.800	55.893
Min.	1.000	25.000	0.004	242.000	1.000	2.340
Max.	5.000	85.000	0.670	4229.000	9.000	440.000
Weather Conditions						
	High % RH	Low % RH	High Temp	Low Temp	Tank Cap (gal)	Wind speed (mph)
N	45	45	45	45	36	NA
Average	61.511	40.822	80.511	58.600	398.333	6 to 10 MPH
Min.	30.000	16.000	48.000	43.000	130.000	0 to 5 MPH
Max.	93.000	85.000	96.000	82.000	900.000	>10 MPH
Sampling Conditions						
	Air Time (min.)	Air LOQ (ug)	Air Vol (L)	Dermal Time (hr)	Der. LOQ(ug/cm2)	Hand LOQ (ug)
N	42	42	42	50	48	44
Average	158.071	0.094	283.895	2.884	0.013	23.097
Min.	6.000	0.025	9.300	0.100	0.0001	0.0300
Max.	321.000	0.400	578.000	8.125	0.075	60.000

PHED contains a series of calculation functions which develop unit exposure estimates based on skin loading rates. As illustrated by the breadth and depth of the information available in PHED (see Table 2-2, Figure 2-5and USEPA, 1995a) the Agency opted to approach occupational handler exposure estimates using a tiered approach that was developed in an international effort under the auspices of the Organization For Economic Cooperation and Development (OECD, 1997). The first part of this tiered approach is to utilize data in a systematic way that does not require and does not require active ingredient-specific data. This approach resulted in the development of the *PHED Surrogate Exposure Guide* (USEPA, 1998b). This approach also allows for a more consistent risk assessment process within the Agency since the analyses of the data are standardized in the first tier of the process. Further analyses could be required depending upon the nature of individual assessments (e.g., if only large acreage equipment for a specific chemical use pattern might be typical).

A major step in interpreting any PHED-based assessment is determining which data are to be included in the calculations. EPA thinks it is preferable that the best quality information be used. The Agency defines high quality data as data derived from studies which were well conducted and have adequate analytical quality control data. The Agency approach has always been to address exposure scenarios with the highest quality data available but if sufficiently high quality data are not available the Agency would always use the best available data even if there could be quality issues associated with it (e.g., there may be a low number of monitoring events such as for Scenario 15 in Table 2-1 but these data are the only available for that scenario. In cases such as this, the data would be used in an assessment but appropriate language would also accompany the assessment to characterize the results). In those cases, however, the Agency would typically require that additional confirmatory information be collected to support any final regulatory decision as the Agency has done for a number of pesticides during reregistration. The criteria in the *PHED Surrogate Exposure Guide* that the Agency uses to grade data (i.e., describe the data quality based on analytical methods performance) are summarized in Table 2-3.

Table 2-3: PHED Grading Criteria					
Data Grade	% Lab Recovery	CV* for Lab recovery	% Field Recovery	% Storage Stability	Data Corrected For:***
A	90-110	≤15	70-120	**	Field Recovery
B	80-110	≤25	50-120	**	Field Recovery
C	70-120 70-120	≤33 ≤33	30-120 or missing	** 50-120	Field Recovery
D	60-120	≤33	**	**	Field Recovery if available; if not then storage stability, if not then lab recovery
E			Does not meet above criteria		

* CV = Coefficient of Variation
** Does not matter if available or missing
*** If a field recovery of 90% or greater is obtained, no correction of the data is necessary

As described above, PHED contains many fields and codes that are intended to capture raw data on field conditions, exposure factors, exposure monitoring methods, and exposure monitoring results. Table 2-4 below presents an example of the actual exposure monitoring results used to calculate the unit exposure estimates for Case Study Scenario 1 which is open mixing/loading of dry flowable formulations. These data differ from above in that they reflect the actual skin loading measurements which have been collected and not the ancillary exposure factors data described above which characterize the conditions under which they were collected.

Table 2-4: Example Summary Of Raw Exposure Data Used To Calculate Unit Exposure Values For PHED Scenario 1 – Open Mixing/Loading Of Dry Flowables

[Note: "0"s indicate no samples taken for that location. All residues are ug/cm2 and under clothing or protective gloves unless noted with the term "out" which indicates bare skin; -1.000 = sample residues were not detected so 1/2 LOQ used for the corresponding calculation of exposure.]

	Air (ug)	Head Out	Neck Out	Both Hands (ug)	Both Hands [Without protective glove] (ug)	R-Hand (ug)	L-Hand (ug)
N	42	32	10	12	7	26	26
#NDs	0	3	0	2	0	16	16
Min.	0.027	-1.000	0.006	-1.000	58.400	-1.000	-1.000
Max.	258.000	25.686	0.656	1200.000	930.300	399.000	339.000
	R-FrtArm	L-FrtArm	R-Shoulder	L-Shoulder	R-Chest	L-Chest	R-Back
N	38	38	0	0	32	48	48
#NDs	17	17	0	0	5	17	20
Min.	-1.000	-1.000	0.000	0.000	-1.000	-1.000	-1.000
Max.	0.815	0.815	0.000	0.000	0.815	0.815	0.815
	R-Thigh	L-Thigh	R-Shin	L-Shin	R-Calf	L-Calf	R-Ankle
N	48	38	38	28	12	12	22
#NDs	13	17	17	16	5	5	6
Min.	-1.0000	-1.0000	-1.0000	-1.0000	-1.0000	-1.0000	-1.0000
Max.	12.085	0.512	1.458	0.151	0.104	0.104	0.104

As indicated above, PHED is a database which is used to store raw data records such as those illustrated in Tables 2-2 and 2-4. Its second major function is as a calculator that has been used to develop unit exposure estimates which are based on segmenting the data to reflect a specific exposure scenario (this process is referred to as subsetting in the PHED Reference Manual; USEPA, 1995a). For example, one could determine the unit exposure to the bare hands for all mixer/loaders regardless of formulation type (e.g., solids of varied types along with liquids) or the data can be segmented based on specific solid type such as a dust or dry flowable (which is how the Agency uses the data). Tables 2-5 and 2-6 below are intended to provide an example of this calculation process using the dry flowable scenario from the case study. Table 2-5 is an actual output from PHED where the data have been subsetted to reflect exposures of mixer/loaders using a dry flowable formulation in an open mixing process. In this evaluation, individuals are wearing typical work clothing (i.e., long pants and long-sleeved shirts) along with some sort of protective gloves (i.e., they were not barehanded). In the dataset upon which this calculation is based, there were also a sufficient number of monitoring events to develop unit exposure estimates based on better quality data (i.e., AB Grades - see Table 2-3 above). It should be noted that in Table 2-4 as many as 48 monitoring events are available for the scenario. However, when only "AB" grade data are selected the maximum number of records for body location specified in the Table 2-5 output is 26 monitoring events. This result means that 22 records had data of lesser quality (i.e., grades "C", "D" or "E") and excluded from this analysis. Once records are identified the selected data are used to populate arrays based on differing body locations. PHED then uses a statistical test (i.e., Kolomogorov-Smirnov) to determine the distribution which best reflects the data in that array. Most have been log-normally distributed. PHED then calculates unit estimates by combining the univariate statistic that best reflects the measure of central tendency for that body location. For example, a geometric mean is used for log-normal distributions while the arithmetic mean is used when data are normally distributed.

Table 2-5: PHED Output, Summary Statistics for Calculated Dermal Unit Exposures
(Dry Flowable, Open Mixing and Loading, Long Pants, Long Sleeves, Gloves - Dermal/Hand AB Grade)

Patch Location	Distribution	Unit Exposure (ug/lb ai handled)				
		Median	Mean	Coefficient of Variation	Geo. Mean	Observations
Head (All)	Log-normal	13.65	30.50	125	**11.99***	19
Neck. Front	Log-normal	8.06	13.91	103	**5.84***	16
Neck. Back	Log-normal	0.47	3.29	170	**0.75***	19
Head/Neck Unit Exposure = 18.6 ug/lb ai handled						
Upper Arms	Log-normal	5.82	8.35	99	**6.59***	23
Chest	Log-normal	7.10	8.93	67	**6.79***	26
Back	Other	**6.04***	6.79	73	4.88	26
Forearms	Log-normal	2.42	3.71	66	**3.10***	23
Thighs	Log-normal	8.79	90.27	297	**11.36***	26
Lower Legs	Log-normal	4.40	17.83	299	**4.29***	26
Upper and Lower Arm, Chest, Back, Thigh and Lower Leg Unit Exposure = 38.2 ug/lb ai handled						
Hands	Normal	10.67	**9.74***	53	7.13	21
Hands Unit Exposure = 9.7 ug/lb ai handled						

*The numbers in bold font are those used for each unit exposure and are based upon the data distribution for each body part. The geometric mean is used when the data distribution is log-normal, the mean is used when the distribution is normal and the median is used when the distribution is other.

Above, the Agency described its tiered approach for calculating occupational exposure estimates (OECD, 1997). In order to systematically accomplish typical Tier 1 assessments, the Agency developed the *PHED Surrogate Exposure Guide* (USEPA, 1998b). The reference values commonly used for open mixing dry flowables are presented in Table 2-6. The results from the PHED output described in Table 2-5 above have been used to populate the guide presented in Table 2-6. Results from the above analysis represent individuals wearing normal work clothing so the estimate for dermal exposure (excluding head, neck and hands) is reported below as 0.0382 mg/lb active ingredient handled which corresponds to the above PHED output for that scenario. Likewise the head/neck and hand estimates (for individuals wearing protective gloves) also correspond. It should also be noted that the number of observations are consistent in that 16 to 26 monitoring events were used to calculate the dermal (nonhand) exposures and 21 monitoring events were used to calculated hand exposures. The Agency has completed this sort of calculation for all of the 37 scenarios listed above the agricultural handler scenarios it routinely considers in its Tier 1 assessments but wanted to present this one to illustrate how PHED is used to develop unit exposure estimates. The full details of the "calculator" capability of PHED and of the processes used in the system can be found in the Reference Manual (USEPA, 1995a).

Table 2-6: Example PHED Surrogate Guide Excerpt For Scenario 1, Open Mixing/Loading Of Dry Flowables

SCENARIO 1. DRY FLOWABLE, OPEN MIXING and LOADING (MLOD)

Dermal Exposure

Clothing Scenario	Head and Neck (mg/lb ai handled)		Upper and Lower Arm, Chest, Back, Thigh and Lower Leg (mg/lb ai handled)		Hand (mg/lb ai handled)	=	**TOTAL Dermal Exposure** (mg/lb ai handled)
No Clothing	0.0186		1.05		0.00952	=	**1.1**
Single Layer, No Gloves	0.0186		0.0382		0.00952		**0.066**
Single Layer, Gloves	0.0186	+	0.0382	+	0.0097		**0.066**

Clothing Scenario	**Data Confidence/Items of Note**
No Clothes	Dermal = 16 - 19 replicates, AB grade. Hand = 7 replicates, AB grade. **Low Confidence** due to the small number of hand replicates.
Single Layer, No Gloves	Dermal = 16 - 26 replicates, AB grade. Hand = 7 replicates, AB grade. **Low Confidence** due to the small number of hand replicates.
Single Layer, Gloves	Dermal = 16 - 26 replicates, AB grade. Hand = 21 replicates, AB grade. NOTE: this run has a lot of non-detects for the glove exposure values. **High Confidence**

The use of PHED, as well as other datasets, allow the Agency to develop exposure assessments in a more systematic and consistent process. However, the Agency (as well as its other regulatory partners such as PMRA and DPR) and industry, realized that there are a number of possible refinements that could be implemented with additional data and development of

updated analytical methodologies. As a result, there has been a significant level of interest over the last few years in generating additional occupational exposure monitoring data. The goal in these efforts has been to eliminate many of the limitations inherent in much of the data which is currently used for regulatory purposes. Some of the key limitations which have been identified as well as the Agency's proposed approach for addressing them are summarized in Table 2-7.

Table 2-7: Summary of Key PHED Limitations & Agency Proposals For Addressing Them	
Limitation	Proposed Approach To Address Limitation
As illustrated above, a variety of data are available for different scenarios (e.g., Scenario 3 has 43 studies while Scenario 15 has 2 studies) which could limit the ability to accurately extrapolate these data across many situations in agriculture (e.g., from small family farms to large commercial operations)	The impact of modern agricultural practices and equipment would be evaluated and a range of situations would be monitored
It is not possible to equally evaluate inter- and intra-personal variability since varying numbers of individuals were used in the sample collection process	Statistical approaches would used to ensure that the scope of any research plan would provide sufficient information to address occupational exposure assessment issues.
The studies used to develop unit exposure estimates include a number of varied designs as illustrated in Figures 2-1 through 2-4 (e.g., patches or whole-body dosimetry, combining or not samples from similar body locations) - also see the "Observations" column in Table 2-5 that presents the number of samples for each body part used in the calculation [Note: This disparity among combined data is sometimes referred to as the "Frankenstein" approach which limits how the data can be utilized - e.g., a distributional assessment would not be appropriate in many cases.];	Similar sampling regimens be used which would eliminate possible uncertainties related to combining data from disparate study designs;
The studies used to develop unit exposure estimates include a number of varied sample collection media as illustrated in Figures 2-1 through 2-4 (e.g., patches or whole-body dosimetry of varied material or different hand monitoring methods including soap and alcohol washes or the use of cotton gloves) which may introduce uncertainties in the calculated unit exposures as the sampling media were treated equally when combined	Monitors would be consistent in newer studies to eliminate the uncertainty of combining results using several different sampling media (e.g., AHETF uses whole-body dosimetry with aqueous surfactant hand washing)
Patch data are used to calculate dermal exposures by adjusting dermal loading rates using standard skin surface areas while dosimetry reflects the size and body shape of those individuals who were monitored	Whole-body dosimeters would be used. Additionally, monitoring methods would be standardized to allow better comparisons between newer studies
Some scenarios, especially when higher levels of personal protective equipment or engineering controls are used, could be biased because of the limits of quantification used to analyze the samples (e.g., many would be considered relatively high by modern analytical chemistry standards)	Modern analytical techniques would be used to ensure that appropriate limits of detection and quantification were used
Modern agricultural practices and equipment may not be adequately reflected in the current data - e.g., systems such as induction bowls, bulk or mini-bulk transfer are represented in limited fashion or not at all in the current data	The impact of modern agricultural practices and equipment would be evaluated
Note: The AHETF has developed criteria for accepting existing data into its AHED database that is under development. These criteria are outlined in Appendix A of their multi-year research proposal (AHETFa, 2006). Similarly, the AEATF has developed criteria for accepting existing data in its effort. These criteria are outlined in their acceptance criteria document (AEATFb, 2006).	

3. Monitoring Methods

This section of the document provides the background information needed for the panel deliberations related to the sampling methods recommended by the Agency for exposure monitoring (see guidelines described above with the latest thinking outlined in the document from the 1998 SAP review available at http://www.epa.gov/scipoly/sap/1998/march/contents.htm).

There are two basic approaches of either using passive dosimetry which employs some sort of physical monitor that traps residues from the surface of the skin (i.e., they absorb or remove - such as a dosimeter or a wash) to determine dermal exposure (i.e., also referred to as a potential dose) or biological monitoring which is usually employed to quantify absorbed dose (i.e., also referred to as body burden). Outside of these, there appear to be limited other techniques for calculating risks from dermal exposure that can provide similar types of results (e.g., first-principles models are very limited for this purpose). Thus, as the Agency moves toward the development of new, more refined data it is important to examine how the performance of these two basic approaches compares. If there is a systematic bias between the two methods, the Agency wishes to address possible approaches for compensating in order to account for that bias. Over time, the Agency has conducted several analyses of the comparability of exposure estimates using passive dosimetry and biological monitoring. But EPA is revisiting this issue now because more data are available compared to the previous examinations and the Agency and other affected stakeholders are prepared to proceed with the generation of a large amount of additional data. As a result, the Agency desires that these issues be addressed to reduce uncertainties related to methodological issues before the next major phase of data development begins.

The passive dosimetry methods (e.g., patches, gloves, dosimeters or washes) that are included in current Agency guidelines were described in the scientific literature as early as the 1950s but seminal work includes publications by Durham and Wolfe (1962), the World Health Organization (1982), and other investigators (e.g., Fenske and Popendorf). The Agency also accepts monitoring data based on the collection of biological media such as urine or blood. Biomarker data can also be used for predicting exposures. In addition to biological sampling media, the Agency also requires that additional supporting pharmacokinetics and/or pharmacodynamic information be submitted that can be used to develop exposure and/or risk estimates.

Even though the Agency had developed guidance for collecting dermal exposure data, a number of passive dosimetry techniques have been historically used to quantify dermal exposures by field investigators in studies which have been submitted to the Agency for regulatory purposes. For example, EPA's PHED database contains large numbers of studies in which dermal exposure was estimated using patches but many other studies used whole-body dosimeters. Even though a technique such as a patch or whole-body dosimeter is used, there may still be inherent bias in results due to the nuances of how that technique was employed. For example, a dermal monitoring patch may be constructed of gauze or alpha-cellulose which may trap and retain residues at different rates. Also, hand monitoring could be accomplished using cotton or Tyvek® gloves or varying wash media that have ranged from acetone to various alcohols or soap solutions. The use of a 100 percent shaking approach in a hand sampling event as opposed to allowing for mechanical agitation like normal hand washing may also impact results. Clearly,

solubility of the residues being quantified, polarity of solutions, glove material and the use of mechanical agitation could impact the residues that are collected.

Biological monitoring results can also be used for quantifying exposures given that appropriate samples are collected, the time-course of the metabolites being screened for is reflected in the sampling regimen, and there are not significant interferences from exposure to other chemical agents (e.g., some pesticides have metabolites that are ubiquitous in the environment). The rate of transformation and kinetics of dissipation and/or excretion must also be well characterized for these types of data to also be used in a quantitative manner.

Based on discussions with stakeholders and scientific experts over time, the Agency has identified several key issues related to the ruggedness and performance of the available exposure monitoring methods. These include:

- Examination of the potential for a systematic bias between biological monitoring and passive dosimetry methods;

- Whether dermal absorption could cause a significant underestimate of exposure when residue removal methods are used (e.g., swiping or washing techniques);

- Whether residue breakthrough from whole-body dosimeters could cause a significant underestimate of exposure; and

- Examination of the hand monitoring methods to determine if there is a systematic bias due to whether the method is based on residue trapping (e.g., gloves) or residue removal (e.g., washing) or the nature of the media used (e.g., alcohol or solvents and aqueous soap solutions).

The Agency believes that when results based on passive dosimetry and biological monitoring are compared that the first three of the above issues can be addressed. Discussion pertaining to these topics is included in *Section 3.1: Relative Predictive Capability Of Passive Dosimetry and Biological Monitoring*. The remaining hand monitoring issue is addressed separately in *Section 3.2: Systematic Evaluation of Hand Sampling Methods*. Hand exposure monitoring is addressed separately because hands can be major contributors to overall exposure estimates for many scenarios and the related data and mechanistic issues differ from the analysis in Section 3.1.

3.1. Relative Predictive Capability of Passive Dosimetry and Biological Monitoring

Risk from exposure to pesticides can result in toxicity when sufficient dose is absorbed and transmitted to a target tissue in the body where an adverse effect can occur. In order to more accurately predict these types of risks, concentrations of the toxicologically active compound (which could be the pesticide active ingredient or one its metabolites) at the target organ, tissue, cell, or cellular component need to be quantified. In most cases, however, the information required for this type of approach is not available. The mode of action of a specific pesticide at the cellular level may not even be known.

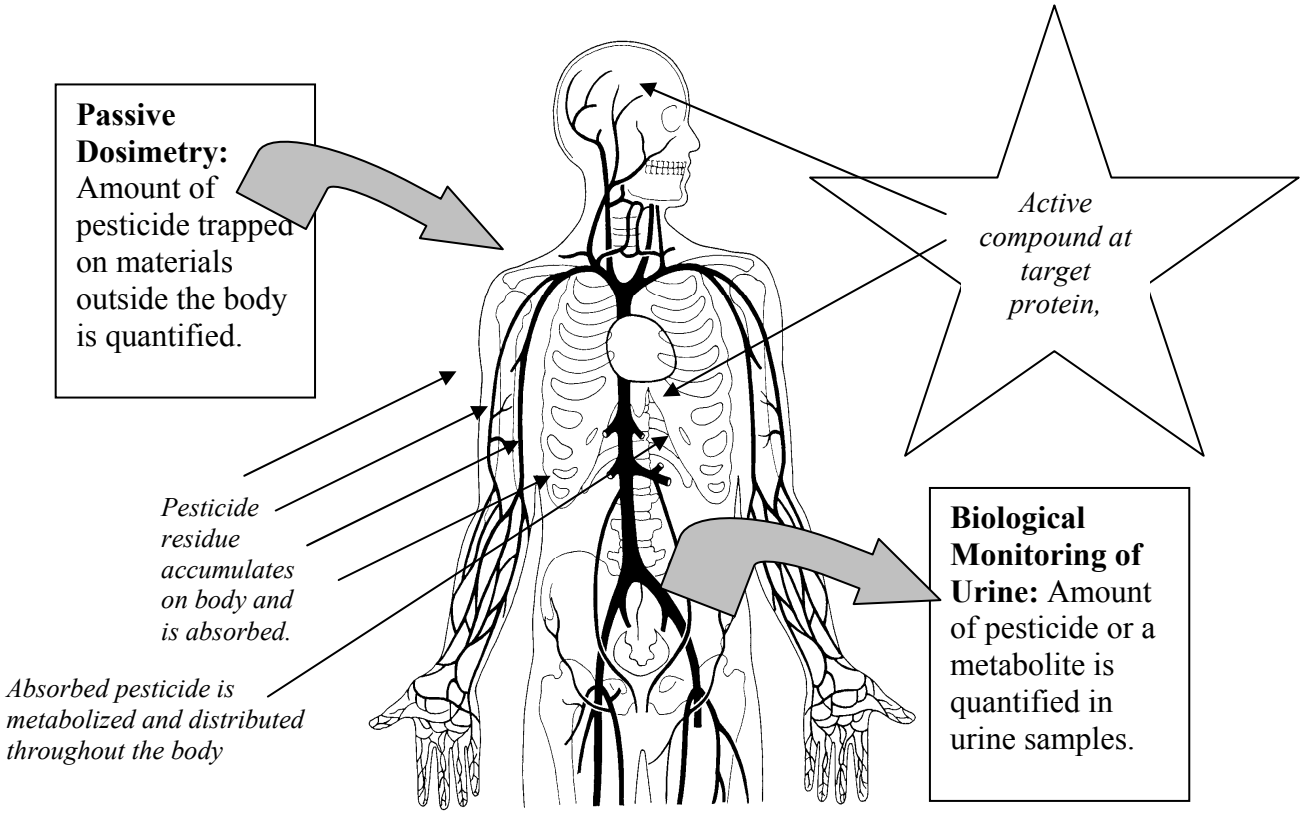
Even if such mechanistic information is known, the concentration of the active compound at a target site may be difficult or impossible to quantify. In lieu of concentrations of active compounds at target sites, risk assessment for pesticides often relies on data that are used to quantify overall body burdens which are then compared to toxic endpoints that have been derived on a similar basis (e.g., mg/kg/body weight). As described above in *Section 2.1.2 Algorithms Used For Risk Calculations* and in *Section 3: Monitoring Methods* either passive dosimetry or biological monitoring methods are used for this purpose. It should be noted that, in theory, the results based on these methods could also be used to develop target tissue concentrations but the data are generally lacking to develop target tissue estimates from body burdens. Agency guidelines allow for the collection of the following kinds of data to quantify exposure:

- *Passive dosimetry* measures the amount of a chemical impinging on the surface of the skin or the amount of the chemical available for inhalation through the use of appropriate trapping devices.

- *Biological monitoring* measures body burden in selected tissues or fluids or the amount of pesticide or its metabolites eliminated from the body.

Figure 3-1 below provides an illustration of the relationship between these methods.

Figure 3-1: Overview of Relationship Available Exposure Monitoring Methods [a]



[a] Text in star represents information needed to most accurately predict toxicity from pesticide. Text in boxes represents techniques used to collect data used in estimating exposure to a pesticide. Human figure from Cull (1989).

Passive dosimetry and biological exposure monitoring techniques are evaluated and compared in this document, and the usefulness of both techniques in monitoring exposures is discussed. Most exposure data currently available for estimating handler and reentry exposure are come from passive dosimetry-based studies. It is important to ascertain, given the quantity of data now available, how well this approach supports accurate estimates of exposure. The purpose of this section is to compare the performance of passive dosimetry as a predictive tool for exposure assessment purposes with biological monitoring data. Comparisons among data sets generated using these diverse techniques provide some support for estimates based on both techniques. *Section 3.1.1: Passive Dosimetry* describes the attributes and limitations of that technique while *Section 3.1.2: Biological Monitoring* does the same for that method. [Note: These are summary in nature and more information can be in the Agency guideline documents referenced above.] *Section 3.1.3 Comparison of Passive Dosimetry and Biomonitoring Techniques* provides the results of the comparisons of the two methods completed by the Agency. The AHETF also developed an analysis for this purpose which is summarized along with the Agency response to this document. *Section 3.1.4: Conclusions* describes the Agency's summary interpretation and conclusions based on the analyses contained in this section.

3.1.1. Passive Dosimetry

Dermal penetration and inhalation are the major routes of occupational pesticide exposure. Multiple studies with several different pesticides (outside of highly volatile chemicals such as fumigants) have shown that inhalation generally contributes much less to exposure than the dermal route (Ware *et al*., 1973; Popendorf *et al*., 1979; Zweig *et al*., 1984; Zweig *et al*., 1985). [Note: Based on these results and the relative uncertainties associated with dermal monitoring methods that are not associated with inhalation monitoring techniques, this analysis is focused on the limitations and uncertainties related to dermal monitoring.] Dermal exposure is defined by U.S. EPA (1996b) as the process of pesticide residue deposition on the skin, as well as the measurement of the deposited residue. Dermal exposure to the clothed portions of the body is usually monitored either with absorbent pads (patches) placed on the body at fixed locations, or by whole-body dosimeters (WBD). Both techniques have been reviewed by numerous authors, including Durham and Wolfe (1962), Chester (1993), Fenske (1993), and Soutar *et al.* (2000). Exposure to hands is typically measured by either hand washes or glove dosimeters.

Assumptions of Passive Dosimetry: Passive dosimetry relies on several assumptions. A key assumption is that residues removed from the skin, extracted from dosimeters next to skin, and trapped in breathing zone are available for absorption into the body. Another assumption, important in cases where monitoring intervals differ from exposure intervals of interest, is that exposure is constant over each exposure interval. That is, workers who handled 10 pounds of active ingredient would be assumed to accumulate about twice as much pesticide as a worker handled 5 pounds of active ingredient. To the extent this assumption is true, durations of exposure monitoring intervals would not affect results. However, studies in which exposure monitoring intervals varied suggest that monitoring intervals affect results. For example, in a study of peach harvesters exposed to azinphos-methyl, normalized (by hours worked in this case) dermal exposure estimates were proportionately higher after 2-hour monitoring intervals than after 3- to 7-hour intervals, suggesting that extrapolation of short monitoring intervals to longer workdays can result in overestimating exposure (Spencer *et al.*, 1995). It is assumed that the

amount of a dose penetrating skin can be extrapolated from laboratory studies, and that this amount is consistent between individuals. Laboratory studies of dermal penetration may rely on human, non-human primate, or rodent subjects. When patches are used to monitor dermal exposure, it is assumed that exposure over the body is uniform and can be represented by the small area sampled by each patch.

Advantages of Passive Dosimetry: U.S. EPA (1996a) identified the major advantages of passive dosimetry as "the ability to differentiate exposure received during discrete work activities within a work day and in differentiating the relative contributions of the dermal and respiratory exposure routes for each separate work activity." These are advantageous because they allow evaluation of measures intended to reduce exposure. Another advantage identified by U.S. EPA (1996a) is that "the study participants are typically under the supervision of the investigator during the entire period when exposure data are being collected." Passive dosimetry also allows creation of generic exposure databases, under the assumption that in many cases deposition of residues on the skin is essentially independent of chemical properties of the pesticide (U.S. EPA, 1996a). Such databases contain data collected under known conditions, and allow a limited number of studies to support exposure estimates for a wide range of pesticides.

Fenske (1993) argued that it is necessary to estimate dermal exposure using data from passive dosimetry rather than biological monitoring under the following circumstances:

- When there are no major target analytes available in an accessible biological medium;
- When adequate human pharmacokinetic data are lacking; or
- When there are obstacles to complete sampling of exposed individuals; for example, when workers refuse cooperation, the sampling schedule is too complex to be feasible, or when analytical costs are too high.

Disadvantages of Passive Dosimetry: Perhaps the most important disadvantage of passive dosimetry is that absorption of the pesticide into the body must be estimated which would then be compared to an endpoint derived from an oral administration toxicity study. Voluntary human *in vivo* dermal penetration studies yield the most comparable results; however, these studies are not always feasible, especially for highly toxic chemicals. When human *in vivo* data are unavailable, surrogate *in vitro* or animal *in vivo* data may be used, but these data introduce additional uncertainties. [Note: EPA tends not to use *in vitro* data.] Relationships between *in vivo* and *in vitro* test results, or between laboratory animal and human results, have not been reliably established for many classes of compounds, and have been shown to vary for compounds that have been tested (Franklin *et al*., 1989; U.S. EPA, 1992; Wester and Maibach, 2000).

Another way in which dermal absorption affects estimates of absorbed dose is that for several pesticides percent dermal absorption has been shown to vary inversely to concentration of the pesticide on dosed skin (Thongsinthusak *et al*., 1999). While the percentage absorption drops as the amount of pesticide loaded onto skin increases, the total amount of pesticide absorbed continues to increase with increasing concentration on the skin. Applying a fixed percentage for dermal absorption for any amount of pesticide likely may overstate the absorbed dose for higher concentrations of pesticide. Conversely, fixed dermal absorption estimates may be under-estimated at lower dermal loading concentrations. However, as the significance of this effect

cannot be quantitatively ascertained under field conditions, it adds to the uncertainty of estimating the magnitude of dermally absorbed doses.

In addition to the issues attendant to dermal absorption, another disadvantage of passive dosimetry is the uncertainty that results from the various methods of measuring dermal absorption. Patch dosimetry could over- or underestimate exposure due to extrapolation of residues from the relatively small surface area of the patches to much larger body surface areas. Splashes or placement of a patch in a relatively high-exposure location on the body can lead to overestimated exposure; conversely, placement of a patch in a relatively low-exposure location on the body can lead to underestimated exposure (U.S. EPA, 1996a). While placement of patches has been standardized by U.S. EPA (1996a), available data show that exposure patterns differ by activities, suggesting that extrapolations from patch dosimetry might have varying effects on exposure estimates. Also, many investigators use non-standard patch construction and placement, confounding comparisons between studies.

Materials used in patches or WBDs can result in different exposure monitoring results, as pesticide residues on dosimeters can be unstable, and be lost through evaporation or binding to dosimeter materials (Serat *et al*., 1982; Wester *et al.*, 1994). Use of field-fortified dosimeter samples is an essential quality control requirement. The results of these samples are essential components of the PHED grading criteria presented above.

Hand washes and gloves can overestimate or underestimate dermal exposure on the hands. Several studies provide evidence that exposure estimates based on gloves are often higher than estimates based on hand washes. Although some authors (e.g., U.S. EPA, 1996a) interpret such differences as evidence that gloves overestimate exposure, data are lacking to support the accuracy of one method above the other. Several studies have been published in the literature or submitted to DPR in which cotton gloves were compared to hand washes for monitoring hand exposure. While gloves gave higher results than hand washes in most studies (e.g., Davis *et al*., 1983; Fenske *et al.*, 1999), at least over short sampling intervals, that is not consistently true (e.g., Fenske *et al.*, 1989; Meikle, 1991). As pointed out by Fenske *et al.* (1999), the accuracy of either method has never been determined. In one of the few documented validation studies available, Fenske *et al.* (1999) used a laboratory removal efficiency study with a surrogate chemical - and a different hand wash solution - to develop a value with which they corrected hand wash samples. The removal efficiency study (Fenske *et al.*, 1998) used an isopropanol solution rather than the surfactant solution used by Fenske *et al.* (1999). [Note: There is a more detailed discussion of this issue below in *Section 3.2: Systematic Evaluation of Hand Sampling Methods*.]

It has been argued that cloth gloves provide a more absorptive matrix for pesticides than skin. While a layer of cloth may hold more pesticide than an equivalent layer of skin, a glove does not have blood circulation that can carry away absorbed residues. Hand washes supposedly measure the amount of pesticide loaded onto the skin of a worker during a given period of time. This is an operational definition in that only the amount of pesticide that can be washed off the skin is considered for exposure calculations. However, radiolabelled pesticide, applied experimentally to hands that were then washed at various times, could not be fully recovered even after a few seconds of time (Wester *et al*., 1992). Thus, hand washing may underestimate dermal exposure, as not all of the pesticide loaded onto hands during occupational activities can be recovered by hand washes. Conversely, in at least one study (Zweig *et al*., 1984), the early

morning dew absorbed by gloves decreased the amount of pesticide taken up by the gloves, potentially leading to an underestimate of exposure.

3.1.2 Biological Monitoring

For practical reasons, biological monitoring ("biomonitoring") to estimate worker exposure to pesticides in the field typically uses compounds measured in urine samples collected from the workers (U.S. EPA, 1996a). Although monitoring of blood (plasma or red blood cell) acetylcholinesterase levels in workers exposed to organophosphate and carbamate pesticides is a common assay, because of individual variability in enzyme activities it provides at best only a qualitative estimate of exposure. And while target compounds could be monitored in blood or other tissues or fluids, urine collection is less invasive than blood sample collection and urine is a major excretion route for metabolites of many pesticides, making it a logical choice for monitoring. Biomonitoring procedures have been reviewed by many authors, including Franklin *et al.* (1986), Woollen (1993), Maroni *et al.* (2000), and Cocker *et al.* (2002). U.S. EPA (1996c) recommends collecting a series of 24-hour samples, starting with one 24-hour sample before the exposure period begins, and continuing as long as indicated by the excretion profile from a properly conducted human pharmacokinetic study.

Biological Monitoring Assumptions: Perhaps the most important assumption of biological monitoring is that collecting urine for analysis is the best sampling approach because urine is typically a major elimination route for a pesticide of interest or its metabolite and it can refine passive dosimetry estimates. Fortunately, this has been shown to be the case for many pesticides, including OPs (Nutley and Cocker, 1993), pyrethroids (Kuhn *et al*., 1999), and many other classes of pesticides (Kolmodin-Hedman *et al.*, 1983; Libich *et al.*, 1984). The pharmacokinetics relating absorbed dose to compounds recovered from urine can be extrapolated from laboratory studies but it can have an associated uncertainty depending upon the quality of the data used to develop the relationship. However, such studies tend to be conducted in humans only for compounds with anticipated low toxicities (Harris *et al.*, 2001).

Another assumption is that residues recovered from urine are entirely (or at least substantially) due to pesticides absorbed from exposures occurring during shifts of interest. This assumption is verified with the required baseline pre-exposure samples to check for presence of monitored compound (U.S. EPA, 1996c). For compounds that are metabolites of multiple pesticides (e.g., alkylphosphates), it is also assumed that the occupational exposures result in substantially greater excretion than background amounts due to other sources such as diet. For alkylphosphates, this assumption is supported by multiple studies (e.g., Nutley and Cocker, 1993).

Creatinine corrections assume a constant excretion of creatinine (Boeninger *et al.*, 1993). Urine output is assumed to have little effect on concentrations of pesticides and metabolites (Boeninger *et al.*, 1993).

Biological Monitoring Advantages: If sufficient information is available about the pesticide and if biomonitoring is conducted properly, a quantitative estimate of absorbed dose may be obtained. By definition, these resulting dose estimates integrate exposure across all routes. Such an estimate of absorbed dose, which avoids potential confounding from assumptions

of dermal penetration or inhalation retention, may be more useful in assessing risk than route-specific doses estimated from passive dosimetry.

The calculation of absorbed dose from amount of pesticide or metabolite recovered from urine is straightforward. For a metabolite, a simple multiplication of the amount recovered from urine times the ratio of pesticide to metabolite molecular weights and adjusting for other appropriate pharmacokinetic factors (e.g., percentage of total parent equivalents excreted which could be difficult to define) gives an estimate of absorbed dose of pesticide.

Biological Monitoring Disadvantages: A thorough understanding of pharmacokinetics of the pesticide of interest is required before biomonitoring can provide adequate estimates of absorbed dose (Woollen, 1993; Wessels et al., 2003). Thus, a prerequisite for any biomonitoring study is a pharmacokinetic study. If the dermally applied dose used is too great, then absorption processes may be saturated (e.g., Meuling et al., 2005), potentially giving misleading results. In other words, the prerequisite studies are subject to the same pitfalls as the dermal penetration studies that are used with results of passive dosimetry to estimate exposure.

Inherent variability in pharmacokinetics contributes to uncertainty in biomonitoring results. Metabolism of a pesticide, its distribution in the body, and rate of excretion can vary considerably among individuals for many reasons. Factors affecting variability include exposure route (e.g., inhalation or ingestion versus dermal); body composition (relative amounts of water and fat in the body); individual differences in enzyme activities; and environmental factors such as concurrent exposure to other chemicals (Silvaggio and Mattison, 1994; Kuhn *et al*., 1999; Garfitt *et al.*, 2002). Data from well-conducted pharmacokinetic studies are essential to extrapolating absorbed doses from compounds analyzed in urine samples, yet as acknowledged by Woollen (1993), even when these data are available they can at best provide an "indication of the extent of this variability." Pharmacokinetic studies are often done with only four or six human subjects, giving little chance of capturing the potential range of variability. Such variability may result in over- or underestimation of exposure.

Biological monitoring generally requires a greater degree of cooperation from study participants in the collection of samples than passive dosimetry, because biomonitoring samples are often collected outside the workday. Participants may need to collect, store, and transport 24-hour urine samples before, during, and after the exposure period (U.S. EPA, 1996a). While passive dosimetry can be supervised through the entire monitoring period, biomonitoring often requires unsupervised collection of samples. Compliance in 24-hour sample collections may be difficult for some test subjects, and some samples may be omitted, spilled, or improperly collected through misunderstanding of instructions (Greenberg *et al*., 1989). The completeness of sampling is typically estimated by measuring creatinine levels in urine samples, with abnormally low levels suggesting that sampling was incomplete. Incomplete sampling can result in underestimation of exposure; attempts to correct results for sample incompleteness can result in over- or underestimation.

For chemicals with a long half-life relative to the sampling period, biomonitoring results can be affected by absorbed material not yet excreted (resulting in underestimated exposure) or by previous exposures (resulting in overestimated exposure). In particular, the interval in which sequential 24-hour urine samples are collected must be long enough in order for the human body

to excrete nearly all of the chemical being monitored. Even in cases where the target analyte urinary excretion half-life is less than 24 hours, the biomonitoring interval may have to be longer than 4 or 5 days as it takes longer for a dermal dose than an oral dose (used to estimate the half-life) to be absorbed into the body and hence to be excreted from the body. The total absorbed dose would be underestimated if it were based on incomplete urinary excretion data. Alternately, pre-exposure samples would sometimes show higher results than samples collected during and following exposure (e.g., Honeycut and DeGeare, 1993). When the pre-exposure concentration is subtracted from such samples, a negative exposure results (Geer *et al.*, 2004). This necessitates either use of a default result in place of the sample result, or the loss of the sample for purposes of estimating exposure. It should also be noted that peak exposures can be of concern depending upon the nature of the toxicological effect. For example, with carbaryl cholinesterase inhibition is rapidly reversible which made peak exposures more of a concern than total integrated exposure over time. More information regarding this issue can be found at: (http://www.epa.gov/scipoly/sap/meetings/2004/december2/finalreportdec22004saprev1.pdf).

The correct choice of compound to monitor is key for biomonitoring; the compound must be one for which a valid analytical method exists, and it should also be a major metabolite of the pesticide to minimize errors of extrapolation. Candidate compounds for monitoring must be obtainable in pure form for analysis, and must be stable (Cruz Marquez *et al*., 2001). If minor metabolites, accounting for 10 percent or less of the total dose, are used as target analytes in biomonitoring, then errors of extrapolation are magnified when the dose is back-calculated from the amount of metabolite found. Exposures could be under- or overestimated due to such extrapolation errors.

Many metabolites are common to more than one chemical, and some metabolites are common to non-pesticide chemicals as well as pesticides. Furthermore, some pesticide metabolites are widely used chemicals (e.g., the parathion metabolite, 4-nitrophenol). Assuming that the entire amount of these chemicals recovered in urine is due to metabolism of a specific pesticide would result in exposures being overestimated (Krieger *et al*., 2003). Additionally, it should be noted that if biomonitoring data are to be used generically, a calculation that develops skin loading estimates from absorbed dose levels would require adjusting these levels by an inverse of dermal absorption estimates which could create a level of uncertainty based on the potential differences in dermal absorption rates.

3.1.3 Comparison of Passive Dosimetry and Biomonitoring Techniques

Both passive dosimetry and biomonitoring have advantages and limitations. Fenske and Day (2005) suggested that, as regulatory agencies receive studies conducted with both techniques concurrently, the concordance between results within these studies can be examined in more detail. The Agency desires to evaluate the possible concordance between these two methods in order to assess the level of confidence associated with the use of either technique for regulatory purposes. Any conclusions would also be developed in the context of the typical uncertainty and variability that is associated with such data.

The analysis below presents that examination. Several investigators have conducted comparisons of exposure estimates based on biomonitoring and estimates based on passive dosimetry. These results are summarized below along with similar analyses completed by the Agency and AHETF. These types of comparisons can take one of two approaches that include:

- **Concurrent Analysis**: A comparison of concurrent monitoring results in which subjects wear dosimeters of some sort and also provide biological specimens related to the same monitored activity (i.e., reflects results for the same person at the same time). Typically, absorbed dose estimates would be used for comparison necessitating use of dermal absorption factors together with results based on passive dosimetry. Similarly, adequate pharmacokinetics information would be required to estimate absorbed dose from the biological monitoring results. Both of these additional factors can introduce uncertainty into the results (e.g., depending upon skin loading concentration dermal absorption can vary, for chlorpyrifos 1% is supported by Griffin et al, 1999; 3% is supported by Nolan et al, 1984; and 10% is supported by Krieger et al, 1995 – US EPA used 3% in its assessments, DPR uses 9.6% in its assessments). U.S. EPA (1996a) also acknowledged that studies of this type can confound results because passive dosimeters may intercept a portion of the residues that otherwise would reach the skin and thus may negatively bias biological monitoring results. However, studies having this design can inform assumptions about the potential for passive dosimetry residue breakthrough under field sampling conditions. For example, if biological monitoring does not quantify measurable residues, then it likely demonstrates that there was no or minimal breakthrough to the skin in a study. Conversely, if biological monitoring measures residues were much higher than predicted using passive dosimetry it could be a sign that residue interception or removal was incomplete (e.g., high absorption into hands before handwash samples collected). The AHETF completed a similar analysis (AHETFc *et al*, 2006). The Agency essentially concurs with their results but a more detailed analysis of this document is included below.

- **Retrospective Analysis:** Another approach for comparing biological monitoring and passive dosimetry is to complete a retrospective analysis in which absorbed dose estimates generated using biological monitoring would be compared to passive dosimetry results that have been separately generated (e.g., Spencer *et al*., 1993). One approach would be to apply PHED and exposure factors to which the results are to be compared to generate estimates of exposure for the conditions under which from the biological monitoring was performed (e.g., for a similar scenario and activity, acres treated and application rate). Alternatively, researchers could conduct a separate passive dosimetry duplicative study of the conditions of the biological monitoring. U.S. EPA (1996a) noted that this latter approach would eliminate the possibility of negatively biasing biological monitoring results. Comparison of biomonitoring results for workers with and without concurrent dermal monitoring should give identical results if both sets of workers did approximately the same activities under the same conditions, and if the dosimeters did not interfere with pesticide residues reaching the skin. However, as will be described below, there can be intra-personal variability which has been noted in various monitored test subjects which could lead to limitations in the conclusions that could be drawn on this approach. The AHETF completed a similar analysis (AHETFd, 2006). The Agency essentially concurs with their results but a more detailed analysis of this document is included below.

Prior to using the results from studies measuring absorbed dose from biological monitoring to review the concordance with passive dosimetry monitoring methods, the accuracy of the biological monitoring itself needs to be properly determined. However, because the review provided in this section is based on existing studies not specifically designed to compare monitoring methods, highlighting the limitations of study design discussed in Sections 3.1.1 and 3.1.2 above for both biological and passive dosimetry monitoring methods is important. Uncertainties in both methods highlighted below may explain some of the variability of the results presented in this section.

The absorbed dose measured from biological monitoring methods is dependent upon the accuracy of the pharmacokinetics of the chemical monitored as discussed in Section 3.1.2. Assuming accurate pharmacokinetics, some of the factors that may affect the absorbed dose monitored in the studies presented in this section include:

- Incomplete urine collection from test subjects, previous exposure to the same chemical, and use of concurrent passive dosimetry may intercept potential exposure.
- In the comparisons that are presented below from non concurrent analysis of biological and passive dosimetry estimates, minor differences in study design parameters (e.g., PPE, personal hygiene, equipment types and configuration, nozzle pressures, product and dilute concentrations, etc.) will influence the potential exposure.

Estimating total absorbed dose from passive dosimetry monitoring methods is also dependent on many factors that affect the comparison of methods in this section. For inhalation, nearly all of the monitoring techniques presented are based on personal air sampling using filter cassettes. Inhalation exposures are based on all of the particulates collected on the filters, assuming all particulates are either inhalable or respirable. Pump flow rates and breathing rates are standardized among most of the studies. The dermal portion of the total absorbed dose introduces even more variability. As discussed in Section 3.1.1 above, some of the confounding factors associated with the dermal passive dosimetry in the comparison presented below are attributed to the following:

- Inconsistent dermal monitoring techniques are used in some of the studies presented below including whole body dosimeters versus patches and hand washing techniques/solvents versus cotton gloves. Additionally, for some of the chlorpyrifos studies, the dermal estimates are based on measured clothing penetration factors that also introduce uncertainties.
- Chlorpyrifos is used in many of the examples presented below and a 3 percent dermal absorption is used (Nolan et al 1984) while the range of dermal absorption for chlorpyrifos has been reported in the literature from 1 percent (Griffin et al 1999) to 10 percent (Krieger 1995).
- A single dermal absorption value is used to estimate absorbed dose from dermal measurements when the actual dermal absorption over various loading concentrations is not expected to be constant (Zendzian 2000).

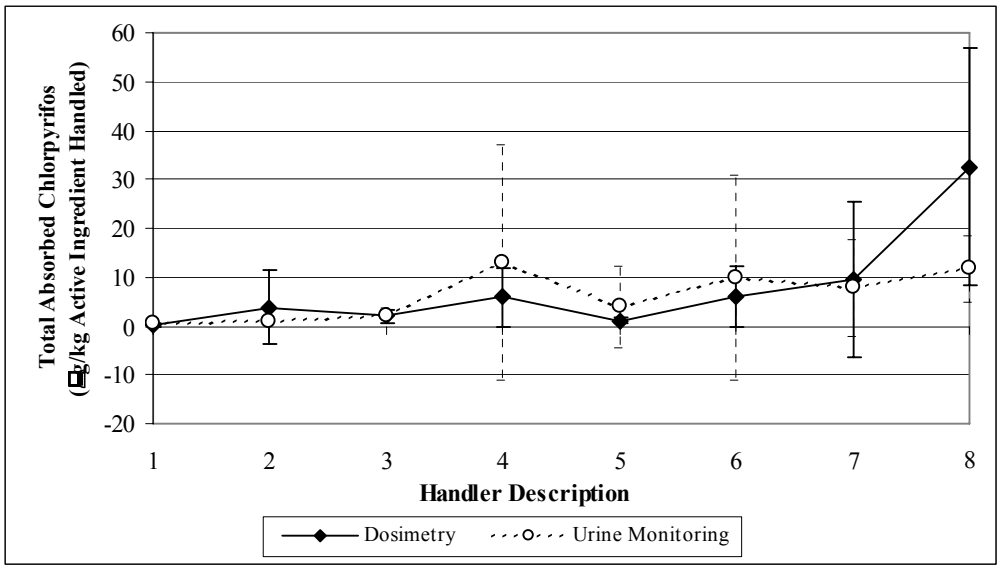
The following describes many of the analyses that have been completed for the purposes of comparing passive dosimetry and biological monitoring results. It should be noted that although

some of these results are inconclusive, they were included to show the Agency's current in-house data base.

Comparisons Involving Chlorpyrifos: Chlorpyrifos has been the compound of choice in numerous studies featuring biomonitoring. The metabolite, 3,5,6-trichloropyridinol (TCP) is specific to chlorpyrifos; furthermore, it represents a majority of the absorbed chlorpyrifos dose. Nolan *et al.* (1984) recovered 70% ± 11% of the applied dose four days following a 0.5 mg/kg oral dose of chlorpyrifos to six volunteers (range: 49-79%). Eight days following a 5.0 mg/kg dermal application of chlorpyrifos to five volunteers, Nolan *et al.* (1984) recovered 1.28% ± 0.83% of the applied dose (range: 0.50-2.60%); the lower recovery of the dermal dose is consistent with a dermal absorption of 3%. This study provides the basis for biomonitoring of chlorpyrifos, with urinary TCP considered to represent 70% of the absorbed chlorpyrifos and an elimination half-life of 26.9 hours. A more recent study suggested that the half-life of dermally applied chlorpyrifos yields an elimination half-life of about 41 hours, indicating that full urine clearance following dermal exposure could take a week or more (Meuling *et al.*, 2005).

Comparisons between passive dosimetry and biomonitoring among multiple studies with chlorpyrifos show that both methods generally give similar results. For example, Fenske and Day (2005) compared multiple handler studies using both passive dosimetry and urinary biomonitoring, which had been submitted to U.S. EPA in support of the reregistration of chlorpyrifos (Leighton, 2000). Figure 3-2 summarizes geometric mean internal doses reported by Fenske and Day (2005), from exposure estimates calculated by Leighton (2000). Eight studies were used in the comparison. In the eight studies summarized in Figure 3-2, the ratios of mean estimates derived from passive dosimetry vs. biomonitoring range between approximately 0.3 and 3.3, and the greatest difference between mean exposures was about 3-fold. This suggests that the differences in exposures estimated by the two methods at the means were not very large, nor did one method consistently result in greater estimates than the other. At higher percentiles of exposure, these differences could vary which is difficult to predict because of the limited utility of PHED for developing distributional estimates of exposure.

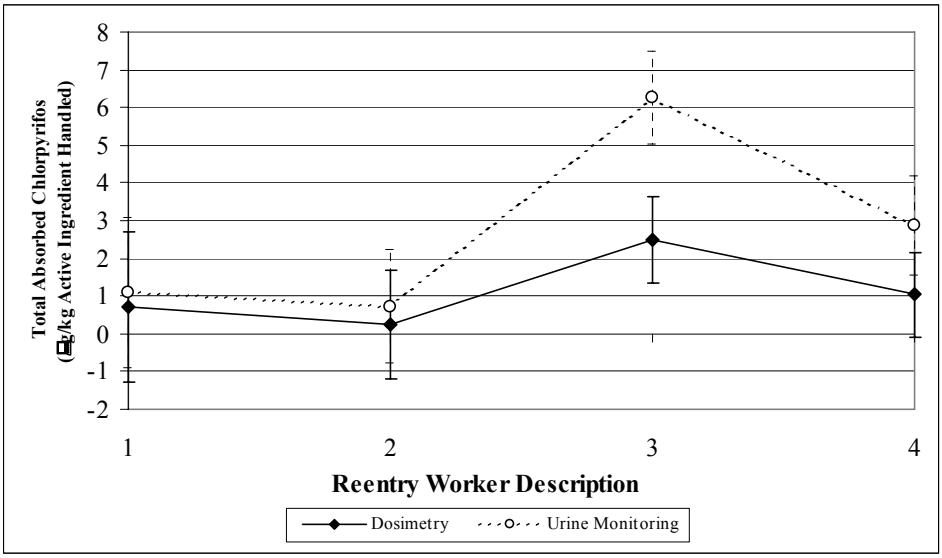
Figure 3-2. Comparison of Concurrent Biomonitoring and Passive Dosimetry Data from Selected Studies Monitoring Handler Exposure to Chlorpyrifos [a]



[a] Each point represents the geometric mean of absorbed dose (ug/kg active ingredient handled) calculated from either passive dosimetry (closed circles and solid lines) or biomonitoring (open circles and dotted lines), as reported by Fenske and Day (2005) from calculations made by Leighton (2000). Numbers across the horizontal axis represent groups of handlers performing similar activities within a study. 1: Mixer/loader/applicator (M/L/A) handling a granular formulation (N=12; Bischoff, 1998). 2: M/L/A applying a microencapsulated formulation with a high-pressure handwand (N=13; Contardi *et al*., 1993). 3: Groundboom applicator (N=9; Shurdut *et al*., 1993). 4: Airblast applicator (N=15; Honeycutt and DeGeare, 1994). 5: Mixer/loader (M/L) handling an emulsifiable concentrate (EC) formulation (N=13; Knuteson *et al*., 1999). 6: M/L handling an EC formulation (N=15; Honeycutt and DeGeare, 1994). 7: M/L handling an EC formulation (N=3; Shurdut *et al*., 1993). 8: M/L handling a wettable powder formulation (N=6; Shurdut *et al*., 1993).

Honeycutt *et al.* (2000) compared multiple handler and reentry worker studies using both passive dosimetry and urinary biomonitoring of chlorpyrifos, and summarized results of the comparison with both arithmetic and geometric mean estimates of exposure for each study. All of the handler studies evaluated by Honeycutt *et al.* (2000) were also reviewed by Fenske and Day (2005), and are included in Figure 3-2. In addition to the studies involving handlers, Honeycutt *et al.* (2000) also reviewed two studies involving reentry workers (Honeycutt and DeGeare, 1993; Shurdut *et al.*, 1993). Figure 3-3 summarizes results from these reentry studies.

Figure 3-3. Comparison of Concurrent Biomonitoring and Passive Dosimetry Data from Selected Studies Monitoring Reentry Exposure to Chlorpyrifos [a]



[a] Each point represents the geometric mean of absorbed dose (ug/kg active ingredient handled) calculated from either passive dosimetry (closed circles and solid lines) or biomonitoring (open circles and dotted lines) in studies reported by Honeycutt *et al.* (2000). Numbers across the horizontal axis represent groups of reentry workers performing similar activities in treated crops within a study. 1: Scouts in cover crops, small trees, tomatoes, and cauliflower (N=10; Shurdut *et al*., 1993). 2: Citrus harvesters (N=5; Honeycutt and DeGeare, 1993). 3: Citrus pruners, wet weather (N=5; Honeycutt and DeGeare, 1993). 4: Citrus pruners, dry weather (N=5; Honeycutt and DeGeare, 1993).

As with the doses absorbed by handlers summarized in Figure 3-2, the absorbed doses estimated by passive dosimetry and biomonitoring for reentry workers differ at most by about 3-fold. This is a small difference considering the variability that is typical in such studies. Honeycutt *et al.* (2000) plotted geometric and arithmetic means of passive dosimetry vs. biomonitoring data, and found a good correlation ($r^2 = 0.79$ and $r^2 = 0.86$, respectively).

Geer *et al*. (2004) examined exposure monitoring data from five studies, four of which were also reviewed by Fenske and Day (2005), Honeycutt *et al*. (2000), or both. These four studies included Contardi *et al.* (1993), Shurdut *et al*. (1993), Bischoff (1998), and Knuteson *et al.* (1999). The fifth study monitored five M/L/A doing termiticide applications with a handheld spraygun (Barnekow and Shurdut, 1998). Using a simple regression model of urinary TCP against the absorbed dose estimated from passive dosimetry on 71 monitoring events from the five studies, Geer *et al*. (2004) found a positive association between these two parameters and that 29% of the variability in urinary TCP levels could be explained by the simple regression model. It should also be noted that Geer *et al* (2004) considered the impact of the possible values related to the dermal absorption of chlorpyrifos which could impact any comparison of results by as much as a factor of 10 since absorption estimates range from 1 to 10 percent.

Comparisons Involving Other Organophosphorus Pesticides (OPs): Several OPs in addition to chlorpyrifos have specific metabolites that have been quantified in urine. These include chlorfenvinphos, diazinon, fenitrothion, malathion, methyl-parathion and parathion (Maroni *et al.*, 2000; Wong and Anderson, 2000; Tuomainen *et al.*, 2002). Alternately, dialkylphosphate metabolites, which are common to multiple OPs, can be monitored (Griffin *et al*., 1999). Several studies have been done in which exposure estimates based on passive dosimetry have been correlated with metabolites excreted in urine. Although these did not feature comparisons of absorbed dose estimates, as the correlations involving a range of exposures they provide support for the idea that the two methods both give reasonable estimates of absorbed dose.

For example, Aprea *et al*. (2004) monitored respiratory and dermal exposures to dimethoate of eight applicators spraying olive trees. Absorbed doses were calculated from these exposures assuming 10% dermal absorption and 100% inhalation absorption. Applicators also provided urine samples for 24 hours before and 24 hours following exposure; the alkylphosphates dimethyldithiophosphate (DMDTP), dimethylthiophosphate (DMTP), and dimethylphosphate (DMP) were quantified in these samples. Linear regression showed moderate correlation between estimated absorbed dose and excreted alkylphosphates ($r^2 = 0.60$; $p = 0.024$).

Spencer *et al.* (1993) monitored harvester exposure in peach and apple orchards treated with azinphosmethyl and phosmet. Dermal exposure was monitored with clothing dosimeters (long-sleeved t-shirts and socks), hand wipes followed by hand washes, and face/neck wipes; azinphosmethyl and phosmet were quantified in all samples. 24-hour urine samples were collected and analyzed for DMDTP, DMTP, and DMP. Passive dosimetry and biomonitoring were done concurrently in 48 harvesters at five study sites; an additional 22 harvesters participated in urine monitoring without passive dosimetry. Excretion of alkylphosphates into urine did not differ significantly between harvesters subject to dermal exposure monitoring and those who were not. A linear regression of mean potential dermal exposure against mean excreted alkylphosphates at the five sites resulted in a moderate correlation ($r^2 = 0.64$; $p < 0.10$).

In addition to the numerous studies where passive dosimetry data correlated well with biomonitoring results, several studies have been published in which estimated absorbed dose did not correlate with biomonitoring. Often in these studies, correlations were adversely affected by factors including small sample sizes (as few as three monitoring events; e.g., Tuomainen *et al.*, 2002); history of exposure to a pesticide prior to the exposure monitoring period (e.g., Grover *et al.*, 1986); incomplete passive dosimetry (e.g., no monitoring of hand exposures; Krieger and Dinoff, 2000); or short urine sampling intervals (as short as 2 hours; e.g., Krieger and Dinoff, 2000). Comparison of partial samples with full 24-hour urine collections suggests that sampling for shorter intervals yields unreliable results for at least some OPs (Franklin *et al.*, 1981).

In a preliminary study, Tuomainen *et al.* (2002) monitored malathion exposure of three applicators in greenhouses using handheld lance sprayers, using the specific metabolite, monocarboxylic acid (MMA). Dermal exposure was monitored by analysis of patches cut from the cotton coverall each applicator wore, with patches cut in locations dictated by OECD guidelines. Hand exposure was estimated with outer glove washes and by shaking

the gloves with ethanol. Respiratory exposure was not monitored; however, full face respirators were worn by all three applicators, which would be anticipated to substantially decrease exposure. A regression of excreted MMA against potential hand exposure to malathion (residues extracted from gloves) was highly correlated ($R^2 = 0.82$), while a regression of excreted MMA against potential total dermal exposure to malathion was ($R^2 = 0.44$) was poor. Tuomainen *et al.* (2002) suggested that the poor correlation of potential total dermal exposure with excreted MMA was possibly due to the small sample size.

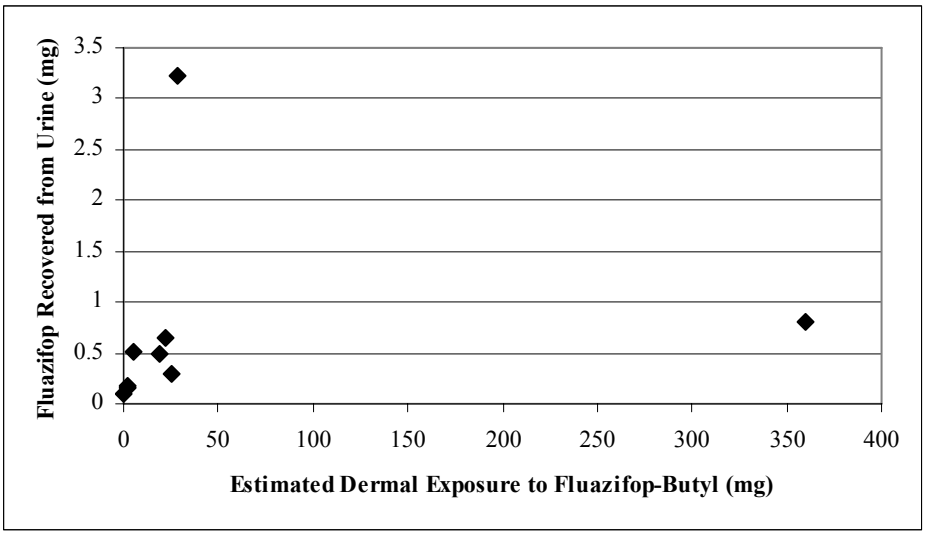
In some cases, even when urine samples were collected over a short interval, pesticide metabolites in urine may correlate with exposure. For example, Weisskopf *et al.* (1988) monitored exposure of 15 handlers applying a granular formulation of diazinon to planters and shrub areas. Dermal exposure was monitored with patches and hand rinses; a collar patch was used to estimate head exposure. Dermal samples were collected during lunch (morning shift) and at the end of the workday (afternoon shift). Urine samples were collected at the beginning and the end of the workday and analyzed for the metabolite, diethylthiophosphate (DETP). A log-log plot of morning shift dermal exposures correlated moderately well ($R^2 = 0.65$) with afternoon DETP levels in urine samples (Weisskopf *et al.*, 1988).

Comparisons Involving Non-OP Pesticides: Several biomonitoring studies and preliminary investigations have been reported on pesticides other than OPs. Typically, urine is analyzed for a specific metabolite or occasionally the unchanged pesticide; non-chemical-specific metabolites analogous to alkylphosphates are rarely used. However, difficulties are frequently encountered in finding metabolites that account for at least 30% of the absorbed dose, confounding such studies. For example, biomonitoring studies with captan generally rely on the metabolite, tetrahydrophthalimide (THPI), and some conducted concurrent passive dosimetry (Winterlin *et al.*, 1986; de Cock *et al*., 1995; de Cock *et al*., 1998). Yet pharmacokinetic studies done in the rat suggest that just 2% of an absorbed captan dose is excreted as THPI (van Welie *et al.*, 1991), limiting its ability to provide quantitative estimates of captan exposure. However, de Cock *et al.* (1995) reported that while THPI recovered from the urine of growers applying captan did not correlate well with total exposure estimates, there were correlations with estimates of exposure to exposed skin, as well as use of protective equipment.

Some non-OP pesticides have major metabolites that are excreted into urine. For example, Chester and Hart (1986) monitored a group of thirteen mixer/loader/applicators (M/L/As) who applied the herbicide, fluazifop-butyl, using vehicle-mounted sprayers. Each M/L/A was monitored during two separate applications; first, with biomonitoring (24-hour urine samples for two days pre-exposure and 7 days post-exposure); then, after urine collections were complete, a second application was monitored with WBDs (synthetic coveralls, cotton gloves and face masks). Dosimeters were analyzed for fluazifop-butyl and urine for the metabolite, fluazifop. This study was unusual in that it did not feature concurrent passive dosimetry and biomonitoring. It is perhaps not surprising that no correlation was found between the estimated dermal exposure of each M/L/A to fluazifop-butyl and the fluazifop residues recovered from the urine ($R^2 = 0.009$). Figure 3-4 shows the results of biomonitoring vs. estimated dermal exposure; Chester and Hart (1986) adjusted the dermal exposure estimates to account for differences in amounts handled between the first and second applications (amounts handled were not reported).

However, Woollen (1993) reported on subsequent laboratory studies suggesting that dermal absorption was inversely related to dermal exposure at applied doses corresponding to the range estimated by Chester and Hart (1986). Depending on the magnitude of the effect, it could confound estimates of absorbed dose from passive dosimetry. Conversely, a correlation might be apparent if absorbed doses were normalized by amount of active ingredient handled. More information is needed about amounts of active ingredient handled by each replicate, and about residues recovered from dosimeter sections, before the effectiveness of the study design can be evaluated.

Figure 3-4. Comparison of Results of Sequential Biomonitoring and Passive Dosimetry of Mixer/Loader/Applicators Handling Fluazifop-Butyl [a]



[a] Each point represents one replicate doing two applications; the first application was monitored with 24-hour urine samples collected for 7 days and the second application was monitored with coveralls, cotton gloves and disposable face masks (Chester and Hart, 1986). Dosimeters were analyzed for fluazifop-butyl and urine for the metabolite, fluazifop. Chester and Hart (1986) adjusted the dermal exposure estimates to account for differences in amounts handled between the first and second applications (amounts handled were not reported).

Cowell *et al.* (1991) monitored exposure of M/L/As handling dithiopyr during applications to turfgrass at sites in three cities: Atlanta, Georgia, Cincinnati, Ohio, and Cleveland, Ohio. Concurrent passive dosimetry and biomonitoring were conducted with six handlers at each site, using cotton gauze patches, hand washes, personal air monitors, and 24-hour urine samples collected for 72 hours post-application. Absorbed dose was estimated from passive dosimetry data, assuming a dermal absorption of 0.08% from an earlier study using rhesus monkeys. Data from that study also supported biomonitoring, by showing that rhesus monkeys dosed dermally with dithiopyr excreted an average of 64.5% of the absorbed dose in the urine as the metabolite, dicarbothioic acid (DCTA). During analysis of urine samples, DCTA was methylated to dithiopyr and quantified; however, none of the samples had dithiopyr residues above the limit of quantification of 5.4 ppb. About two-thirds of the samples had dithiopyr residues above the limit of detection (LOD); the LOD varied from day to day, but averaged 0.32 ppb. Absorbed

doses estimated from biomonitoring were based on results above the LOD, with ½ LOD substituted for non-detects. Estimates of absorbed dose calculated from passive dosimetry data averaged 0.0809 ± 0.0575 µg/kg body weight/lb active ingredient handled, nearly twice the average absorbed dose based on biomonitoring, 0.0460 ± 0.0238 µg/kg body weight/lb active ingredient handled.

Additional Concurrent Analysis: In addition to the analyses prepared above, the Agency evaluated all of the data in PHED and its risk assessments and not just for the scenarios in the case study in order to identify additional studies that used a concurrent biomonitoring and passive dosimetry approach. This included a review of the PHED data and of results for risk assessments completed over several years by the Agency. Much of the data which were identified have already been addressed in the analyses described above. Data which are not redundant have been included below (Table 3-1 & Figure 3-5). A ratio that compares mean dose estimates from each study has been calculated. If the values exceed 1 then it illustrates that absorbed dose estimates based on passive dosimetry exceed those calculated using concurrent biomonitoring.

Table 3-1: Summary of Concurrent Biomonitoring & Passive Dosimetry Results Based On PHED & Agency Risk Assessments

Chemical	Study Reference	Scenario/ Equipment (Scenario #)	mean lb ai/ sample size	Clothing/PPE	Dosimeters	Passive Dosimetry Dose (Dermal and Inhalation)	Biomonitoring Dose	Ratio Mean Passive Dosimetry/ Biomonitoring
Chlorpyrifos	Contardi et al. 1993. 43027901 as cited in USEPA 2000 (RED ORE chpt, June 19, T. Leighton)	mixer/loader/ applicator liquids: Backpack sprayer (1)	0.13 lb ai / N=2	Coveralls represented single layer of normal work clothing (also used for dosimetry)	Coveralls torso sections used in conjunction with briefs/T-shirts to estimate penetration factor. Arm and leg sections of coveralls adjusted for penetration factor to determine dermal exposure values. Total dermal exposure calculated as sum of arm/leg adjusted coverall values, t-shirt/brief values (torso), head patch/headband/neckband (dependent on worker), and hand rinse.	0.07 ug/kg and 0.09 ug/kg (3% dermal abs, 100% inh)	0.6 ug/kg and 0.1 ug/kg	0.51
		mixer/loader/ applicator liquids: low pressure handwand (2)	0.06 lb ai / N=1			0.13 ug/kg (3% dermal abs, 100% inh)	0.1 ug/kg	1.30
		mixer/loader/ applicator liquids: high pressure handwand (3)	0.47 lb ai (mean) / N=13			3.85 ± 7.7 ug/kg (A.M.) range: 0.21-28 ug/kg (3% dermal abs, 100% inh)	1.15 ug/kg ±1.13 (A.M.) range: 0.1- 4.2 ug/kg	3.35
Chlorpyrifos	Shurdut et al. 1993, 42974501 as cited in USEPA 2000 (RED ORE chpt, June 19, T. Leighton)	open mixer/loader, wettable powder (4)	50 WP formulation ; 32.6 lb ai; N=6	Coveralls represented single layer of normal work clothing (also used for dosimetry). Workers also wore ½ face respirator.	Coveralls torso sections used in conjunction with briefs/T-shirts to estimate penetration factor. Arm, leg and torso sections of coveralls adjusted for penetration factor to determine dermal exposure values. Total dermal exposure calculated as sum of arm/leg/torso adjusted coverall values, head patch, and hand rinse.	32.5 ± 24.2 ug/kg (A.M) range: 3.8-61.7 ug/kg (3% dermal abs; 100% inh)	11.7 ± 6.9 ug/kg (A.M.) range: 4.2-22 ug/kg	2.78
		open mixer/loader - liquids (5)	4E formulation ; 107 lb ai; N=3			9.6 ± 16 ug/kg (A..M) range: 0.2 - 28 ug/kg (3% dermal abs, 100% inh)	7.8 ± 10 ug/kg (A.M) range: 2.1 - 20 ug/kg	1.23
Chlorpyrifos	Shurdut et al. 1993. 42974501 as cited in USEPA 2000 (RED ORE chpt, June 20, D. Smegal)	groundboom applicator-- open cab liquid application (6)	27-330 lb ai; n=9			Dermal: 0.96 ug/kg Inhalation: 1.7 ug/kg; Total absorbed dose = 1.63 ug/kg	9.8 ug/kg	0.17

Table 3-1: Summary of Concurrent Biomonitoring & Passive Dosimetry Results Based On PHED & Agency Risk Assessments								
Chemical	**Study Reference**	**Scenario/ Equipment (Scenario #)**	**mean lb ai/ sample size**	**Clothing/PPE**	**Dosimeters**	**Passive Dosimetry Dose (Dermal and Inhalation)**	**Biomonitoring Dose**	**Ratio Mean Passive Dosimetry/ Biomonitoring**
Chlorpyrifos	Honeycutt and Day 1994. 43138102 as cited in USEPA 2000 (RED ORE chpt, June 19, T. Leighton)	mixer/loader (open mixing) (7)	78 lb ai; N=15	Coverall (also used for dosimetry), short sleeve shirt, pants, socks, work boots, chemical resistant gloves, helmet, goggles, and chemical respirator. The short sleeve shirt and pants were designed to be an intermediate layer of clothing which is required to be worn under coveralls as a protective garment in addition to coveralls by the State of California.	Inner body dosimeters: 100% cotton T-Shirts and briefs. Outer whole body dosimeters: coveralls. Coveralls torso sections used in conjunction with briefs/T-shirts to estimate penetration factor. Arm, leg and torso sections of coveralls adjusted for penetration factor to determine dermal exposure values. Total dermal exposure calculated as sum of arm/leg/torso adjusted coverall values, head patch, and hand rinse.	6.2 ± 6.2 ug/kg (A.M.) range: 0.67-26 ug/kg (3% dermal abs, 90% PF for inh)	10 ± 21 ug/kg (A.M) range: 1-85 ug/kg	0.62
		airblast applicator--open cab (8)	78 lb ai; N=15			5.9 ± 6 (A.M.) range: 0.73-20 ug/kg (3% dermal abs and 90% PF for inh)	13 ± 24 ug/kg (A.M.) range: 1.4 - 95 ug/kg	0.45
Chlorpyrifos	Murphy 1998 (Bischoff 1998 in ORE chpt), 44483501 as cited in USEPA 2000 (RED ORE chpt, June 19, T. Leighton)	granular--loading/ applying (enclosed cab) (9)	77.8 lb ai; n=16 dosimetry; n=12 biomonitoring	Cotton coverall represented single layer or work clothing (also used as dosimeter), socks and a hat	Coveralls torso sections used in conjunction with briefs/T-shirts to estimate penetration factor. Arm and leg sections of coveralls adjusted for penetration factor to determine dermal exposure values. Total dermal exposure calculated as sum of arm/leg adjusted coverall values, t-shirt/brief values (torso), head patch, and hand rinse.	0.3 ± 0.36 ug/kg (A.M) range: 0.056-1.4 ug/kg (3% dermal abs and 100% inh)	0.73 ±0.33 ug/kg (A.M) range: 0.13-1.39 ug/kg	0.41
Chlorpyrifos	Knuteson et al. 1999; 44739302 as cited in USEPA 2000 (RED ORE chpt, June 19, T. Leighton, and Study DER)	mixing/ loading emulsifiable concentrate for aerial application (10)	n=15 dosimetry; n=13 biomonitoring (avg 89 min exposure)	Cotton coverall represented single layer or work clothing (also used as dosimeter), socks and a hat	Coveralls torso sections used in conjunction with briefs/T-shirts to estimate penetration factor. Arm and leg sections of coveralls adjusted for penetration factor to determine dermal exposure values. Total dermal exposure calculated as sum of arm/leg adjusted coverall values, t-shirt/brief values (torso), head patch, and hand rinse.	1.13 ug/kg ± 0.66 (A.M) range: 0.66-2.54 ug/kg (3% dermal abs and 100% inh)	3.61 ug/kg (A.M.) 1.32 ug/kg (G.M) range: 0-32 ug/kg	0.31
Chlorpyrifos	Barnekow and Shurdut 1998; 44729401 as cited in USEPA 2000 (RED ORE chpt, June 20, D. Smegal)	hose-end sprayer; applicator (11)	2.17 lb; avg 1.5 hr turf treatment; n=15	Cotton coverall represented single layer or work clothing (also used as dosimeter), socks and a hat	Coveralls torso sections used in conjunction with briefs/T-shirts to estimate penetration factor. Arm and leg sections of coveralls adjusted for penetration factor to determine dermal exposure values. Total dermal exposure calculated as sum of arm/leg adjusted coverall values, t-shirt/brief values (torso), head patch, and hand rinse.	0.88 ± 0.62 ug/kg (A.M) range: 0.21-2.24 ug/kg	0.65 ± 1.43 ug/kg (A.M.) (n=15) Range: 0 - 4.84 ug/kg 0.4 ug/kg (G.M) (n=8) (7 workers had exposure less than background)	1.35
Chlorpyrifos	Barnekow et al. 1999; 44739301 as cited in USEPA 2000 (RED ORE chpt, June 20, D. Smegal)	screw top bottle (12)	0.00073 lb ai; n=15	Cotton coverall with the sleeves cut off to simulate a short sleeve shirt and a hat.	Coveralls torso sections used in conjunction with briefs/T-shirts to estimate penetration factor. Leg sections of coveralls adjusted for penetration factor to determine dermal exposure value. Exposure to the forearms determined using a 2.5 cm wide arm band around each forearm. Total dermal exposure calculated as sum of arm bands, leg adjusted coverall values, t-shirt/brief values (torso), head patch and hand rinse.	0.25 ug/kg (A.M.) range: 0.03-0.86 ug/kg	0.49 ug/kg (A.M.) 0.24 ug/kg (G.M.) Range: 0-1.9 ug/kg	0.51

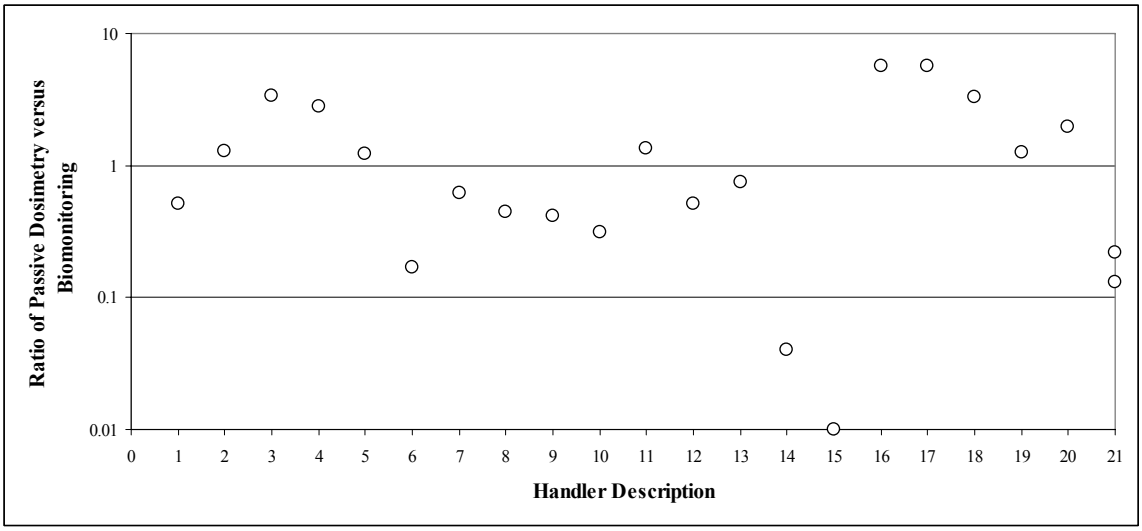
Table 3-1: Summary of Concurrent Biomonitoring & Passive Dosimetry Results Based On PHED & Agency Risk Assessments								
Chemical	**Study Reference**	**Scenario/ Equipment (Scenario #)**	**mean lb ai/ sample size**	**Clothing/PPE**	**Dosimeters**	**Passive Dosimetry Dose (Dermal and Inhalation)**	**Biomonitoring Dose**	**Ratio Mean Passive Dosimetry/ Biomonitoring**
Chlorpyrifos	Barnekow and Shurdut, 1998.44729402 as cited in USEPA 2000 (RED ORE chpt, June 20, D. Smegal)	mixer/loader/ applicator--hand held sprayer or injection rod (13)	10.72 lb ai; n=15 dosimetry and n=5 biomonitoring	Cotton coverall represented single layer or work clothing (also used as dosimeter), socks and a hat	Cotton long underwear (for non-biomonitoring replicates) or cotton briefs and T-shirt (for biomonitoring replicates). Coveralls torso sections used in conjunction with briefs/T-shirts to estimate penetration factor. Arm and leg sections of coveralls adjusted for penetration factor to determine dermal exposure values. Total dermal exposure calculated as sum of arm/leg adjusted coverall values (or long underwear values), t-shirt/brief values (torso), head patch, and hand rinse.	2.5 ug/kg (G.M for 15 replicates) (3% dermal abs) and 0.91 ug/kg inhalation (G.M.) (no protection) total dosimetry = 3.24 ug/kg (based on n=5 individuals used in biomonitoring)	4.3 ug/kg (n=5)	0.75
Propanil	Honeycutt, 2003, 46075501; as cited in USEPA 2004 Study Review, DP 293906	Mixing/ Loading Using Probe Extractors (14)	710 lb ai. N=30	**Mixer/loaders:** long sleeved shirts (100% cotton), long pants (100% cotton), t-shirt (100% cotton), briefs (100% cotton), socks, full rubber boots over socks, a baseball type cap, chemical resistant apron, goggles and a pair of chemical resistant gloves. **Pilots:** long sleeved shirts (100% cotton), long pants (100% cotton), t-shirt (100% cotton), briefs (100% cotton), socks, tennis shoes, helmet with visor and chemical resistant gloves worn when outside of the airplane (removed inside the plane).	Inner dosimeter: t-shirt/briefs. Outer dosimeter: long sleeved shirt and long pants. Outer dosimeter torso sections used in conjunction with inner dosimeter to estimate penetration factor. Arm, leg and torso sections of outer dosimeter adjusted for penetration factor to determine dermal exposure values. Total dermal exposure calculated as sum of arm/leg/torso adjusted values, head patch, and hand rinse.	Mixer/Loaders = 2.1 ug/kg ai/day	Mixer/Loaders = 55 ug/kg ai/day	0.04
		Aerial Application (15)				Pilots = 0.48 ug/kg ai/day	Pilots 35.5 ug/kg ai/day	0.01
Diazinon (a)	Rosenheck 2000, 45184305; as cited in USEPA 2000 Study Review DP 268247, And November 2000 ORE chpt for dosimetry dose estimates (D.Smegal)	ready to use hose end sprayer-liquid applicator (16)	0.5 lb ai (18-122 minutes) (Dosimetry estimates for 0.5 ac, biomonitoring estimates as in study, 5,000 ft2 or 0.1 ac)	shorts, short-sleeve shirt, shoes, socks.	Long underwear worn under shorts and shirt, face/neck wipes, and handwashes used to calculate dermal exposure.	Dermal: 3.6 ug/kg (8% dermal abs) Inhalation 1.31 ug/kg (G.M.) (n=11)	0.61 ug/kg (G.M) range: 0.08-3.11 (n=15)	5.73
		conventional hose end sprayer (17)	0.5 lb ai (18-122 minutes) (Dosimetry estimates for 0.5 ac, biomonitoring estimates as in study, 5,000 ft2 or 0.1 ac)			Dermal: 5.36 ug/kg (4% dermal abs Inhalation = 0.33 ug/kg (G.M.) (n=12)	0.96 ug/kg (G.M) range: 0.03-10.9 (n=14)	5.70
		handpump sprayer (18)	0.021 lb ai (or 4 gallons diluted product) Assumed 1000 ft2 treated			Dermal = 2.24 ug/kg (14% dermal abs) Inhalation = 0.21 ug/kg (n=10)	0.75 ug/kg (A.M--normally dist) range: 0.09-2.46 (n=13)	3.27

Table 3-1: Summary of Concurrent Biomonitoring & Passive Dosimetry Results Based On PHED & Agency Risk Assessments								
Chemical	**Study Reference**	**Scenario/ Equipment (Scenario #)**	**mean lb ai/ sample size**	**Clothing/PPE**	**Dosimeters**	**Passive Dosimetry Dose (Dermal and Inhalation)**	**Biomonitoring Dose**	**Ratio Mean Passive Dosimetry/ Biomonitoring**
Atrazine (b)	Honeycutt et al. 1996 MRID 43934417 (interim); Selman 1996, MRID 43934418 (interim); Selman and Rosenheck 1996, MRID 44152109 (Final); Honeycutt et al. 1996, 44152111 (Final) 44315403 (amendment) as cited in USEPA 2002 Revised ORE Chpt (April 2002, G. Bangs).	Applicators-groundboom (19)	148-3450 lb atrazine over 2-3 days; n=14 (7 workers for 2 days)	sweatshirt, long sleeved shirt and long pants (for cold weather reps; no sweatshirt for warm weather reps), socks, leather work boots, chemical resistant gloves, goggles (mixer-loaders and truck tenders only) and a belt.	From 43934417 and 44152109 -- Inner body dosimeter: t-shirt and briefs. Outer body dosimeter: sweatshirt and/or long sleeved shirt and long pants (cold weather; no sweatshirt in warm weather). When sweatshirt worn, used as outer dosimeter and long sleeved shirt used as inner dosimeter. Penetration factors determined from outer and inner torso dosimeter samples—used to calculate arm/leg values if needed. Total dermal exposure = adjusted arm/leg values, inner dosimeter torso value, hand rinse, head patch	7.71E-4 mg/lb ai (GM) range: 2.1E-2 to 6.4E-5 mg/lb ai	6.05E-4 mg/lb ai (GM) range: 7.87E-3 to 8.61E-3 mg/lb ai	1.27
		Mixer-loader/truck tenders—groundboom (20)	148-3450 lb atrazine over 2-3 days; n=14 (7 M/L closed system for 2 day)			7.34E-4 mg/lb ai (GM)	3.77E-4 mg/lb ai (GM) range: 7.87E-3 to 8.61E-3 mg/lb ai	1.95
		mixer-loader/ applicators—groundboom (21)	148-3450 lb atrazine over 2-3 days; n=6 (3 closed mixing and closed cab and 1 open mixing/closed cab for 2 days)			1.29E-4 to 1.03E-3 mg/lb ai (GM) range: 1.55E-2 to 1.68E-5 mg/lb ai	Range: 1.03E-3 to 4.59E-3 mg/lb ai	0.13-0.22

(a) Since a dermal toxicity endpoint was used in the risk assessment for diazinon, a dermal absorption factor was not necessary. Although, the Agency HIARC report recommended a dermal absorption factor of 100% based on comparative toxicity studies, the Data Evaluation Record (DER) for this study estimated dermal absorption factors that range from 4% to 14%. The study specific dermal absorption factors were used to estimate the dermally absorbed dose.

(b) A total of 3 chlorotriazine degradates that comprise 12% was used for biomonitoring. Unable to verify complete urine volume. No creatinine. Very variable field recoveries for fortified matrices (22-230%). In all cases but atrazine, dose is reported as ug/kg BW. For atrazine, unit exposure estimates (mg/lb ai handled) were presented in the risk assessment which allowed for a similar comparison of the efficiency of passive dosimetry and biological monitoring.

Figure 3-5. Ratios of Mean Passive Dosimetry versus Biomonitoring for Concurrent Agency Analysis [a]



[a] Each point represents the ratio of the passive dosimetry dose or unit exposure versus the biomonitoring dose or unit exposure. Numbers across the horizontal axis represent different studies for comparison (numbers correspond to scenario numbers in Table 3-1).

Additional Retrospective Analysis: In addition to the analyses prepared above, the Agency evaluated all of the data in PHED and its risk assessments and not just for the scenarios in the case study in order to identify additional studies that could be used for a retrospective biomonitoring and passive dosimetry analysis. Essentially, this type of analysis involve a similar comparison as above except body burdens based on biological monitoring have been compared to estimates for the same scenarios which were developed using the exposure factors obtained from the biological monitoring data. For example, if in a biological monitoring study 20 acres were treated with an open cab groundboom applicator at a rate of 1 lb active ingredient per acre then the passive dosimetry estimate to which it was compared would be based on PHED and similar inputs. Data which are not redundant to that described above have been included below (Table 3-2 & Figure 3-6). The ratio that compares mean dose estimates from each study has been calculated. If a unit exposure was provided in the biomonitoring study (rather than a dose), then the appropriate PHED unit exposures were identified (according to the application equipment and PPE identified in the study), were totaled (dermal plus inhalation), and were then compared to the biomonitoring unit exposure, to obtain a ratio of mean passive dosimetry to biomonitoring. If the values exceed 1 then it illustrates that absorbed dose estimates based on passive dosimetry exceed those calculated using concurrent biomonitoring. It should be noted that the range of dermal absorption estimates has been considered in this analysis in order to illustrate the sensitivity of the results to that parameter.

Table 3-2: Summary of Retrospective Biomonitoring & Passive Dosimetry Analyses Based On PHED & Agency Risk Assessments

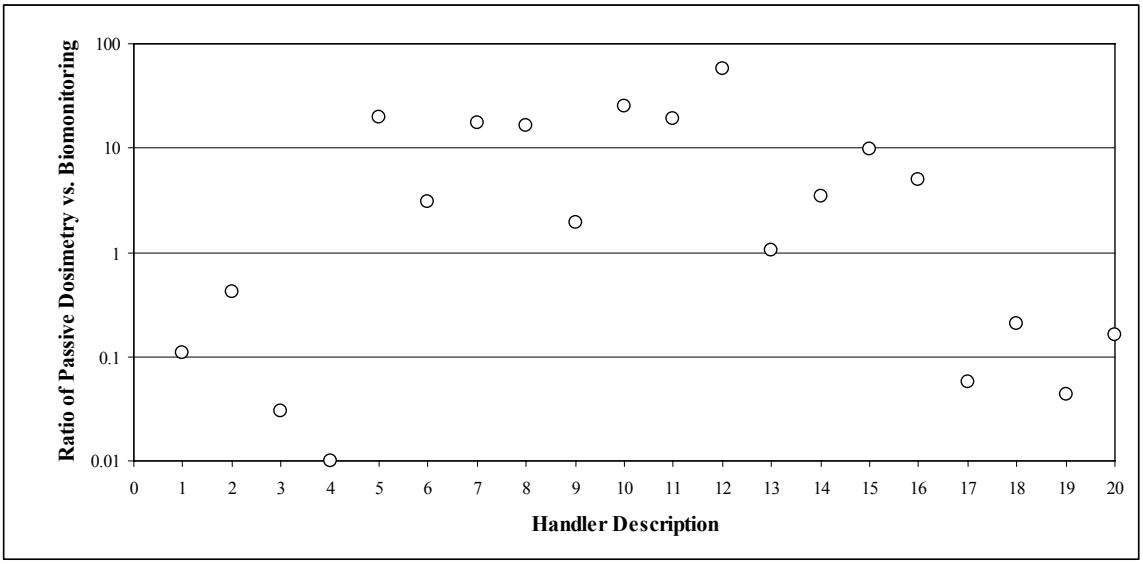
Study Citation	Chemical	Application rate from study	Application equipment	Dermal absorption	PPE worn	Ratio Passive Dosimetry (dermal + inhalation) / Biomonitoring	
Scott, R.C.; Chester, G.; Hart, T.B.; Woolen, B.H.; Ward, R.J.; Laird, W.J.D. (1983). Fluazifop-butyl: a spray trial to assess knapsack spraying.	fluazifop-butyl	5 g/L = 0.042 lb ai/gal and 21.38 gal/A = 0.898 lb ai/A	knapsack sprayer	2% (high exposure) and 9% (low exposure) from D316892	T-shirts, shorts and shoes	(1)[a] 2% dermal absorption:	0.11
						(2) 9% dermal absorption:	0.42
Findlay, M.L. (1997). Molinate; Biological Monitoring of Workers During Loading of Arrosolo 3-3E into Airplane Hoppers	molinate	states max rate as 4 lb ai/A for product; average gallons handled provided for each worker level	M/L for aerial application	40%	All mixer loaders wore chemical resistant gloves, half-face respirator and chemical resistant footwear. Additional protection consisted of one of the following: (1) Level 1: Activated carbon suit worn underneath 'Kleenguard' coveralls; (2) Level 2: 'Kleenguard' coveralls worn over normal work clothing and (3) Level 3: Normal work clothing, recommended as long sleeved shirt and long trousers.	(3) SL w/gloves:	0.03
						(4) DL w/gloves:	0.01
Barney, W.P. (2001). Occupational Exposure Monitoring of Aerial Mixing/Loading of PENNCAP M® Utilizing Biological Monitoring	methyl parathion	1 lb ai/A	aerial	6%	M/L: Long sleeved shirt, long pants, coveralls, socks, rubber boots, goggles, dust/mist respirator, and neoprene gloves	(5) Ratio of unit exposures (dermal + inhalation PHED and 90th percentile biomonitoring UE):	19.5

Table 3-2: Summary of Retrospective Biomonitoring & Passive Dosimetry Analyses Based On PHED & Agency Risk Assessments							
Study Citation	**Chemical**	**Application rate from study**	**Application equipment**	**Dermal absorption**	**PPE worn**	**Ratio Passive Dosimetry (dermal + inhalation) / Biomonitoring**	
Siemer, S.R. (1995). The Evaluation of Worker Exposure During Loading and Spray Application of Dormex to Dormant Grapevines	hydrogen cyanamide	biomonitoring study rate= 8.7 to 21.6 lb ai/A; application rates used in risk assessment for hydrogen cyanamide taken from labels: peach=12.9 lb ai; grape=17.2 lb ai; apple=34.4 lb ai	closed-cab over-the-row sprayer	11% (from D306179)	Applicators only: chemical resistant rainsuits, gloves, rubber boots, long sleeve-shirt, long pants, respirators	(6) Ratio of unit exposures assuming groundboom equipment (dermal + inhalation PHED and geomean biomonitoring UE):	3.02
						(7) Ratio of unit exposures assuming airblast equipment (dermal + inhalation PHED and geomean biomonitoring UE):	17.6
Hicks, S.C. (1998). The Evaluation of Spray Applicator Exposure During Airblast Spray Application of Dormex® to Dormant Fruit Trees	hydrogen Cyanamide	biomonitoring study rate= 11.2 to 26.6 lb ai/A application rates used in risk assessment for hydrogen cyanamide taken from labels: peach=12.9 lb ai; grape=17.2 lb ai; apple=34.4 lb ai	open-cab airblast	11% (from D306179)	Applicators only: chemical resistant rainsuits, gloves, rubber boots, long sleeve-shirt, long pants, respirators	(8) Ratio of unit exposures (dermal + inhalation PHED and geomean biomonitoring UE):	16.4
Siemer, S.R. (1990). The Determination of N-acetylcyanamide in Urine of Workers Exposed to Dormex7, as a Measure of Exposure	hydrogen cyanamide	biomonitoring study rate= 17.2 - 22.4 lbai/A application rates used in risk assessment for hydrogen cyanamide taken from labels: peach=12.9 lb ai; grape=17.2 lb ai; apple=34.4 lb ai	closed-cab airblast	11% (from D306179)	Applicators only: chemical resistant rainsuits, gloves, rubber boots, long sleeve-shirt, long pants, respirators	(9) Ratio of unit exposures (dermal + inhalation PHED and average biomonitoring UE) :	1.95
Belcher, T. (2001). Biomonitoring Assessment of Worker Exposure to Methyl Parathion During Application to Potatoes Using Penncap-M Microencapsulated Insecticide: Final Study Report: Lab Project Number: KP-2001-02: ERS21007. Unpublished study prepared by	methyl parathion	1.5 lbs ai/A	ground spray applications	100%	coveralls over long-sleeved shirt and long pants; chemical resistant gloves, socks, and footwear; protective eyewear; chemical-headgear for overhead exposure; and dust/mist filtering half-face respirator (OSHA/NIOSH approval number prefix TC-21C).	(10) Ratio of unit exposures (dermal + inhalation PHED and 90th percentile biomonitoring UE):	25.3
Willard, T.R. (2001). Occupational Exposure Monitoring of Mixing/Loading Activities for Aerial Application of PENNCAP M® Microencapsulated Insecticide Utilizing Biological Monitoring	methyl parathion	1.0 lbs ai/A	aerial spray applications	100%	cotton coveralls over long-sleeved shirt, undershirt, and long pants; chemical resistant boots; long nitrile gloves; full-face shield; overhead exposure; dust/mist filtering half-face respirator (OSHA/NIOSH approval number prefix TC-21C); chemical resistant nitrile apron; and Tyvek® hat.	(11) Ratio of unit exposures (dermal + inhalation PHED and 90th percentile biomonitoring UE):	19.3

Table 3-2: Summary of Retrospective Biomonitoring & Passive Dosimetry Analyses Based On PHED & Agency Risk Assessments								
Study Citation	**Chemical**	**Application rate from study**	**Application equipment**	**Dermal absorption**	**PPE worn**	**Ratio Passive Dosimetry (dermal + inhalation) / Biomonitoring**		
Merricks, D.L. (2001). Biological Monitoring of Workers Mixing and Loading a 4 lb/gallon Emulsifiable Concentrate Formulation of Methyl Parathion for Aerial Application (Using a MICRO MATIC 'DV' Liquid Transfer Valve System)	methyl parathion	0.75 lbs a.i./Acre	aerial mixer/loaders	100%	coveralls over long-sleeved shirt and long pants; chemical resistant gloves; chemical resistant footwear and socks; protective eyewear; chemical-resistant apron; and dust/mist filtering half-face respirator (OSHA/NIOSH approval number prefix TC-21C)	(12) Ratio of unit exposures (dermal + inhalation PHED and 90th percentile biomonitoring UE):		56.9
Rosenheck, L. (2004). Determination of Exposure During the Mixing, Loading and Application of Curacron 8E (Profenofos) by Air Through the Use of Biological Monitoring: Final Report. Project Number: 184/99. Unpublished study prepared by Syngenta Crop Prot	profenofos	1 lb ai/acre	aerial mixer/loaders and aerial applicators	50%	mixer/loaders: long-sleeved shirt, long pants, shoes and socks, a chemical-resistant apron, and chemical- resistant gloves; applicators: long-sleeved shirt, long pants, shoes, and socks	(13) Mixer/loader:		1.06
						(14) Applicator:		3.49
Krolski, M. (2004). Azinphos-Methyl - Biomonitoring of Applicators Following Airblast Treatment of Orchard Crops using Open and Closed Cab Equipment: Final Report. Project Number: 201054, GU264704, GU264705. Unpublished study prepared by Bayer Cropscience	AZM	1.5 lb ai/A used for comparison; from study, application rates were 0.534 to 1.098 for open cab and 0.62 to 2.052 for closed cab	airblast	42%	For open cab one- or two-piece chemical-resistant coveralls made from TYVEK, SARANEX, PVC or similar material , long-sleeved shirt and long pants, chemical-resistant footwear plus socks, chemical-resistant gloves, chemical-resistant headgear, and protective eyewear. In addition, workers wore a respirator with either an organic vapor removing cartridge with a prefilter approved for pesticides. For closed cab field trials, the Study Report states that workers wore long-sleeved shirts, long pants, and shoes plus socks	(15) Mix/Load/Apply Open Cab Airblast		9.75
						(16) Mix/Load/Apply Closed Cab Airblast		4.92
Chester, G.; Hart, T.B.; Sabapathy, N.N.; Woolen, B.H.; Atreya, N. (1985). Fluazifop-butyl: spray operator exposure on Malaysian plantation.	fluazifop-butyl	1.5 lb ai applied	knapsack (backpack)	2% (high exposure) and 9% (low exposure) from D316892	Workers wear shorts, T-shirts, plimsolls	Mixer/loader	(17) 2% dermal absorption:	0.057
							(18) 9% dermal absorption:	0.209
						Applicator:	(19) 2% dermal absorption:	0.044
							(20) 9% dermal absorption:	0.16

a Numbers in parentheses correspond to handler description numbers in Figure 3-6.

Figure 3-6. Ratios of Mean Passive Dosimetry versus Biomonitoring for Retrospective Agency Analysis [a]



[a] Each point represents the ratio of the passive dosimetry dose or unit exposure versus the biomonitoring dose or unit exposure. Numbers across the horizontal axis represent different studies for comparison (numbers correspond to scenario numbers in Table 3-2).

Although many studies of passive dosimetry and biological monitoring are available to draw generalized conclusions, none of the studies were designed with the sole purpose of "validating" passive dosimetry. Nor is a ratio of 1 expected (i.e., exact duplicative results from both methods). Although the confounding factors discussed in the beginning of this section prevent any conclusive statements, the following observations were noted in the comparison of passive dosimetry to biological monitoring:

- For the chlorpyrifos examples, when comparing biological monitoring to passive dosimetry one method did not consistently result in greater absorbed dose estimates over the other when assuming 3 percent dermal absorption. A lower dermal absorption of 1 percent as suggested by Griffin et al (1999) would result in passive dosimetry estimates lower than biological monitoring results. Conversely, assuming a 10 percent dermal absorption suggested by Krieger (1995) would result in passive dosimetry overestimating the absorbed dose from the biological monitoring data.

- When comparing biological monitoring to passive dosimetry for other organophosphorus pesticides, numerous studies showed that the passive dosimetry data correlated well with the biomonitoring results. However, several other studies showed that the absorbed dose did not correlate with biomonitoring. The poor correlation may be due to small sample sizes, short sampling intervals, prior exposure to pesticides, or incomplete measuring of passive dosimetry.

- Although some studies show that the passive dosimetry data support biomonitoring results for non-organophosphorus pesticides, several factors make it difficult to identify any

definitive trends among these studies. Identifying a metabolite that accounts for at least 30% of the absorbed dose may be difficult. Furthermore, the dermal absorption factors selected could confound estimates of absorbed dose from the passive dosimetry since absorption may be inversely correlated to dermal dose.

- The concurrent passive dosimetry to biological monitoring comparison presented in Table 3-1 indicates that the ratio of passive to biological monitoring methods ranged from 0.01 to 5.73 with a ratio below 1 for 10 scenarios (indicating passive dosimetry under predicting the biological absorbed dose) and a ratio greater than 1 for 10 scenarios (indicating passive dosimetry over predicting the biological absorbed dose). Of the 20 scenarios, 90 percent of the ratios were within 1 order of magnitude of a ratio of 1. For the scenarios that relied on individual replicate clothing penetration factors, 10 scenarios have ratios that are below 1 and seven scenarios have ratios that are greater than 1. For the chlorpyrifos examples, eight scenarios have ratios below 1 and five scenarios with ratios greater than 1. For the non chlorpyrifos examples, two scenarios have ratios below 1 and five scenarios greater than 1.

- The retrospective analysis presented in Table 3-2 indicates that eight of the scenarios have ratios below 1 and 12 scenarios have ratios greater than 1. The ratios for 10 of the 20 scenarios presented are within an order of magnitude of 1. The ratios ranged from 0.01 to 56.9.

In conclusion, the passive dosimetry to biological monitoring ratios for the 40 scenarios used in EPA risk assessments (i.e., Tables 3-1 and 3-2) indicate that 70% of the scenarios were within an order of magnitude of the ratio of 1. The range of the ratios is from 0.01 to 56.9; based on the limitations of the data presented, to conclude anything more than most of the data are within an order of magnitude of 1 or most of the data range within 2 orders of magnitude, specific studies designed to "validate" the accuracy of passive dosimetry would be needed. Also of note is the fact that using biological monitoring data to develop a surrogate data base would introduce additional uncertainties because of the need for accurate dermal absorption data for back-calculating a measured absorbed dose to estimate the chemical contact with the skin (and the need for the determination of the inhalation route) along with the need for accurate dermal absorption data for the chemical to be assessed using the surrogate data.

AHETF Concurrent & Retrospective Analysis: In preparation for this meeting the AHETF prepared a similar analysis in order to compare in a concurrent and retrospective approach both biological monitoring and passive dosimetry estimates of exposure (AHETFc *et al*, 2006 & AHETFd, 2006). In large part, the Agency concurs with the approaches and data utilized by AHETF. Here are the critical issues and considerations that the Agency identified in the review of these documents. These include:

- The uncertainties associated with the AHETF analysis are similar to those inherent to the analyses completed above.

- In many cases, the same data were used by both the Agency and AHETF yet the numerical results varied slightly in many cases. This is due to varied inputs being used such as for defining pharmacokinetics or dermal absorption.

- The results for the AHETF analysis appear to be consistent with those developed by the Agency.

- It is believed that biological monitoring should be included in any sampling plan of this nature because it can provide information to characterize dosimeter performance and quantify exposures that have not been captured using other methods (e.g., compare biomonitoring to wipe, inhalation, and handwash results).

3.2 Systematic Evaluation of Hand Sampling Methods

Historically, hand sampling methods have included two basic approaches that involve quantifying residues from the surface of the skin as described in the guideline documents referenced above. In some cases, monitors provide an absorptive layer on the surface of the skin that traps impinging residues (e.g., cotton gloves removed and analyzed for residues) or a removal method is used that typically involves some sort of handwash or swipe method. Different investigators over time have used various materials as monitors such as cotton or Tyvek© gloves and many types of wash solutions that have included acetone, a variety of alcohols or aqueous soap solutions.

The use of washing (i.e., removal) methods to estimate hand exposure from pesticides has been an industry standard since the early 1990's. The shift from trapping media (e.g., gloves) occurred because of the general belief that the use of gloves tended to over-estimate residue levels on the hands because cotton gloves trapped more residues than would normally be retained on the skin. The use of removal methods such as washes of different types, however, has been subject to criticism because of its potential, conversely, to underestimate exposure to the hands. Studies conducted by Fenske and colleagues are often cited as evidence of the limited recovery of residues from hands by the hand rinse method (see below for further information). There are a number of factors that may influence the interpretation of data using this method. These include the physical-chemical properties of the chemical being measured and the type of solvent used for the hand rinse. Other factors include the duration of the exposure monitoring event (one hour or several hours), the length of time the hand rinse was performed after the monitoring event, the nature of the chemical being monitored (concentrate, dilute spray, field residue/soil/plant material matrix), the concentration of the chemical on the skin ($\mu g/cm^2$), and the level of mechanical agitation that is used during sampling (e.g., in some cases subjects shook their individual hands in soap solutions while in other cases subjects vigorously washed their hands together).

If there is a systematic bias associated with hand sampling methods, the Agency wishes to address possible approaches for compensating in order to account for that bias. The Agency also desires to better understand the ruggedness of the available methods for application to settings

where concentrated liquids, dilute sprays, or solid materials may reflect the physical nature of the pesticide being monitored. Two approaches have been used in the evaluation of hand sampling methods. These include:

- **Mechanistic Analysis**: Based on a variety of data, the Agency has examined how factors such as solubility, K_{ow}, molecular weight, and other physical-chemical factors can influence hand exposure results. The techniques used by investigators have also been considered in the interpretation of the results.

- **Field Performance Analysis:** Another approach for completing a comparison between various hand monitoring techniques is to evaluate the relative performance of different methods under actual field conditions. In this case, hand monitoring results from the case study (see Section 2 above) were used to examine how factors such as sampling media or nature of the contaminant being screened for can influence results.

Section 3.2.1: Mechanistic Hand Methods Analysis describes the available data which has been used to illustrate the mechanistic factors that can influence hand exposure levels. In *Section 3.2.2: Hand Method Field Performance Data* the Agency has examined how various methods have performed under field conditions based on the case study data described above. *Section 3.2.3: Conclusions* describes the Agency's summary interpretation and conclusions based on the analyses contained in this section.

3.2.1: Mechanistic Hand Methods Analysis

The Agency is unaware of any comprehensive study that compares the performance of hand rinses and absorbent gloves for estimating true hand exposure. However, articles have appeared in the published literature that address key factors the Agency believes can impact the interpretation of exposure data relying on hand rinses. The seminal study for this discussion is Davis et al., 1983 where the authors reported results of a study comparing two methods for measuring hand exposure; hand rinses and gloves (cotton and nylon).

Potential Exposure of Apple Thinners to Azinphos-methyl and Comparison of Two Methods for Assessment of Hand Exposure: James E. Davis, Edwin R. Stevens, and Donald C. Staiff. Bull. Environ. Contam. Toxicology, 31: 631-638, 1983.

The study involved apple thinners working in orchards treated with azinphos-methyl. Davis suggested that the hand rinse method described in Durham and Wolfe (1962) had limitations despite being a recognized standard. The limitations include identifying solvents that remove residues without injuring the skin, the potential for causing interferences in laboratory analysis and that residues that penetrate the skin during the exposure period would not be included in the measurement.

Mean hand measurements using cotton gloves were reported to be 4.7 to 5.5 times higher than ethanol based hand rinses for workers thinning apples in azinphos-methyl (azm) treated orchards. Two separate monitoring periods were evaluated for a duration of two hours. One monitoring period was two days after an application of azm and another 9 days after the application. Unfortunately, a description or discussion of the absorptive

capacity of the type of cotton gloves used in the study was not provided. Nor did the authors attempt to discern what percent of the hand rinse represented true hand exposure.

Methods for Assessing Fieldworker Hand Exposure to Pesticides during Peach Harvesting: R.A. Fenske, S.G. Birnbaum, M.M. Methner and R. Soto. Bull Environ. Contam, Toxicology, 43:805-813, 1989.

In this study, Fenske and colleagues explored the impact of exposure duration (hours) on the differences between the use of hand rinses and cotton gloves in workers harvesting peaches in captan treated orchards. They found that the absorptive capacity of the gloves was greater for short exposure durations (0.5 and 1 hour sampling periods) than the longer (1.5 and 3 hour) exposure durations. Results from the shorter exposure durations demonstrated that gloves produced significantly higher measurements than hand rinses. However, comparisons of the hand rinse and glove measurements at the 1.5 and 3 hour time periods, showed no significant differences between the methods.

The authors considered glove loading (defined as total mass of captan deposited on the glove) as a possible explanation for the lack of significant differences in the hand rinse/glove comparison for the longer exposure durations. They also hypothesized that decreases in the absorptive capacity of the gloves may have been due to moisture, soil and or sweat combined with captan residues. The authors also noted captan residues were recovered beneath gloved hands indicating breakthrough. Summary statistics from this study are shown in Table 3-3.

Table 3-3: Glove and handwash exposure rates by sampling time

Time (hours)	Glove exposure rate (mg/hr)			Hand exposure rate (mg/hr)			Glove/Hand Ratio
	Mean	Median	Std Dev	Mean	Median	Std Dev	
0.5	43.6	43	28	18	17	9	2.4
1.0	32.5	31	18	15.5	15	9	2.1
1.5	23.2	25	8	16.6	16	8	1.4
3.0	21	19	9	14.7	13	9	1.4
n=8 for all results							

The results from this study indicated glove measurements (short exposure durations) were 1.5 to 2.5 fold higher than hand rinses while Davis et al., 1983 observed an approximate 5 fold difference. In the Fenske study, light weight (11.6 mg/cm^2) cotton gloves (marketed for use in photographic darkrooms) were used while it was speculated that heavier weight gloves may have been used in the Davis study. Heavier weight cotton gloves are assumed to be more absorptive.

Comparison of Three Methods for Assessment of Hand Exposure to Azinphos-Methyl (Guthion) During Apple Thinning: Richard A. Fenske, Nancy J. Simcox, Janice E. Camp, and Cynthia J. Hines. Applied Occupational and Environmental Hygiene Volume 14(9): 618-623, 1999.

Hand measurement techniques used in this study consisted of cotton gloves, hand rinses (washing hands in a polyethylene bag containing a surfactant/distilled water solution) and hand wipes (surgical gauze wipes sprayed with the surfactant/distilled water solution). The study subjects performed apple thinning in azinphos-methyl treated orchards for a duration of 2 hours. The results showed that glove exposure (6.48 mg/hr) was 3.5 times higher than the hand rinse rate (1.38 mg/hr) which was 6.4 times higher than the hand wipe rate (0.28 mg/hr). In conclusion the authors asserted that gloves resulted in a 2.4 fold overestimate while hand wipes indicated a 10 fold underestimate. In this study the authors proposed adjusting hand rinse (**wash**) measurements by using a correction factor from a laboratory study discussed in Fenske et al., 1998 (Table 3-4).

Table 3-4: Dislodgeable foliar residues (DFR) data collected by Fenske

Sample day(s)	Days post application	N	Mean foliar residue ($\mu g/cm^2$)	CV (%)	Hand sampling method
Day 1	4	7	1.05	26	Glove
Day 2	5	4	0.98	21	Wash, wipe
Day 3	6	4	1.48	43	Wash, wipe
Day 4	9	8	1.38	22	Glove
1 and 4	--	15	1.22[A]	27	Glove
2 and 3	--	8	1.23[A]	42	Wash, wipe

[A] Authors determined that mean foliar residues for days 1 and 4 compared to days 2 and 3 were not different (using a t-test).

The mean measured exposure rates for the three methods are shown in Table 3-5.

Table 3-5: Mean Measured Exposure Rates

Method	N	Mean measured exposure rate (mg/hr)[A]	CV (%)	Percent of estimated true exposure rate
Glove	15	6.48	28	240
Wash	12	1.83	27	68[B]
Wipe	12	0.28	33	10

[A] Hourly exposure for two hands. Means were determined to be significantly different using ANOVA ($p < 0.001$).
[B] Assumed handwash removal efficiency of 68% from Fenske et al., 1998. See table 12 below.

The authors adjusted the hand rinse (wash) data by using the rinse efficiency of captan as discussed in Fenske et al., 1998. *[A discussion of Fenske 1998 follows.]* Although the

removal efficiency of azinphos-methyl is unknown, the authors assumed that azm may have a rinse efficiency similar to captan because both chemical's have similar log octanol: water partition coefficients ($K_{o/w}$). The octanol/water partition coefficient is defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. A comparison of parameters for three chemicals considered relevant to hand wash removal is presented in Table 3-6.

Table 3-6: Comparison Of Factors Related To Handwash Removal Of Residues

Chemical	log $K_{o/w}$	Formulation type	Removal efficiency at 1 hour
Captan	2.35	Wettable powder	68%
Azinphos-methyl	2.75	Wettable powder	Unknown
Chlorpyrifos	4.96	Liquid concentrate	22%

Incomplete Removal of the Pesticide Captan from Skin by Standard Handwash Exposure Assessment Procedures. R.A. Fenske, C. Schulter, C. Lu and E.H. Allen. Bull. Environ. Contam. Toxicol. (1998) 61:194-201.

The hand rinse removal efficiency of captan using rinses was investigated by Fenske and colleagues in a laboratory study designed to simulate occupational hand exposure. Volunteers contacted test tubes spiked with captan (10 times). After grasping the test tubes, the participants rubbed their fingers against the palm of the same hand for even distribution of the captan. Another group of volunteers performed a similar routine.

The hand rinses (washes) consisted of two washes using separate polyethylene bags containing isopropanol in distilled water. In this mass balance study, captan was measured on the hands and the amount that was transferred to the hand was accounted for by measuring what was left on the test tubes after the volunteers contacted them (Table 3-7). In addition, the study design included an ability to explore the impact of the timing of hand rinse collection after exposure/contact (immediately and 1 hour after exposure).

Table 3-7: Summary Data For Captan Removal Using Handwash Methodology

Time (hr)	N	Total spike (mg)	Captan transferred to hand (mg)	Captan removed from hand (mg)	Handwash removal efficiency			
					2 washes (%)	CV (%)	First wash only	CV (%)
0	12	7.43	4.37	3.81	90.7	22	78.1	--
0	6	5.62	5.25	4.10	77.8	18	67.1	22
1	12	5.88	5.62	3.85	68.4	7	58.9	--

The authors acknowledge that exposure to captan (as reported in Fenske et al., 1989 and discussed above) has been reported at rates of 10 to 20 mg/hour with DFR's of 6.4 $\mu g/cm^2$. This study highlights the impact of time with respect to hand wash collection.

Determination of Handwash Removal Efficiency: Incomplete Removal of the Pesticide Chlorpyrifos from Skin by Standard Handwash Techniques. Richard A. Fenske and Chensheng Lu. Am. Ind. Hyg. Assoc. J 55(5):425-432, 1994.

This study predates Fenske et al., 1998 described above but has a similar mass balance study design and investigated the rinse efficiency of chlorpyrifos which has lower water/alcohol solubility than captan. The volunteers' hands were rinsed with either ethanol or an isopropanol/water mixture and showed lower removal efficiency than was seen with the pesticide captan. The study does not address the impact of long term repeated contacts representative of field reentry workers.

The biggest impact appeared to be the lag (0 or 1 hour) between hand exposure and hand rinse collection. Higher efficiencies were observed when hand rinses were performed immediately after contact with the test tubes. The hands were exposed for a relatively short duration compared to worker reentry tasks conducted for more than 4 hours (Table 3-8).

Table 3-8: Summary Data For Chlorpyrifos Removal Using Handwash Methodology

Time (hr)	N	Test tube spike level (µg)	Transfer efficiency	Skin loading (µg/cm^2)	# washes	Removal efficiency (%)	
						Mean	Std. Dev.
ethanol							
0	12	2500	45.5	7.9	2	27.0	4.8
1	12	2500	54.7	6.2	2	31.3	6.2
Isopropanol/water							
0	12	2500	64.4	12.3	2	42.6	24.1
1	12	2500	60.8	11.1	2	22.6	9.0
0	10	250	52.9	0.97	1	21.2	7.1
0	12	25	87.6	0.13	1	23.1	7.2
0	12	2.5	92.9	0.024	1	38.5	4.8

Acephate Exposure and Decontamination of Tobacco Harvesters' Hands. Brian D. Curwin, Misty J. Hein, Wayne T. Sanderson, Marcia Nishioka and Wayne Buhler. Journal of Exposure Analysis and Environmental Epidemiology (2003) 13, 203-210.

As noted, the efficiency of hand rinses using isopropanol and ethanol were investigated in Fenske et al., 1998 and Fenske and Lu, 1994 and indicated a wide range of hand rinse efficiencies (23 – 90.7%). Curwin and colleagues studied the effectiveness of soap and water washes for removing pesticide residues from field workers' hands after harvesting tobacco treated with the water soluble pesticide acephate. Hand wipes as described in Geno et al., 1996) were used to sample the hands. Briefly, the method relies on the use of SofWick® dressing sponges moistened with 10 ml of 100% isopropanol. First, the entire hand is wiped then, with a second sponge each finger is wiped separately. Both sponges are combined to represent one sample. The samples were collected at 4 times during the work day; day 1 morning, day 1 afternoon, day 2 morning, day 2 afternoon. The exposure duration was approximately 4 hours. The fact that the hands were reportedly heavily covered with plant residue and soil removed any doubt among the investigators that

potential handedness (left-handedness versus right-handedness) was a factor. Therefore, the investigators modified the sampling scheme to account for "inter-worker variability by randomizing the workers to have either (i) their right hand samples prewash and then their left hand sampled postwash, or (ii) their left hand sampled prewash and then their right hand sampled postwash. The workers were instructed to wash their hands as they normally would." Wipes were also collected from leaf surfaces using the aforementioned sponges and a template (clamped to leaves) yielding a surface area of 200 cm^2. Upper and lower leaf surfaces were wiped for a combined surface area of 400 cm^2. Hand rinses were converted from µg/sample to µg/cm^2 by assuming a single hand surface area of 420 cm^2. The authors reported that hand washing reduced the acephate residues on the hands by 96%. The high efficiency of the hand wash was thought to be due to the workers washing their hands shortly after working and the water soluble nature of acephate. Summary statistics are presented in Table 3-9.

Table 3-9: Summary Data For Acephate Removal From Tobacco Harvester Hands

Field	Sample order	N	GM (ng/cm^2)	GSD	Range (ng/cm^2)
1	Prewash	18	6.6	4.0	0.6-103
	Postwash	18	0.2	3.2	0.04-1.2
2	Prewash	12	12.6	4.2	0.5-64.7
	Postwash	12	0.7	2.8	0.07-2.4
3	Prewash	6	8.1	5.3	0.4-36.6
	Postwash	6	0.4	1.6	0.2-0.68
4	Prewash	6	59.0	2.3	32.1-257
	Postwash	6	2.3	1.3	1.7-3.7
5	Prewash	6	6.5	10.3	0.07-46.5
	Postwash	6	0.1	1.7	0.06-02

In a similar study evaluating nicotine exposure (green tobacco illness) for tobacco harvesters, 96% of the nicotine was removed from the harvesters hands after washing with soap and water (Curwin et al., 2005).

Hand Wash and Manual Skin Wipes. Derk H. Brouwer, Mark F. Boeniger and Joop van Hemmen. Am. Occup. Hyg. Vol. 44 No. 7, pp. 501-510. 2000.

In this paper, a discussion of hand wash efficiency results based on different hand rinsing procedures for various pesticides (one non-pesticide) is presented. In Table 3-10, results of hand rinse efficiency studies conducted by Fenske and investigators in The Netherlands are shown. Variables such as residence time and hand loading (µg) are presented. The two Fenske studies have been discussed previously.

In the studies performed in The Netherlands (Brouwer and Marquart) the investigators relied on direct spiking of residues onto the hands whereas Fenske and colleagues relied on volunteers contacting spiked test tubes. The rinse efficiency results indicate a range of 22 to 96% with a median of 73%.

Table 3-10: Comparison Of Hand Wash Efficiency Studies						
Pesticide	Method	Loading (µg)	Wash efficiency (%) Mean	Std (%)	N	Reference
Captan	B	1500[b] 15000[b]	94 63	11 13	4 4	Brouwer *et al.*, 2000[a]
	B	5620[c] (1 h) 5250[c] (0 h)	68 78	5 14	6 3	Fenske *et al.*, 1998
Carbendazim	B	500[b] 5000[b]	94 59	8 13	3 3	Brouwer *et al.*, 2000[a]
Chlorothalonil	A	4400[b]	74	11	4	Brouwer *et al.*, 2000[a]
Chlorpyrifos	B B C	1700[c] (0 h) 1570 (1 h) 1100 (1 h)	43 23 27	24 9 5	6 6 6	Fenske and Lu, 1994
Mancozeb	A B D	2275[b] 2275[b] 5000; 15,000; 30,000[b]	81 66 86	10 5 5	4 5 12	Brouwer *et al.* 2000[a], 1992 Marquart *et al.*, 2002
Methiocarb	D	500[b] 1800[b] 7000[b]	77 84 84	3 3 6	4 4 4	Brouwer *et al.*, 2000[a]
Methomyl	D	300[b] 1490[b]	71 70	3 4	4 4	Brouwer *et al.*, 2000[a]
Prochloraz	B	500[b] 5000[b]	95 96	14 6	4 4	Brouwer *et al.*, 2000[a]
Propoxur	D	175[b] 575[b] 1400[b]	66 71 72	8 13 10	4 4 4	Brouwer *et al.*, 2000[a,b]
		500, 5000, 7500[b]	46	3	12	Marquart *et al.*, 2002
Vinclozolin	D	59.2 227 384[b]	81	5	3	Brouwer *et al.*, 2000[a,b]

[a] (A) 2-propanol rinsing, 2 hands 500 ml, PE-bag; (B) 2-propanol rinsing, 1 hand 250 ml, PE-bag; (C) ethanol rinsing, 1 hand 250 ml, PE-bag; (D) water-soap rinsing, 2 hands, tap water; N= number of test subjects per level of loading.
[b] Direct repeated spiking of 0.5 ml on the hands.
[c] Mass balance approach from transfer of a contaminated tube.

In the paper, existing studies relying on wipe methods were also considered. Generally, it was determined that wipe sampling is less efficient than the described hand rinse methods.

Comparison of Solvents for Removing Pesticides from Skin Using an *In Vitro* Porcine Model. Jerry Campbell, Mary Alice Smith, Mark A. Eiteman, Phillip L. Williams, Mark F. Boeniger. AIHAJ (61) January/February 2000, Ms. #906.

The removal efficiency of four wash solutions were compared in a trial using dorsal porcine skin fortified with four different pesticides at varying concentrations (0.5, 2.0 and 8.0 $\mu g/cm^2$). The pesticides were selected on the basis of their solubility in water: glyphosate (12,000 mg/L), alachlor (240 mg/L), methyl parathion (55 mg/L) and trifluralin (0.3 mg/L). The wash solutions consisted of 1-propanol, 10% soap and water (Ivory® Liquid), polyethylene glycol (PEG) and a mixture of surfactants in propylene glycol (D-TAM). Wipe samples were collected after the pesticide had dried on the skin. The residence time was 90 minutes (Table 3-11).

The authors concluded that the amount of pesticide applied to the skin (not shown in the following table) had a significant effect on the amount of pesticide recovered from the skin (wash efficiency). In general higher efficiencies were seen at the higher pesticide concentrations (2.0 and 8.0 $\mu g/cm^2$). According to the authors, "The overall recovery of the four pesticides with 1-propanol was significantly higher ($p < 0.05$) than recoveries with all other solvents. Soap and water recovered significantly more ($p < 0.05$) of the four pesticides than either PEG or D-TAM. For glyphosate, alachlor, and methyl parathion, there were no significant differences ($p < 0.05$) among wipe recoveries of the four solvents. On average, the greatest amount of trifluralin was recovered using 1-propanol moistened wipes. However, the recovery of trifluralin using 1-propanol was not significantly different ($p < 0.05$) than recoveries using soap and water."

Table 3-11: Removal Efficiency For Various Solvents Based On Porcine Model

Pesticide	Wash solution	Wash efficiency (%) Mean	Std
Alachlor	1-propanol	57	13
	PEG	55	8
	Soap and water	52	12
	D-TAM	51	6
Glyphosate	1-propanol	44	12
	PEG	41	11
	Soap and water	49	14
	D-TAM	36	9
Methyl parathion	1-propanol	57	17
	PEG	41	18
	Soap and water	50	19
	D-TAM	41	15
Trifluralin	1-propanol	69	10
	PEG	51	15
	Soap and water	56	13
	D-TAM	53	14

Table 3-11: Removal Efficiency For Various Solvents Based On Porcine Model			
Pesticide	Wash solution	Wash efficiency (%) Mean	Std
Alachlor	1-propanol	57	13
Overall recovery	1-propanol	57	16
	PEG	47	14
	Soap and water	52	14
	D-TAM	45	13

The 90 minute residence time was selected for two reasons: 1) because of the reported binding or diffusion of glyphosate (Wester et al., 1991) into the stratum corneum within 30 to 60 minutes and 2) because 90 minutes appeared to be a reasonable amount of time before exposure study investigators could collect hand rinse samples from volunteers. The authors also recognize the higher recoveries using hand rinses described in Geno et al., 1996, (~90%) were likely due to wiping the hands immediately after loading, that is before the substances could be bound to the skin. The authors also recognized that there is a potential for alcohol based solvents to increase the absorptive dose of compounds by removing surface lipids from the skin. For this reason, some investigators have avoided using alcohol based rinses.

Methods of Assessing Dermal Absorption with Emphasis on Uptake from Contaminated Vegetation. P.R. Durkin, L. Rubin, J. Withey, W. Meyland. Toxicology and Industrial Health, Vol. 11, No. 1, 1995 pp. 63-79.

As seen in the previous study discussions and stated in Durkin et al., 1995, "the duration of contact between the skin and the contaminant, as well as the interval between the exposure event and washing, are important parameters that affect the uptake of the contaminant." In an exercise to develop a model that predicts uptake from spills and contaminated vegetation, the authors identify a variety of factors impacting skin contamination. Examples include volatilization, washing, desquamation (shedding of skin) or contact with other surfaces.

A number of the earlier agricultural reentry studies reported in the literature were evaluated in this paper. These studies covered a wide variety of reentry activities and pesticides and are shown in Table 3-12.

Table 3-12: Activities Addressed By Durkin et al				
Chemical	Vegetation type	Activity	Duration of exposure (h)	References
Abamectin	Roses	Cutting and packing	1-1.5	Brouwer *et al*., 1992
Azodrin	Cotton	Inspect and sample	2-4	Ware *et al*., 1975
Benomyl	Strawberries	Picking	8	Zweig *et al*., 1983
Burpirimate	Roses	Cutting	-1	Brouwer *et al*.,

Table 3-12: Activities Addressed By Durkin et al				
Chemical	Vegetation type	Activity	Duration of exposure (h)	References
				1992
Captan	Strawberries	Picking and weeding	8	Zweig *et al*., 1985
Carbaryl		Picking	4	
Chlorobenzilate	Oranges	Picking	8	Nigg *et al*., 1984 Stamper *et al*., 1986
Dodemorph	Roses	Bundling	-1-1.5	Brouwer *et al*., 1992
Azinphos-methyl	Peaches	Picking	2.5	Popendorf *et al*., 1979
Methiocarb	Blueberries	Picking	8	Zweig *et al*., 1985
Methyl parathion	Cotton	Inspect and sample	2-4	Ware *et al*., 1973,1974,1975
Methyl paraoxon			0.5-4	
Parathion				
Paraoxon				
Vinclozolin	Strawberries	Picking	4	Zweig *et al*., 1985
Zolone	Peaches	Picking	~2.5	Popendorf *et al*., 1979.

Recognizing the differences in study designs among the above referenced studies (e.g., placement of patches inside or outside of clothing), the authors focused on the hand measurements collected either as solvent washes or gloves. The hand measurements were converted from µg/hr to µg/(cm^2 × hr) by using a surface area of the 840 cm^2 (both hands). These hand conversions were then plotted on a log scale with their corresponding dislodgeable foliar residue (DFR) measurements (µg/cm^2). The transfer rate (TR) relationship to DFR was expressed as:

$$\text{Log TR} = 1.09 \log \text{DFR} + 0.05.$$

The reported correlation coefficient was 0.78 with significance at $p < 0.00001$. The authors assert that the "equation indicates that the transfer rate, expressed as µg/(cm^2 × hr), is approximately equal to the DFR expressed as µg/cm^2…and that the transfer rate from the vegetation to the skin surface appears to be solely dependent upon, and directly related to, the DFR on the vegetation."

The concept of equilibrium being established between hands and treated/contaminated surfaces is most likely due to repeated contacts. This phenomenon has been considered and evaluated in the context of industrial settings (Brouwer, Kroses, and van Hemmen,

1999) as Brouwer and colleagues explored the impact of repeated hand contacts for modeling dermal exposure to industrial workplace contaminants. Many agricultural reentry tasks also involve repeated contact with treated foliage. Thus, the impact of hand loading and its potential for hand concentrations ($\mu g/cm^2$) to come into equilibrium with treated surface concentration (DFR's - $\mu g/cm^2$) can impact the interpretation of worker dermal exposure studies. In particular, when using dermal exposure studies that have been conducted for short durations and using them to extrapolate longer periods of exposure. The length of dermal exposure monitoring periods and its impact on the development of dermal exposure models (transfer coefficients cm^2/hr) was explored by California Department of Pesticide Regulation (then, the California Department of Food and Agriculture).

Long and Short Intervals of Dermal Exposure of Peach Harvesters to Foliar Azinphos-Methyl Residues. Janet R. Spencer, James R. Sanborn, Bernardo Z. Hernandez, Frank A. Schneider and Sheila S. Margetich. California Department of Food and Agriculture, HS-1578. April 22, 1991.

After considering earlier reentry studies (e.g., Fenske et al., 1989; Davis et al., 1983), Spencer and colleagues found that these data suggested that pesticides may not "transfer to a worker in a linear manner with time or production, but may load on the sampling media during the initial hours." They hypothesized that: "if monitoring media exhibit uneven acquisition or loading effects, then extrapolating from residues transferred over a one or two-hour exposure to an eight–hour exposure may over-estimated dermal exposure." Furthermore, "monitoring a worker for eight hours and assuming the resultant dermal residues were transferred linearly over the workday may underestimate the residues available for dermal absorption during the early portion of the day." This study was also reported in Toxicology Letters under the same title (78 (1995) 17-24).

In the study, two groups of peach harvesters were evaluated: 29 harvesters in Sutter County and 12 in Stanislaus County, California (Table 3-13, Sutter County results). Both orchards were treated with azinphos-methyl. The orchard in Sutter County was treated at a rate of 1.5 lb ai/acre, 50 days before reentry. The Stanislaus County orchard was treated with 0.75 lb ai/acre, 74 days before reentry. The study design included groups of harvesters working different durations before hand rinses were performed and dosimetry patches removed. On the first day, dosimeters and hand wipes were evaluated for 7 workers after 1.5 hours, 3 hours, and 5 hours, and 8 workers at 7 hours (entire work day). On the second day, workers hand wipes and dosimeters were evaluated after 2, 4 and 5.5 hours.

Table 3-13: Summary Of AZM Exposures In Sutter County Workers For Different Durations And Days After Treatment				
		mg Azinphos-methyl + Oxon/Interval		
N	Interval:	Outer dosimeter	Inner dosimeter	Hands
First Day				
7	1.5	13.3 ± 2.9	5.6 ± 0.5	1.4 ± 0.6
7	3	20.8 ± 0.5	7.1 ± 1.7	1.7 ± 0.6
7	5	20.4 ± 7.2	13.9 ± 3.8	2.1 ± 0.6

Table 3-13: Summary Of AZM Exposures In Sutter County Workers For Different Durations And Days After Treatment				
		mg Azinphos-methyl + Oxon/Interval		
N	Interval:	Outer dosimeter	Inner dosimeter	Hands
8	7	21.5 ± 9.7	12.5 ± 2.5	3.5 ± 1.5
Second Day				
7	2	13.1 ± 2.4	6.2 ± 7.0	2.3 ± 7.3
7	4	16.0 ± 3.0	6.8 ± 1.1	1.8 ± 6.0
7	5.5	17.1 ± 7.1	10.6 ± 3.2	1.5 ± 8.2

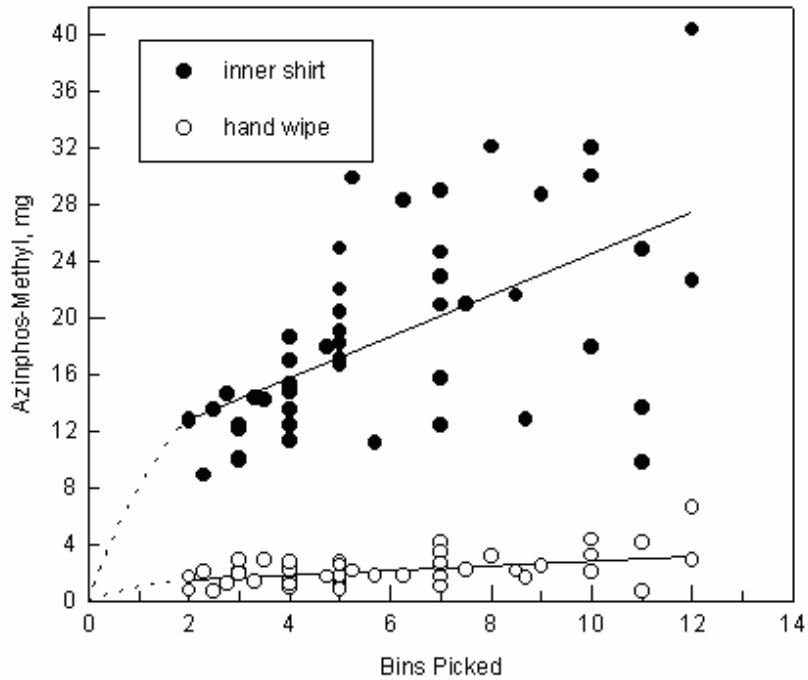
The authors suggest that "equilibrium in the rate of residue acquisition over time would be indicated by equal means for each of the four monitoring intervals. The mean for the first interval, 1.5-2 hours, showed a significantly higher (student's t-test, $p<0.01$) dermal exposure per bin (2.7 mg) than for any of the succeeding intervals. There was no difference among the means for the last three intervals. This 1.5 fold higher exposure for a two hour interval compared to longer intervals indicates that sampling media may have a higher affinity for azm residues early in the exposure (loading) period and may require up to three hours to reach equilibrium. It appears that a sampling interval of three hours would give a dermal exposure that could be extrapolated to longer time intervals without being skewed by the effects of the residue loading seen in the first two hours.

Conservatism in Pesticide Exposure Assessment. John H. Ross, Michael H. Dong, and Robert I. Krieger, 2000. Regulatory Toxicology and Pharmacology 31: 53-58.

Ross and colleagues also considered the work of Spencer et al. in developing Figure 3-7 that shows initial loading and the establishment of equilibrium regardless of a workers performance. By citing Spencer, they suggest that estimates for harvesters could be overestimated by 60% or more if estimates were made using the data from studies conducted for periods of less than 3 hours exposure.

In Figure 3-7 it appears that hand exposures were similar regardless of numbers of bins filled. Perhaps the figure is also illustrative of the residue concentration on peach harvester's hands coming into a steady state with the environment (foliar/fruit surface residues). The dotted lines drawn from the two hour monitoring period to the zero intercept indicate the period of dosimeter loading considered by Fenske and others in the proceeding study synopses.

Figure 3-7. Dermal Monitoring of Azinphos-Methyl Residents vs. Daily Peach Harvest Production (adapted from *Spencer et al*. 1995)



The study synopses presented in this section highlighted factors that can impact the results of worker exposure studies relying on hand rinses. They are as follows:

> Physical chemical properties (solubility, octanol/water partition coefficient ($K_{o/w}$));
> Residence time on the skin before rinsing;
> Type of solvent rinse (e.g., alcohol or soap and water);
> Skin concentration ($\mu g/cm^2$);
> Duration of exposure/monitoring period (hours); and
> The nature of the residues on the hands *[Note: pesticide handlers (applicators and mixer/loaders) are exposed primarily to the pesticide (dilute or concentrate) while reentry workers are exposed to a mixture of pesticide residues, soil, plant materials and sweat.]*

The mass balance studies performed by Fenske and colleagues involving test tubes allowed for potential comparisons of hand rinse efficiency based on a chemical's $K_{o/w}$. Curwin noted that a pesticide's water solubility may have an impact on rinse removal efficiency. Campbell and colleagues looked at the efficiency of the various types of rinse mixtures available to investigators and found minor differences based on the type of rinse used and that skin concentration appeared to be more critical. That is the higher the concentration, the higher the rinse efficiency. Brouwer focused largely on the Fenske data (test tubes) and studies in which hands were spiked with dilute spray. In those studies, concentration did not appear to play as large a role (e.g., propoxur). In general rinse efficiencies were high for all chemicals regardless of concentration and/or physical

chemical properties. The exception appears to be the Fenske chlorpyrifos data which represents dried concentrates rather than dilute sprays. All of these studies appear to have been conducted for short durations (less than three hours).

The skin concentration may be influenced by the length of the exposure study used to model worker exposure. The impact of a chemical binding to the skin at initial loading may be mitigated by longer exposure durations as the skin surfaces come into equilibrium with the surface residues after repeated contacts. Although limited in scope, Fenske saw less of a difference between the performance of gloves and rinses at longer monitoring periods and the potential for a steady state relationship with hands and treated surfaces in Durkin, Spencer and Ross. In more recent studies, exposure duration tends to be longer (~ 4 to 6 hours) than studies performed in the 80s and early 90s.

Curwin's team observed the highest efficiency overall which may have been impacted by study duration, the nature of the residues (soil/plant material/residue matrix), immediate washing after the exposure period and the high water solubility of acephate.

The Agency is considering adjusting dermal exposure measurements to account for any potential residue losses due to incomplete collection using the hand rinse method. The AHETF asserts that adjustments are not required based on their comparison of exposures made using passive dosimetry and biological monitoring. However, the Agency believes it is a prudent to consider such an adjustment when developing a generic database for assessing a wide variety of pesticides. For the AHETF database, the Agency believes this minor adjustment will have a small impact on the total unit exposures since all of the studies will be based on individuals wearing chemical resistant gloves. This adjustment may have a larger impact on studies addressing reentry exposure or residential applications where the use of protective gloves is not considered.

The Agency invites the panel to consider options the Agency may consider to adjust exposure estimates when relying on studies using hand rinses. Various options include:

- Consider the slope of a regression equation based in plots of hand rinse efficiency and log Ko/w. These can be based on such factors such as skin concentrations, rinse solvent, residence time. The adjustment would be identical to the adjustments commonly made for laboratory/field fortifications.
- As part of a field study design, select a surrogate chemical with a known and reliable biomarker and add any remaining residues based on what was found in the urine. (adjustments must consider the inhalation pathway as well).
- Consider additional laboratory-based hand-rinse efficiency studies to further evaluate residue retention and removal properties.
- Make no adjustments based on the conclusions of the passive dosimetry/biological monitoring comparisons.

3.2.2: Hand Method Field Performance Data

In addition to the mechanistic analysis above, an additional evaluation of hand sampling methods was conducted using the data from the PHED-based case study. In this analysis the unit exposures (µg/lb active ingredient handled) were calculated for the combined exposure of both hands. Data were then segmented based on the type of sampling media used, the nature of the contaminant being screened for in each study (i.e., solid pesticide formulation, dilute liquid sprays or liquid concentrates), and whether or not protective (e.g., chemical resistant) gloves were worn. [Note: AHETF proposed studies all require the use of protective gloves at this point. As such, the focus of this analysis is on that scenario instead of on quantifying residues deposited on bare hands which tends to lead to much higher loading rates.]

The data which were obtained for this analysis from the PHED case study were from 3 mixer/loader and 3 applicator exposure scenarios. The data represent 8 different sampling media that included trapping approaches (i.e., gloves and patches) and residue removal methods (i.e., soap solutions, acetone, and various alcohols). All of the data are included in Exhibit B which includes the hand monitoring data as prepared for this analysis. The data have been summarized as follows:

- N (all) = 513 (188 were without protective gloves – i.e., barehanded);
- N (mixer/loaders) = 402 (150 were without protective gloves);
- N (applicators) = 111 (38 were without protective gloves);
- 8 Sampling media used;
    - Removal methods (i.e., washes): ethanol, methanol, acetone, isopropanol, soapy water
    - Trapping methods: cotton gloves, Tyvek© gloves, patches
- Some wore protective (e.g., chemical resistant) gloves, others did not (i.e., they were barehanded) but the focus for this analysis will be on use of protective gloves since labels tend to require their use more routinely for good hygienic practices

The available data, segmented by sampling media and whether or not protective gloves were worn are presented below (Table 3-14 & Figure 3-8). The data itself are illustrated in Figures 3-9 and 3-10. Figure 3-9 presents total exposure estimates that have not been normalized by the pounds of active ingredient handled while Figure 3-10 presents hand unit exposure estimates which have been normalized. [Note: More information is also available in Exhibit B.]

Table 3-14: Summary Of PHED Case Study Hand Analysis Data		
Sample Media	Protective Glove Use	N
Acetone	Yes	12
Aqueous Detergent	No	16
	Yes	108
Ethanol	No	53
	Yes	75
Cotton Gloves	No	79
	Yes	69
Isopropanol	Yes	51
Methanol	No	3
	Yes	10
Patches	No	12
Tyvek Gloves	No	25
Total		513

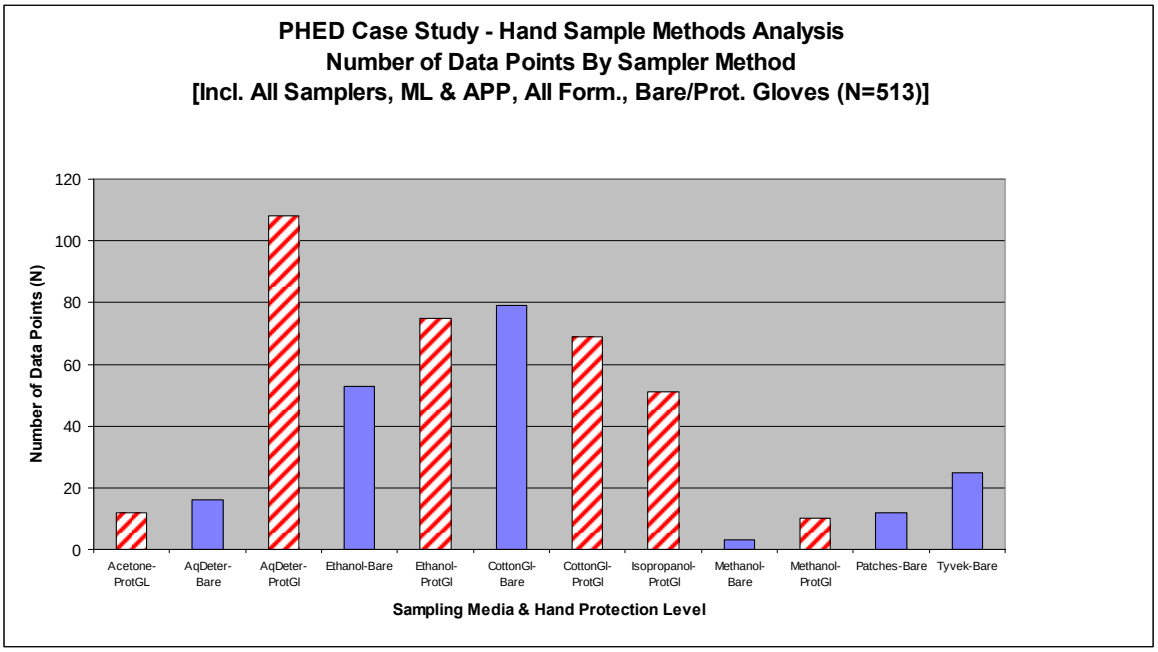


Figure 3-8

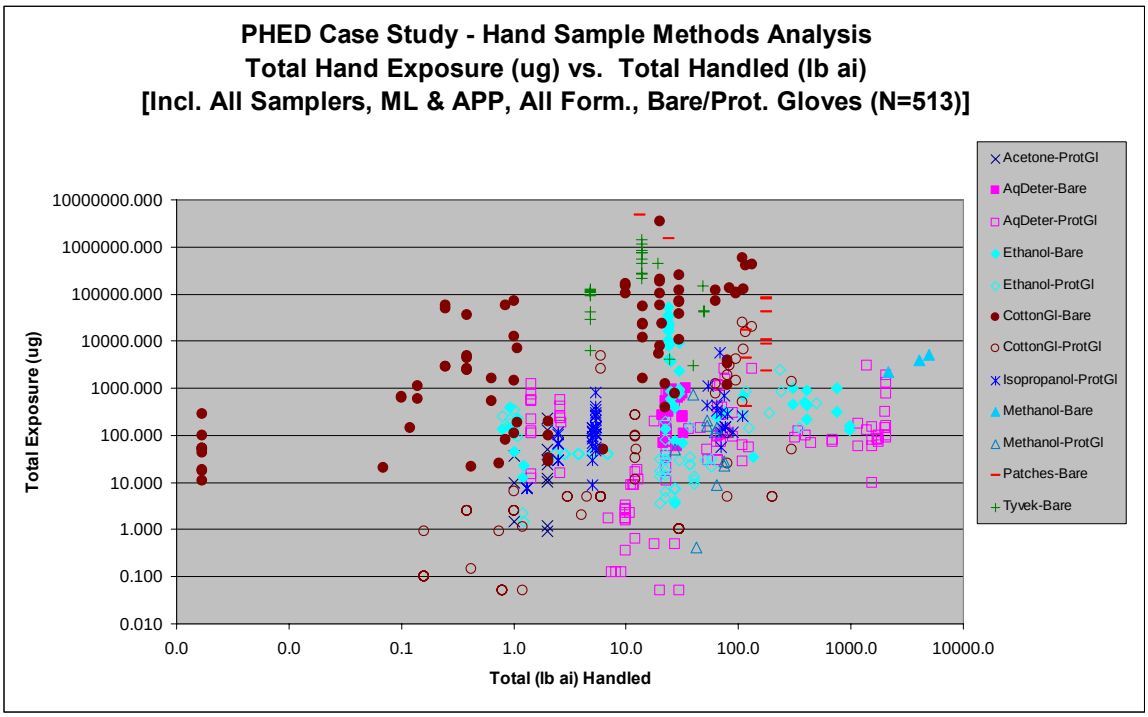


Figure 3-9

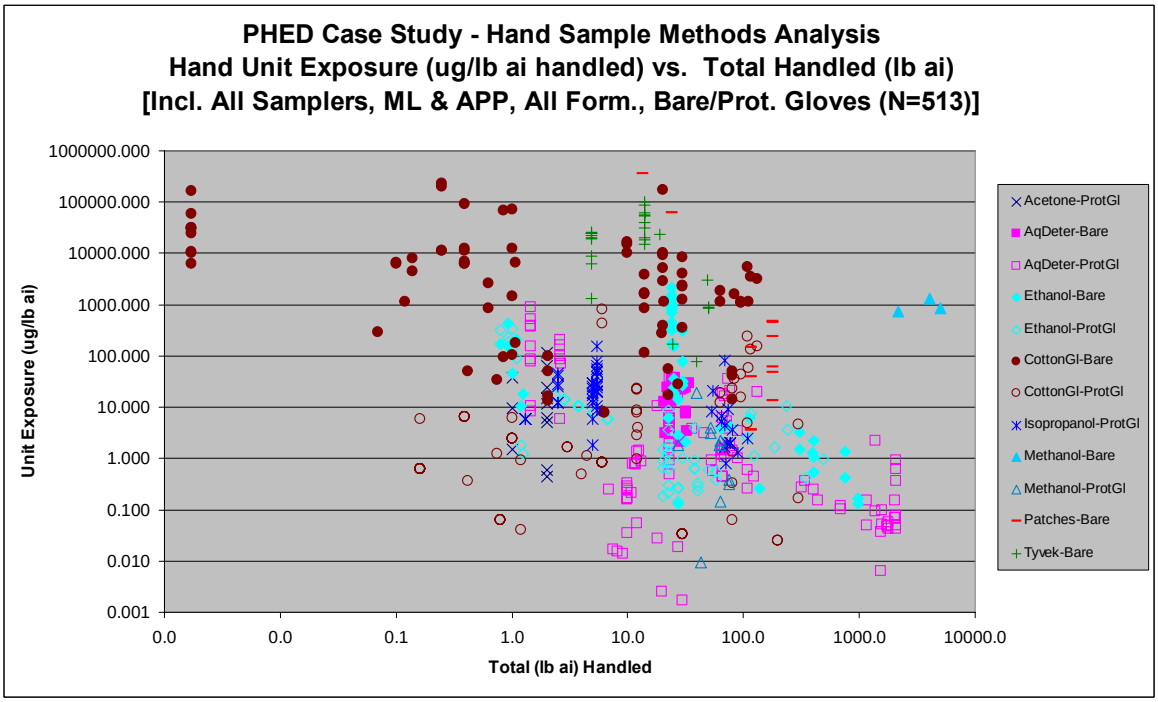


Figure 3-10

Figure 3-11 illustrates how constraining two parameters can decrease the size of the available dataset. These data represent a subset of the total data which have been constrained to represent only those results for applicators who wore protective gloves. It should be noted that these data also include only 4 of the 8 sampling media.

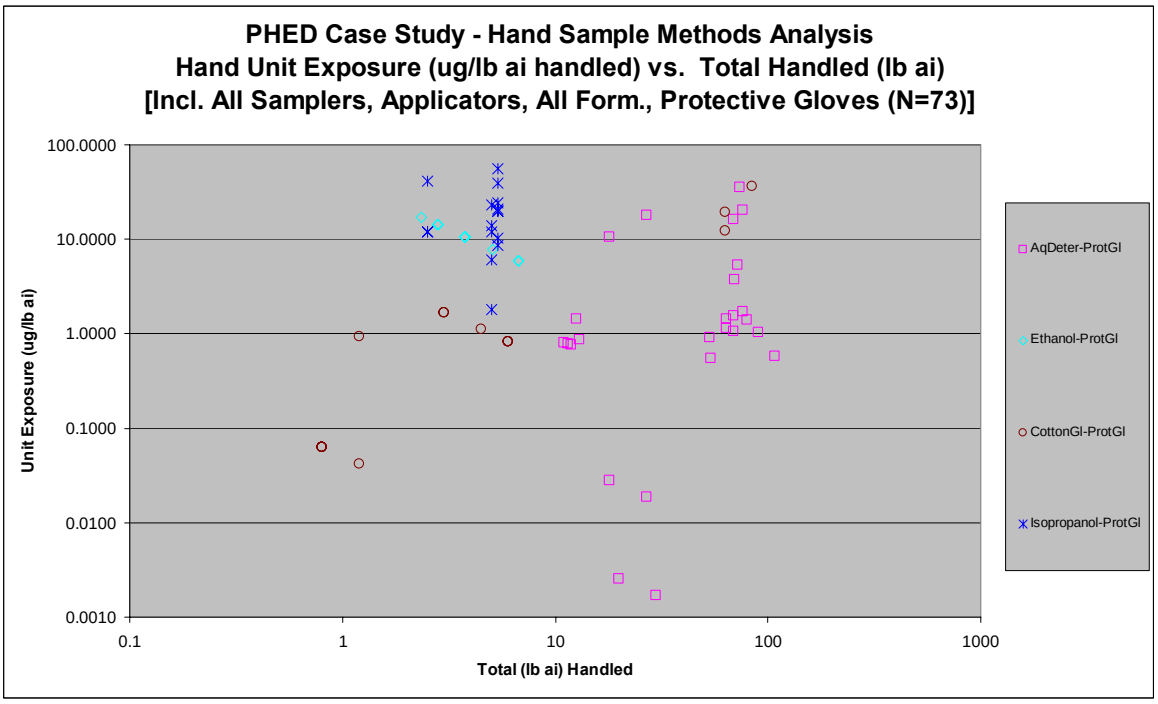


Figure 3-11

In order to supplement the literature data available for investigating the efficiency of hand wash recoveries, the Agency conducted an exploratory analysis to determine if certain types of hand wash methods consistently resulted in better recoveries (i.e. higher unit exposure values). The categories of hand wash methods were "cotton" (cotton gloves), "other" (patches & Tyvek gloves), "soap" (soap solutions), and "wash" (various alcohols and acetone). Unit exposure data were analyzed separately for various scenarios. These scenarios were specified by worker type (mixer/loader vs. applicator), formulation type (liquid vs. solid), and glove type (protective vs. none).

An example of the analyses that have been developed for evaluating the performance of varying hand monitoring methods is presented below (Figure 3-12). The analyses which have been completed for all scenarios are based on the unit exposure estimates calculated in Exhibit B.

A simple ANOVA model was fit to the unit exposure data to determine if the (logged) group means of various wash methods (within a given scenario) were significantly different. The results of the ANOVA model and related significance test are based on the standard ANOVA assumptions that 1) the data being analyzed are normally distributed, 2) the group variances are equal, and 3) samples within a level are independent.

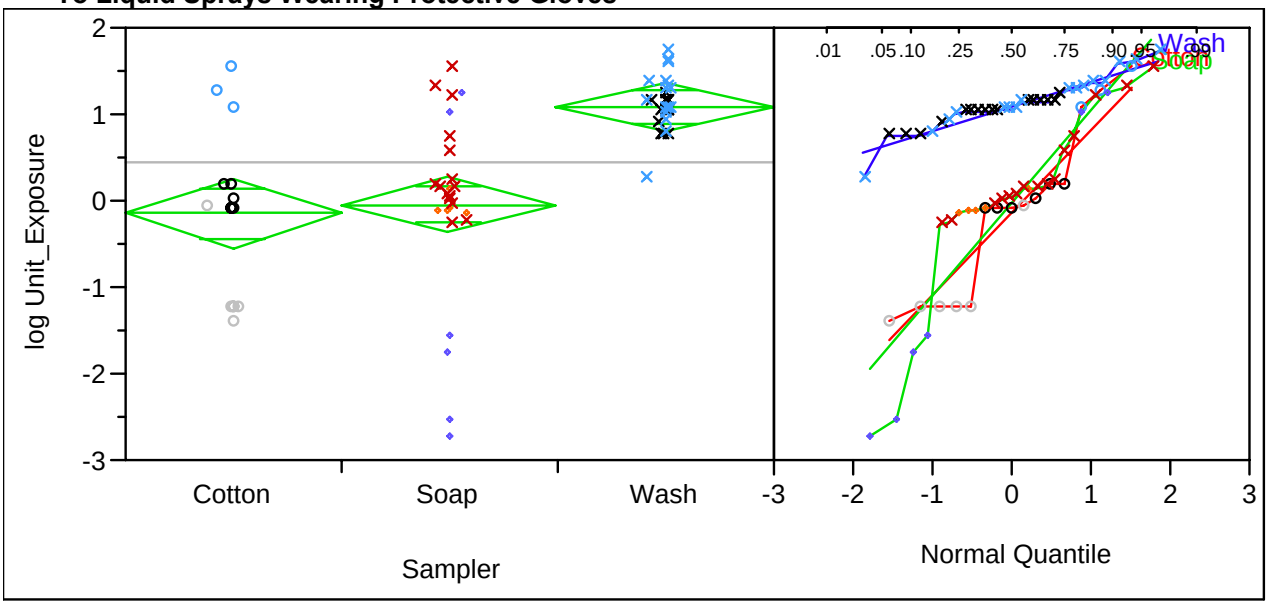
In order to address the first assumption that the data are normally distributed, the logarithms of unit exposure values were analyzed. Probability plots are a useful tool for qualitatively assessing whether or not the data are normal. In Figure 3-12, probability plots of the logs of the unit exposures for each group of hand wash methods are presented (middle graph with "Normal Quantile" on the x-axis). If the data plot along an approximately straight line then they are normally distributed (since the logs of the unit exposure values are plot, the log-normality of

the unit exposure values is being assessed). For this particular scenario, log transforming the data effectively converts the unit exposure data into normal distributions.

The second assumption that needs to be verified is the equality of the variances. The probability plots shown in Figure 3-12 can also be used to qualitatively assess if the group variances are equal. If the group variances are equal, then the slopes of lines will be approximately parallel. For this particular scenario, the "cotton" and "soap" variances appear to be equal, but the "wash" variance is decidedly different.

The third assumption is that the samples within a hand method are independent. In Figure 3-12, the scatter plots (the left graph with the green diamonds) use colored symbols to uniquely identify samples from the same study. A visual inspection of the scatter plots indicate that the samples obtained from the same study tend to "clustered" together. For example, the black, gray, and blue circles are clustered together in the cotton glove scatter plot. This clustering of observations is indicative of intra-study correlation. The intra-study correlation evidenced by the scatter plots implies that the samples are not independent and, as one might guess, unit exposure values from the same study tend to be more similar than those from different studies.

Figure 3-12: Oneway Analysis of log Unit Exposure By Sampler For Applicators Exposed To Liquid Sprays Wearing Protective Gloves



When evaluating the three underlying assumptions of a simple ANOVA analysis and the related significance testing for this exploratory analysis, it was generally found for all scenarios that (1) log transforming the unit exposure values effectively converted the data to normal distributions, (2) the variance of the unit exposure values from at least one hand wash methods was not equal to the other, and (3) the samples from within a study appear to be correlated indicating a lack of independence between the samples within a hand wash method.

Violation of the variance equality assumption and independence assumption implies that one needs to be cautious when interpreting the results of any significance tests based upon the ANOVA results. Additionally, the particular type of non-independence observed in the hand wash data informs the violation of the variance equality. The non-independence observed in the hand wash data suggests that the error structure of the data is not properly modeled by the simple ANOVA approach employed by the Agency for exploratory purposes. The more complex error component can be better modeled by more sophisticated techniques, such as nested ANOVA or mixed linear models. This improper modeling of the error structures in turn affects the modeled group variances of the hand wash methods.

Even given the violation of some basic assumptions, the Agency hoped to gain insight into the relationship of recoveries and hand wash methods using a simple ANOVA analysis and simple graphical techniques. The results from the analysis of the scenario included in this section suggest that the alcohol "wash" hand wash method results in higher unit exposure values (higher recoveries) on average. However, this is not a consistent conclusion derived from examining the unit exposure data from the other scenarios. In general, no overall conclusions, such as "alcohol and acetone washes consistently resulted in higher recoveries for all scenarios" could be drawn from the data. What was consistently observed for all scenarios was that the degree of intra-study correlation is often too large to be ignored if more refined analyses were to be completed in the future. Another consistent, yet preliminary observation of the data was that the study-to-study variation within hand wash methods was generally greater than the method-to-method variation. This observation implies that even with a more sophisticated analysis that appropriately models the nested error structure, much larger differences in unit exposure values between hand wash methods would have to be observed to conclude that significant differences exist between recoveries. Overall, then, a review of the literature as well as a review of available experimental and observational PHED hand wash data suggest that no consistent or reliable conclusions can be reached regarding the efficiency of hand wash methods.

3.3: Summary of Methods Analysis

Passive dosimetry and biomonitoring techniques have been used extensively to estimate exposure to pesticides. Each technique has advantages and disadvantages, and the choice of which to use is determined by how the resulting data will be used. Several studies incorporating both methods concurrently have been reviewed in this document. Concurrent passive dosimetry and biomonitoring studies often give similar or at least correlated results. Likewise, retrospective analyses give similar results. In some cases, insufficient information is available to adequately assess the relationship between results obtained using the two types of techniques.

Exposure monitoring studies typically yield highly variable results. The high variability is inherent in studies conducted in the field, where conditions are less controlled and the natural differences between workers are captured in the results. Because of this variability, ratios in study means that differ by less than an order of magnitude, for example, may be considered to be fairly small. Ratios in mean absorbed doses estimated from passive dosimetry and biomonitoring for the most-studies active ingredient, chlorpyrifos, are within 3-fold of one another for nearly all handler and reentry studies reviewed. As passive dosimetry and biomonitoring represent very diverse approaches, these results tend to support both as providing reasonably consistent estimates of exposure. Given this premise, it is unlikely that dermal absorption during sample collection or breakthrough through dermal dosimeters likely contributes to a negative bias in any

pragmatic application of the results in Agency assessments. The Agency acknowledges that certainly from a theoretical and physical perspective that these events likely take place. One adjustment that could be made to address the possibility of breakthrough under varied field conditions, especially when developing data for a large generic database such as that proposed by the AHETF, would be to select pesticide active ingredients that have well characterized pharmacokinetics. This would enable biological samples to be collected to characterize sampling method performance.

Hand exposure monitoring techniques have also been extensively evaluated as described above. At this point, both the mechanistic and field performance analyses that have been most studied appear to be equivocal with regard to a bias pertaining to the selection of a specific method. This should also be considered with the notion that there are a number of uncertainties associated with any selection related to hand monitoring methodology.

4. Unit Exposure & Applicability Across Anticipated Working Conditions

The Agency's use of unit exposures, defined previously in this document as exposure normalized by the amount of active ingredient handled is based historically upon the broad assertion that levels of exposure are most dependent upon the physical parameters of handling pesticides, not its chemical properties (Severn, 1982; Hackathorn and Eberhart, 1985; Reinart and Severn, 1985; Honeycutt, 1985; USEPA, 1986a). More specifically, Reinart and Severn (1985), said, "…it is our experience that the proper (and logical) conversion factors are amounts of pesticide applied for applicators and the quantity of chemical handled by mixer/loaders. Unfortunately, these data are not always readily retrievable…In such instances, other factors (e.g., tank concentration for applicators or time involved in mixing-loading) must be used."

It is the Agency's intention in this section to examine this claim in terms of the specific relationship assumed for our unit exposure metric: proportionality between exposure and amount of active ingredient handled. For brevity, the amount of active ingredient handled is referred to "AaiH" in this section.

4.1 Proportionality between Exposure and Amount Active Ingredient Handled

The unit exposure, defined as exposure per AaiH, is based on the assumption that the two variables are proportional. That is, if one doubles the amount of pesticide they handled or applied, the resultant exposure will be doubled as well. As described above, this relationship has historically been the principle assumption since the mid-1980s underlying the use of exposure data in the Agency's pesticide handler exposure assessments. This metric is not only practical in terms of risk assessment methodology (discussed in Section 2); it is also practical in terms of regulatory efforts (e.g., limiting, in various ways, the amount of pesticide an applicator can handle).

This section of the document discusses the Agency's exploration of the current PHED data with respect to the relationship between AaiH and exposure. This is done for each of the six case study scenarios described earlier (note: these are numbered, as in previous sections, to correspond to the *PHED Surrogate Exposure Guide* (USEPA, 1998b)):

- Scenario #1: Open Mixing/Loading Dry flowables
- Scenario #2: Open Loading Granules
- Scenario #3: Open Mixing/Loading Liquids
- Scenario #11: Open Air Blast Applications
- Scenario #12: Closed-cab Airblast Applications
- Scenario #15: Open-cab Solid Broadcast Spreader Applications

Importantly, the AHETF is proposing as part of its future studies to investigate proportionality as a secondary objective of its study protocols. AHETF proposes to incorporate more advanced and appropriate statistical concepts and designs in their

analyses to distinguish between complete proportionality and complete independence of exposure and AaiH. Additional information on this approach is provided in the AHETF document entitled *Procedures for Determining the Required Number of Clusters and Monitoring Units per Cluster to Achieve Benchmark Adequacy* (AHETF, 2006b).

Because this relationship is referenced both historically and in proposed future studies, it is the Agency's intention to examine, using our current database, the extent to which this relationship is demonstrated and applicable across the anticipated pesticide handler working conditions. The Agency has presented both a discussion of the methodology used to do so using dermal exposure and findings regarding proportionality for the six PHED scenarios in our case study. Though not considered for the purposes of this exercise, the Agency believes that the methodology presented herein would apply, since proportionality between exposure and AaiH is also assumed, for inhalation exposure.

4.1.1 Proportionality Investigation using Dermal Exposure

Current occupational exposure assessment strategies use PHED data on a body part-by-body part basis (discussed in Section 2). This is based on the premise that data from various body parts in different studies can be averaged and then combined to yield a unit exposure that is the sum of different body parts.[1] Ideally a data set in which total body dermal exposure was measured would be used to describe the relationship between dermal exposure and AaiH. Because not all records in PHED measured total dermal exposure the Agency utilized a method similar to that developed during a Probabilistic Worker Exposure Assessment Workshop sponsored by the International Life Sciences Institute (ILSI) Risk Science Institute (RSI) and described in *Investigating Probabilistic Methods to Assess Mixer/Loader Exposure to Pesticides* (ILSI, 2003)). The authors of this document recognized that the studies within PHED did not follow the same design in terms of location and number of patch dosimeters used and many records were therefore considered incomplete in terms of representing total exposure. As a result, the authors found it necessary to subset the PHED records and use only those records which met certain minimum criteria for body parts in order to "ensure that the body parts measured were consistent across records and that they were the parts likely to be most exposed in the scenario queried." In other words, the ILSI authors recognized the limitations of PHED and determined that it was most appropriate to use only those records which, in their opinion, were sufficiently complete in terms of critical body parts such that total dermal exposures could be reasonably estimated. Following this methodology, the current analysis of the relationship between exposure and AaiH use only PHED records using WBDs and records using patch dosimetry that have at least the minimum-critical body parts determined necessary for the specific scenario of interest[2].

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[1] For example, if study A measured exposure to the hands only and study B measured exposure to the body only, the records for study A and B could be averaged individually and then added together to yield a central tendency unit exposure estimate for the hands and the body.

[2] While it may seem incorrect or illogical to combine records that correctly measure the body component of dermal exposure (e.g., WBD) with those that represent only certain parts of an individual's body (e.g., patch dosimetry), this methodology was considered appropriate considering the data limitations. Without this

4.1.2 Constructing Proportionality Plots

The model the Agency assumes for its unit exposures in pesticide handler exposure assessments is a power relationship:

$E = AW^x$

Where: E = exposure (measured in micrograms)
A = constant
W = AaiH (measured in pounds active ingredient handled)
X = 1

The Agency used ordinary least squares (OLS) regression techniques in order to evaluate the resulting slope of the regression line for the log conversion equation of this model:

log (E) = log (A) + x(log W) with intercept *log (A)* and slope *x*.

If the relationship between exposure and AaiH is directly proportional, then the resultant slope (*x*) should be 1. A non-zero slope other than 1 would indicate an alternative power relationship (e.g., $E = AW^{0.6}$) and a slope of 0 would suggest independence between the variables.

We recognize that there are a number of statistical limitations and caveats to the use of OLS regression with the PHED data – not the least of which is the apparent clustering of data points by study and their lack of independence which may severely compromise some of the statistical tests performed here. Nevertheless, this exercise and the resultant plots are believed to be valuable exploratory tools which graphically illustrate the relationship between exposure and AaiH[3].

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methodology the Agency would have had to plot separately studies utilizing patch dosimetry and studies using WBD, thus minimizing the amount of data for this exercise. Additionally, the Agency has, for all scenarios within the case study, compared results for total dermal exposure (reported in micrograms) with total dermal exposure results normalized for the total body part surface area represented by the corresponding exposure measurements (reported as micrograms per square centimeter) to demonstrate how the minimum-critical body part methodology is adequate for our purposes. The open mixing/loading dry flowables and granules scenarios are used to show this methodology graphically by indicating what body parts are represented by each data point (see "LOG-LOG REGRESSION SUMMARY" tabs in Exhibit C). This comparison resulted in no discernible difference and provides evidence for the notion that by declaring and using the minimum-critical body parts we have captured the majority of exposure.

[3] More appropriate statistical methods for examining the relationship between these two quantities would involved hierarchical linear modeling (aka mixed models) approaches or robust regression techniques which specifically account for the clustering (non-independence) of exposure measurements within studies. When such clustering by study is present, the observations within the study (cluster) may not be treated as independent, but the studies (clusters) themselves are independent. Note that the AHETF recognizes these statistical issues and is proposing more appropriate statistical techniques to be used with its data.

Plots illustrating the Agency's examination of proportionality between exposure and AaiH were generated using the following subsetting criteria (where applicable) for the case study scenarios:

- PHED data grade (e.g., A, B grade only, A, B, C grades, all grades, etc.);
- Exposure location
    - Outer Dosimetry
        - Exposure to bare hands
        - Exposure to the head without protective head gear
        - Exposure to the body without clothing or PPE (i.e., representing "bare skin")
    - Inner Dosimetry
        - Exposure to gloved hands
        - Exposure to the head with protective head gear
        - Exposure to the body underneath a single layer of clothing or PPE

The purpose of this data formatting and presentation was to maximize the Agency's ability to investigate proportionality between exposure and AaiH using PHED. The presentation of differing data grades or outer and inner dosimetry is not meant as a recommendation for using such data sets in unit exposure determination – it was simply meant as a data optimization method for examining proportionality using our current database. However, because pesticide handlers may don differing combinations of clothing and/or PPE, the separation of the body into different regions (e.g., head, body, hands) is practical. Total dermal exposure can then be estimated depending on the "clothing" worn (e.g., exposure to the body while wearing a single layer of clothing plus hand exposure with or without gloves plus exposure to the head with or without protective head gear).

4.1.3 Results

As described previously, if the relationship between exposure and AaiH is indeed proportional, a regression of the log of exposure as a function of the log of AaiH, should result in a regression line with a slope not significantly different than 1. Alternatively, one can also see whether the slope of the regression line is significantly different than 0 (i.e., whether exposure is independent of AaiH).

Descriptions of all data and graphical representations (Figures 4.1 – 4.8) of results for two scenarios within the case study – the open mixing/loading granules and open-cab airblast applications – are provided as examples in this section. Results for all six scenarios within the case study can be seen in the Proportionality Analysis Spreadsheets provided in Exhibit C.

Descriptions and graphical representations (Figures 4.1 – 4.8) of results for two scenarios within the case study – the open mixing/loading granules and open-cab airblast applications – are provided as examples in this section. Results for all six scenarios within the case study can be seen in the Proportionality Analysis Spreadsheets provided in Exhibit C.

The log-log regression plots for each case study scenario and corresponding subsets (e.g., various body part and clothing combinations) contain:

- Individual data points of each study: represented by different colors and/or characters;
- Regression line: represented by a solid black line;
- "Slope = 1" line for comparison: represented by a dashed black line; and,
- 95% confidence intervals for the slope of the regression line: represented by dashed blue lines.

Both the characteristics and potential limitations of PHED studies (described in Table 2.7) and the statistical limitations of our methodology (discussed in Section 4.1.2) should be noted when reviewing the results and discussing any conclusions of the Agency's examination of proportionality between exposure and AaiH.

Scenario #1: Open Mixing/Loading Dry Flowables

Scenario #1 includes individuals exposed during open mixing and loading of chemicals formulated as dry flowables (e.g., water-dispersible granules). Shown in Table 4.1 below are the various subsets used to evaluate proportionality for this scenario. These include the relationship between protected hand exposure (e.g., with chemical resistant gloves) and AaiH for which there are 37 measurements with data quality grades of A through E and the relationship between total dermal exposure (hands plus body) and AaiH measured using outer dosimetry (i.e., bare skin) for which there were 25 measurements graded A through D and 23 measurements graded A through C. The minimum-critical body parts required to represent exposure to the rest of the body (RoB) are listed, as are the number of records available having concurrent hand plus RoB exposure representing total dermal exposure.

Table 4.1 Scenario #1: Open Mixing/Loading Dry Flowables
 # Records by PHED Grade, Dosimetry Location, and Body Section
[Minimum-critical Body Parts representing RoB Exposure: forearms, chest, back, thighs]

PHED Grade	Inner Dosimetry			Outer Dosimetry		
	Hands	RoB	Total Dermal	Hands	RoB	Total Dermal
A – E	37			Not plotted Only 7 records available		Not plotted No records had concurrent hand/body measurements
A – D			25			
A – C	34	38	23		21	
	See ExhibitC_I_c_ML_DF_inner.xls			See ExhibitC_I_b_ML_DF_outer.xls		

Scenario #2: Open Loading Granules

Scenario #2 includes individuals exposed during open loading of chemicals formulated as granules. Shown in Table 4.2 below are the various subsets used to evaluate proportionality for this scenario. These include the relationship between unprotected (bare) hand exposure and AaiH for which there are 10 measurements with data quality grades of D and E and the relationship between protected hand exposure (e.g.,

with chemical resistant gloves) and AaiH for which there are 67 measurements graded A through C. The minimum-critical body parts required to represent exposure to the rest of the body (RoB) are listed, as are the number of records available having concurrent hand plus RoB exposure representing total dermal exposure. Plots for these subsets are provided below as examples (Figures 4.1 – 4.5).

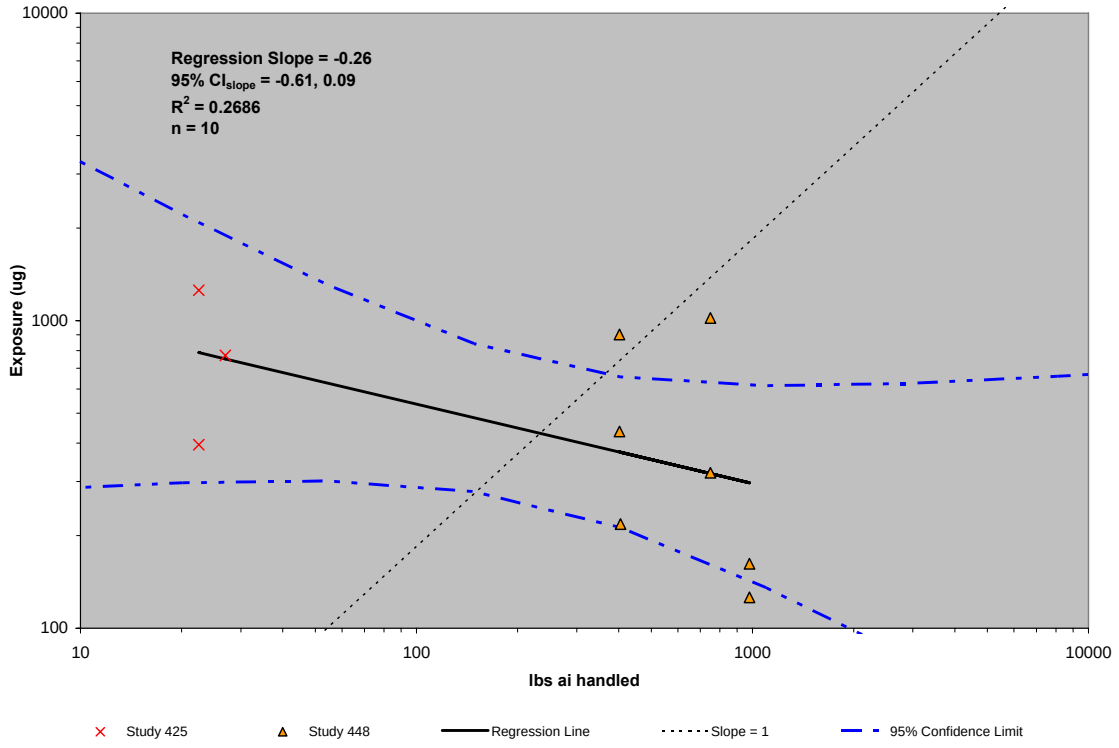
Table 4.2 Scenario #2: Open Loading Granules*
 # Records by PHED Grade, Dosimetry Location, and Body Section
[Minimum-critical Body Parts representing RoB Exposure: forearms, chest, back, thighs]

PHED Grade	Inner Dosimetry			Outer Dosimetry		
	Hands	RoB	Total Dermal	Hands	RoB	Total Dermal
D – E				10		Not plotted Only 7 records had concurrent hand/body measurements
A – C	67				33	
A – B			42			
A only		45				
	See ExhibitC_II_c_L_Gran_inner.xls			See ExhibitC_II_b_L_Gran_outer.xls		

*Study 1027 is not included in this scenario

Open Loading Granules – Bare Hand Exposure: There were 10 monitoring events, where between approximately 20 and 1000 lbs ai were handled, that had bare hand exposure measurements, all classified as either D or E grade data. Figure 4.1, below, shows that the slope of the regression line is significantly different than 1, and not significantly different than 0, suggesting that for bare hand exposure in this scenario, exposure is not proportional, and, in fact, may be independent of AaiH.

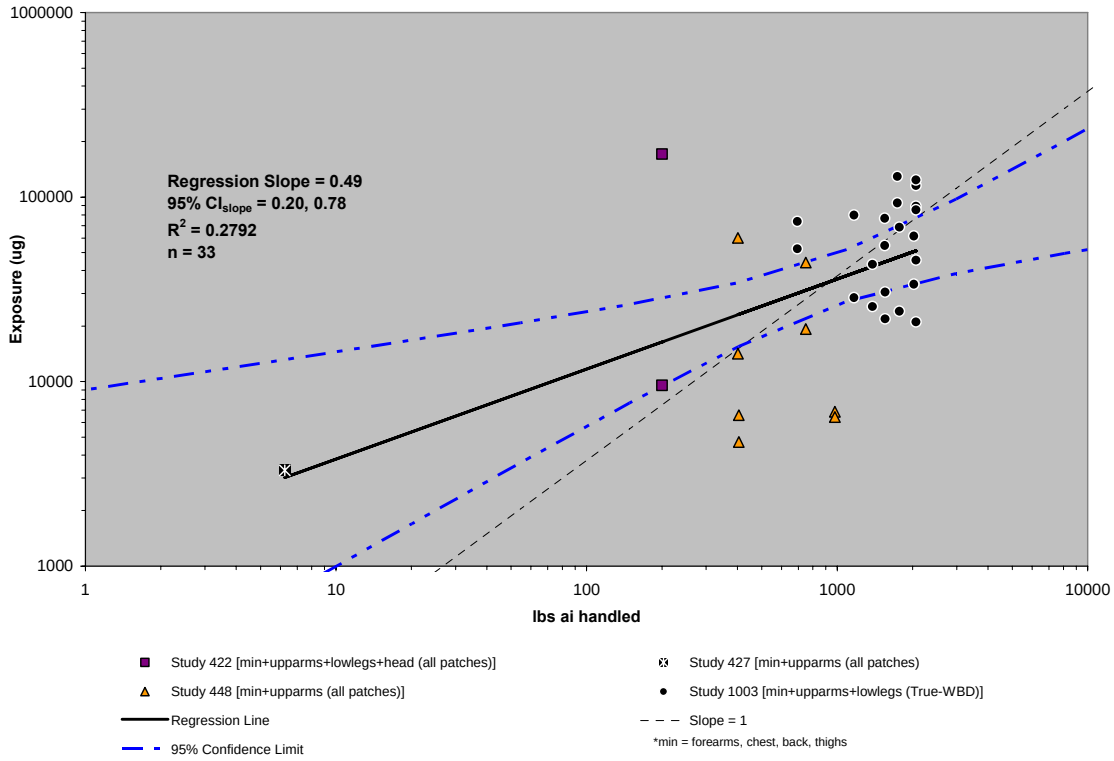
Figure 4.1 Scenario #2: Open Loading Granules (PHED Grades D-E)
Outer Dosimetry - Hand Exposure vs. lb ai handled



Open Loading Granules – Exposure to the Body (excluding hands) Outside Clothing/PPE (i.e., "bare"): There were 33 monitoring events, where between approximately 5 and 2100 lbs ai were handled, that had at least the minimum-critical body parts required to represent dermal body exposure for this subset. These were classified as A, B, or C grade data. Figure 4.2, below, shows the slope of the regression line significantly different than 1, but also significantly different than 0, suggesting that, though it is not independent of AaiH, exposure may not be proportional to AaiH.

The figure additionally provides information on the body part combinations for each study. All monitoring events have at least the minimum-critical body parts representing exposure to the body (see Table 4.2), however, additional body parts above and beyond the minimum-critical were included when available. Additional analysis for this methodology was previously described (e.g., normalizing the sum of exposure by the sum of the surface areas of the body parts measured) and is included in the "LOG-LOG REGRESSION SUMMARY" tabs in the file ExhibitC_II_b_L_Gran_outer.xls.

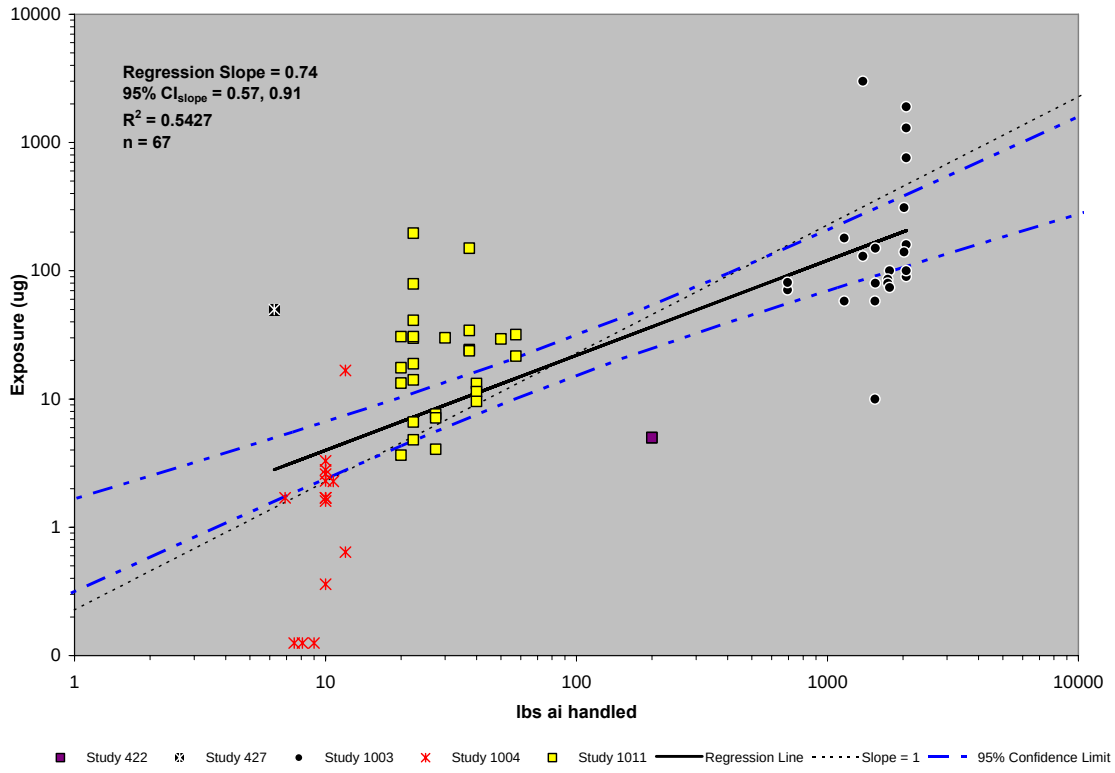
Figure 4.2 Scenario #2: Open Loading Granules (PHED Grades A-C)
Outer Dosimetry - RoB Exposure vs. lb ai handled



Open Loading Granules – Total Dermal Exposure Outside of Clothing/PPE (i.e., "bare" hands plus "bare" RoB): For this scenario only 7 monitoring events had concurrent outer dosimetry measurements for hand and body exposure. The Agency did not examine proportionality for this subset.

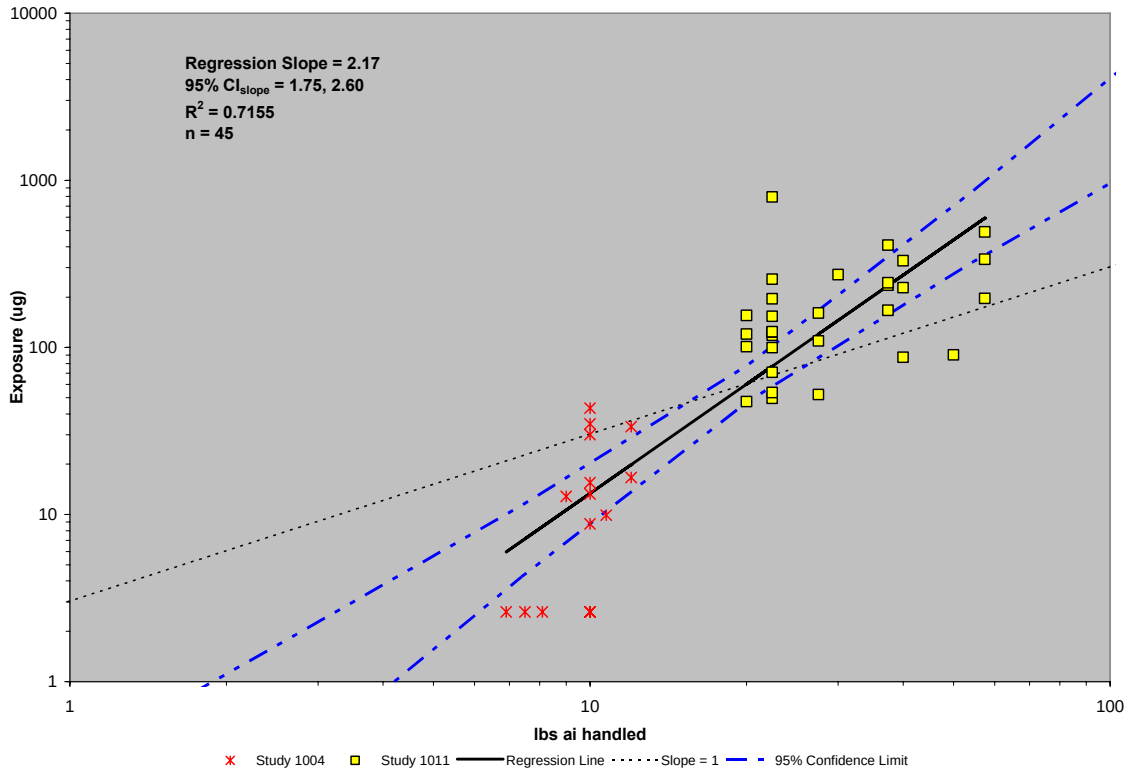
Open Loading Granules – Gloved Hand Exposure: There were 67 monitoring events, where between approximately 5 and 2100 lbs ai were handled, that had gloved hand exposure measurements. These were classified as A, B, or C grade data. In Figure 4.3, below, the slope of the regression line was significantly different than 1, however also significantly different than 0. This suggests that while the relationship may not be proportional, exposure is not independent of AaiH.

Figure 4.3 Scenario #2: Open Loading Granules (PHED Grades A-C)
Inner Dosimetry - Hand Exposure vs. lb ai handled



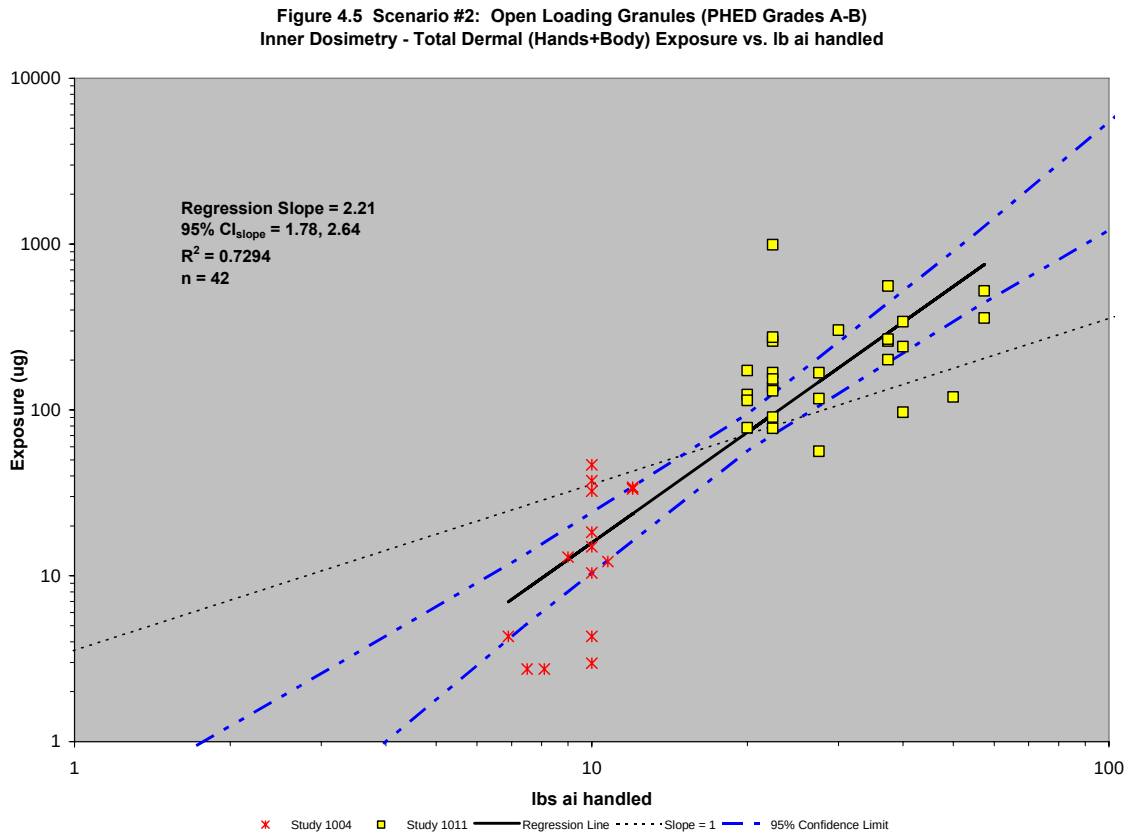
Open Loading Granules – Exposure to the Body (excluding hands) underneath a Single Layer of Clothing/PPE: There were 45 monitoring events, where between approximately 5 and 60 lbs ai were handled, that had at least the minimum-critical body parts required to represent dermal body exposure for this subset. These were all classified as A grade data. In Figure 4.4, below, the slope of the regression line was significantly different than 1, however also significantly different than 0. This suggests that while the relationship may not be proportional, exposure is not independent of AaiH.

Figure 4.4 Scenario #2: Open Loading Granules (PHED Grade A)
Inner Dosimetry - RoB Exposure vs. lb ai handled



Open Loading Granules – Total Dermal Exposure underneath a Single Layer Clothing/PPE (gloved hands plus RoB under Single Layer): There were 42 monitoring events, where between approximately 5 and 60 lbs ai, were handled, that had concurrent gloved hand exposure and at least the minimum-critical body parts required to represent body exposure underneath a single layer of clothing. These were classified as either A or B grade data. In Figure 4.5, below, the slope of the regression line was significantly different than 1, however also significantly different than 0. This suggests that while the relationship may not be proportional, exposure is not independent of AaiH.

One can see by comparing the plot below with the previous plots for gloved hand exposure and RoB exposure underneath a single layer of clothing (Figures 4.3 and 4.4, respectively), that only studies 1004 and 1011 had concurrent hand and body exposure measurements. Note that the data points for each of the two studies shifted upward only slightly when gloved hand exposure is added to the RoB exposure. Additionally the slope of the regression line and additional statistical characteristics only slightly changed. These observations suggest that when using gloves, hand exposure becomes a minimal driver in relation to the rest of the body.



Scenario #3: Open Mixing/Loading Liquids

Scenario #3 includes individuals exposed during open mixing and loading of chemicals formulated as liquids (e.g., soluble concentrates). Shown in Table 4.3 below are the various subsets used to evaluate proportionality for this scenario. These include the relationship between exposure to unprotected (bare) hands and AaiH for which there are 130 measurements with data quality grades of A through E to the relationship between total dermal exposure (hands plus body) with protective clothing (e.g., single layer PPE with chemical resistant gloves) and AaiH for which there are 50 measurements graded A through C. The minimum-critical body parts required to represent exposure to the rest of the body (RoB) are listed, as are the number of records available having concurrent hand plus RoB exposure representing total dermal exposure.

Table 4.3 Scenario #3: Open Mixing/Loading Liquids
 # Records by PHED Grade, Dosimetry Location, and Body Section
[Minimum-critical Body Parts representing RoB Exposure: forearms, chest, back, thighs]

PHED Grade	Inner Dosimetry			Outer Dosimetry		
	Hands	RoB	Total Dermal	Hands	RoB	Total Dermal
A – E	129			130	143	74
A – C	58	80	50	96	139	58
A – B	35	63	36	53	75	35
	See ExhibitC_III_c_ML_LIQ_inner.xls			See ExhibitC_III_b_ML_LIQ_outer.xls		

Scenario #11: Open-cab Airblast Applications

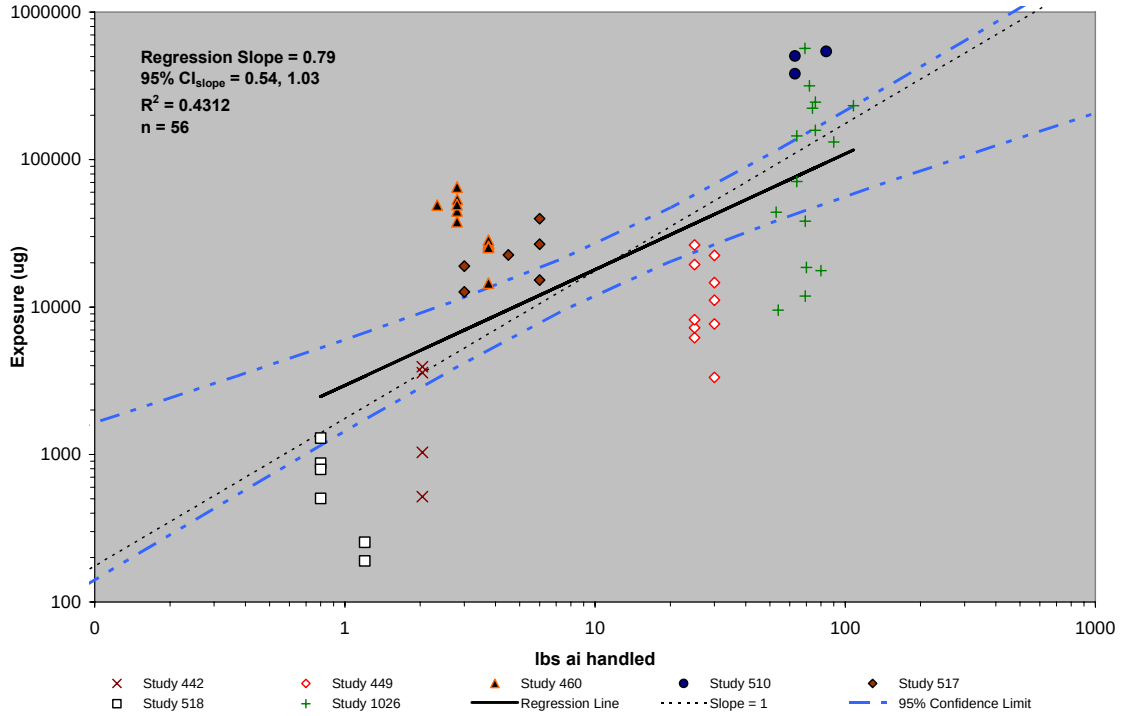
Scenario #11 includes individuals exposed during the application of pesticides using airblast equipment that are not equipped with an enclosed structure in which the applicator would sit (i.e., open-cab). Shown in Table 4.4 below are the various subsets used to evaluate proportionality for this scenario. These include the relationship between unprotected (bare) head exposure and AaiH for which there are 62 measurements with data quality grades of A through E to the relationship between protected body exposure and AaiH for which there are 39 measurements graded A through C. The minimum-critical body parts required to represent exposure to the rest of the body (RoB) are listed. Plots for these subsets are provided as examples below (Figures 4.6 – 4.8).

Table 4.4 Scenario #11: Open-cab Airblast Applications
 # Records by PHED Grade, Dosimetry Location, and Body Section
[Minimum-critical Body Parts representing RoB Exposure: forearms, chest, back, thighs]

HED Grade	Inner Dosimetry		Outer Dosimetry	
	Head only	RoB	Head only	RoB
A – D			62	
A – C		39	61	56
	See ExhibitC_IV_c_APP_Open-cabAirblast_inner.xls		See ExhibitC_IV_b_APP_Open-cabAirblast_outer.xls	

Open-cab Airblast Applications – Exposure to the Body (excluding hands) Outside Clothing/PPE (i.e., "bare"): There were 56 monitoring events, where between approximately 0.8 and 110 lbs ai were handled, that had measurements for at least the minimum-critical body parts required to represent dermal body exposure. These were classified as either A or C grade data. In Figure 4.6, below, the slope of the regression line was not significantly than 1 and also significantly different than 0, suggesting proportionality is reasonable.

Figure 4.6 Scenario #11: Open-Cab Airblast Application (PHED Grades A-C)
Outer Dosimetry - RoB Exposure vs. lb ai handled

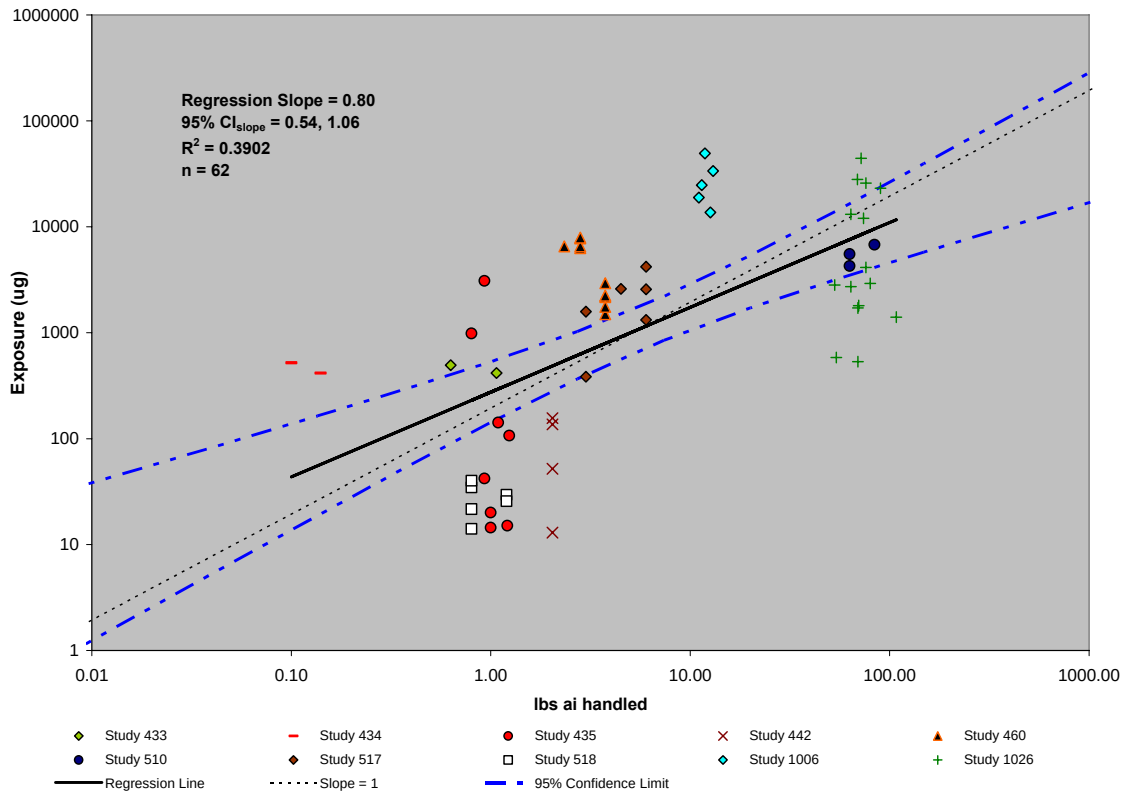


Open-cab Airblast Applications – Total Dermal Exposure Outside of Clothing/PPE (i.e., "bare" hands plus "bare" RoB): There were only 13 monitoring events that had concurrent bare hand exposure measurements and exposure measurements for the rest of the body. Additionally, in these instances, the total dermal exposure was not significantly influenced by the inclusion of the hand exposure measurements. Therefore, the Agency opted to only present the RoB exposure (Figure 4.6, above) as an adequate representation of total dermal exposure.

Open-cab Airblast Applications – Exposure to the Head without Protective Headgear: In addition to the RoB exposure the Agency examined the relationship between exposure to individuals' heads and AaiH. This was considered applicable because head exposure, especially when one is wearing protective clothing over their bodies but no protective head gear, is a significant potential exposure driver for open-cab airblast applications.

There were 62 monitoring events, where between approximately 0.8 and 110 lbs ai were handled, that had bare head exposure measurements. These were classified as A – D grade data (note: there was only one individual with D grade data). In Figure 4.7, below, the slope of the regression line was not significantly different than 1 and also significantly different than 0, suggesting proportionality is reasonable.

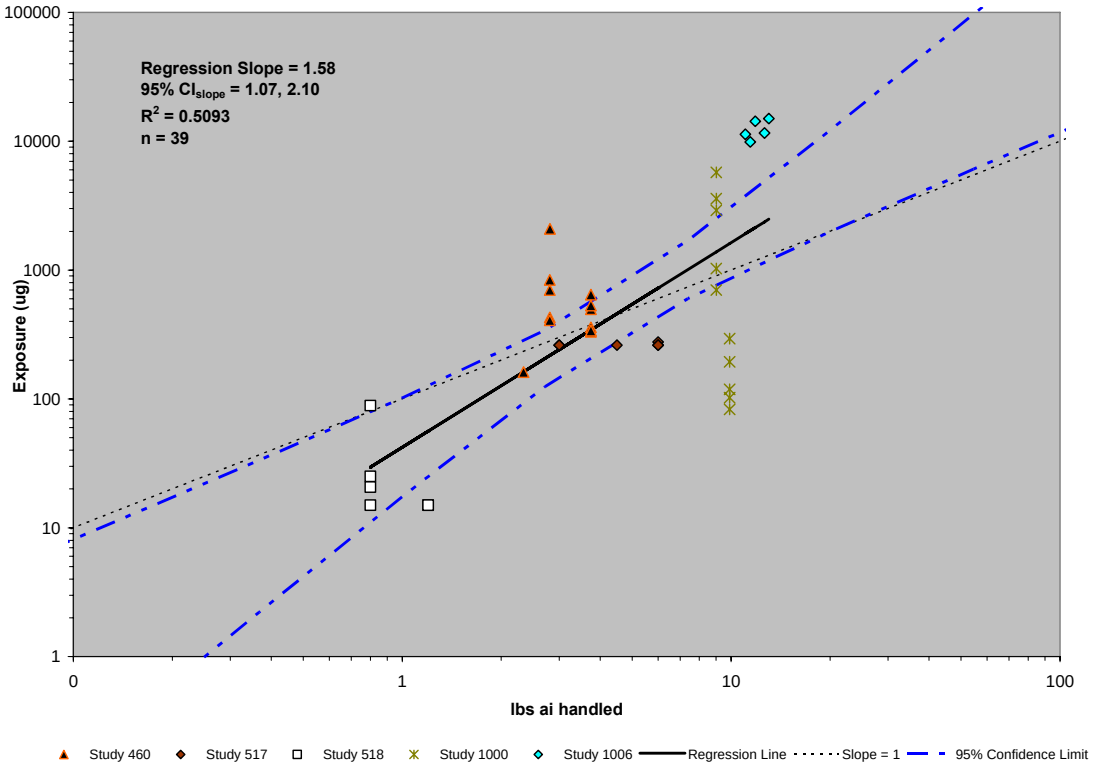
Figure 4.7 Scenario #11: Open-Cab Airblast Application (PHED Grades A-D)
Outer Dosimetry - Head Exposure vs. lb ai handled



Open-cab Airblast Applications – Exposure to the Body (excluding hands) underneath a Single Layer Clothing/PPE: Because gloved hand exposure would not be considered a major driver of total dermal exposure for this subset (as opposed to the situation for total dermal exposure representing a single layer of clothing *without gloves*), the Agency examined proportionality for dermal exposure underneath a single layer of clothing excluding the hands. Additionally, the data would have been minimized considerably having to use only those individuals that had concurrent measurements for gloved hands and body exposure underneath a single layer of clothing.

There were 39 monitoring events, where between approximately 0.8 and 13 lbs ai were handled, that had at the least the minimum-critical body parts required to represent RoB dermal exposure underneath a single layer of clothing for this scenario. These were classified as A, B, or C grade data. In Figure 4.8, below, the slope of the regression line, though positive, was significantly different than both 0 and 1, suggesting that while not independent, the relationship may also not be proportional.

Figure 4.8 Scenario #11: Open-Cab Airblast Application (PHED Grades A-C)
Inner Dosimetry - RoB Exposure vs. lb ai handled



Scenario #12: Closed-cab Airblast Applications

Scenario #12 includes individuals exposed during the application of pesticides using airblast equipment equipped with an enclosed structure in which the applicator sits (i.e., closed-cab). Shown in Table 4.5 below are the various subsets used to evaluate proportionality for this scenario. These include the relationship between unprotected body exposure (represented by outer dosimetry) and AaiH for which there are 20 measurements with data quality grades of A and B to the relationship between protected total dermal exposure (hands plus body) and AaiH for which there are 20 measurements graded A and B. The minimum-critical body parts required to represent exposure to the rest of the body (RoB) are listed, as are the number of records available having concurrent hand plus RoB exposure representing total dermal exposure.

Table 4.5. Scenario #12: Closed-cab Airblast Applications
 # Records by PHED Grade, Dosimetry Location, and Body Section
[Minimum-critical Body Parts representing RoB Exposure: forearms, chest, back, thighs]

PHED Grade	Inner Dosimetry		Outer Dosimetry
	RoB	Total Dermal	RoB
A – B	30	20	20
	See ExhibitC_V_c_APP_Closed-cabAirblast_inner.xls		See ExhibitC_V_b_APP_Closed-cabAirblast_outer.xls

Scenario #15: Open-cab Solid Broadcast Spreader Applications

Scenario #15 includes individuals exposed during the application of solid formulation pesticides (e.g., granules) using a tractor-drawn broadcast spreader not equipped with an enclosed structure in which the applicator sits (i.e., open-cab). Shown in Table 4.6 below is the only subset used to evaluate proportionality for this scenario: exposure to the body underneath a single layer of clothing or PPE, with data quality grades of A and B. The minimum-critical body parts required to represent exposure to the rest of the body (RoB) is listed.

Table 4.6. Scenario #15: Open-cab Solid Broadcast Spreader Applications
 # Records by PHED Grade, Dosimetry Location, and Body Section
[Minimum-critical Body Parts representing RoB Exposure: forearms, chest, back, thighs]

PHED Grade	Inner Dosimetry	Outer Dosimetry
	RoB	RoB
A – B	4	
	See ExhibitC_VI_c_APP_Open-cabSolidSpreader_inner.xls	No ExhibitC file

Overall, results of the Agency's proportionality investigation were mixed. In some cases the slope of the regression line did not significantly differ from 1 and was also significantly different than 0, which would suggest proportionality is a reasonable assumption, while in others the slope of the regression line was significantly different than 1 but not significantly different than 0, which would suggest independence. The Agency is unsure whether the inconsistent results of this investigation were a function of the characteristics or limitations of the data itself (e.g., disparate study designs and others previously discussed in Section 2 and Table 2.7) or that the assumed proportional relationship is, in actuality, not the proper one for certain scenarios.

4.1.4 Conclusion and Discussion

As shown in the open mixing/loading granules and open-cab airblast applications examples above and in the additional case studies in Exhibit C, proportionality between exposure and AaiH appears reasonable in some, but not all cases. As stated previously, the Agency is unsure whether this is a function of limitations of our database potentially solved by additional/replacement data or whether proportionality in some cases is not a reasonable assumption.

In cases where proportionality between exposure and AaiH may not be a reasonable assumption, the Agency believes that information on additional ancillary variables such as mix concentration, duration of exposure, number of tank mixes, etc., also collected during field trials, may assist in characterization of unit exposures. In order to evaluate whether these additional parameters might be significant determinants of exposure, the Agency proposes to construct various multiple regression models in which these parameters are included and also evaluate the resulting models using likelihood ratio tests, stepwise regression, and Akaike (AIC) and Bayesian information criteria (BIC) to determine how useful these additional parameters might be in improving the prediction capability of the model.

Proposed study designs by the AHETF for additional data for various pesticide handling scenarios will allow for a more robust examination of proportionality in certain cases. The methodology for examining proportionality proposed by the AHETF includes accounting for the "clustering" effects of studies by using appropriate statistical modeling including nested models.

The Agency believes that, though neither the studies in our current database nor the proposed studies by the AHETF were designed for the primary purpose of examining proportionality, compared with our current database, the AHETF studies will enable a more thorough discussion of proportionality due to their streamlined and consistent study design across all proposed scenarios and the possibility for more sophisticated statistical analysis.

5. Scope of Research Plan

In previous sections we have seen examples of handler exposure scenario analyses having both large and small numbers of samples (N). In all examples, the issue of a nested data structure (e.g., worker nested in study which is in turn nested in collection method) combined with a variety of other confounding issues appears to be an important factor which can substantially complicate the data analyses. Ideally a given handler scenario would have a reasonable number of samples with the right mix of representative activities which use as large a range of amount of active ingredient handled as possible. These monitored activities would be performed by as many different individuals and at as many different locations as possible. In addition, it is desirable to have the samples collected in as consistent a manner as possible such that confounding by the use of multiple methods is minimized (e.g., patches vs. whole body dosimeters or varied hand monitoring techniques). Finally, there is an ethical component, in that the Agency should not require additional sampling involving intentional dosing if this additional sampling would not significantly contribute to increased confidence in the individual datasets and the predicted exposures.

Historically, the sample size requirements for worker/handler exposure studies have been largely driven by cost and logistics. In a previous SAP, (US EPA, 1986b), the Agency proposed requiring 9 samples for studies of exposure of aerial pesticide applicators and 15 samples for monitoring other handling tasks. Although the proposed sample sizes were acknowledged by the Panel as being "somewhat arbitrary", the SAP agreed with the Agency's approach of determining sample size requirements based on balancing the statistical advantages of large samples and the cost and practicality of conducting these kinds of studies. The Panel also found the sample size requirements to be too rigid. Alternatively, the SAP suggested that the required sample size be based on the variability inherent in the similar data from already existing studies. As a result of a need to systematically address this issue, the Agency, along with PMRA, DPR and industry, developed PHED which is a database of many exposure studies grouped by scenario as described above in Section 2. However over time, the limitations of PHED have been acknowledged, examples of which have been illustrated in this document.

The focus of this section are the documents entitled *Agricultural Handlers Exposure Task Force (AHETF) Technical Summary Document For a Multi-Year Pesticide Handler Worker Exposure Monitoring Program* (AHETFa, 2006)*, Procedures for Determining the Required Number of Clusters and Monitoring Units per Cluster to Achieve Benchmark Adequacy* (AHETFb, 2006) and *American Chemistry Council-Antimicrobials Exposure Assessment Task Force II (AEATF II) Background and Scoping Summary* (ACCa, 2006). However, it is important to characterize the number of agricultural pesticide applicators presently in the United States in order to provide some context for the discussions related to the overall sampling plan proposed by AHETF and AEATF, the proposed sampling intensity, and its representativeness. The Agency believes the nature and the size of the exposed population has a direct bearing on the development of the research plan including the numbers of samples that would be required to adequately predict exposures for that population.

The Agency is not aware of any direct census or survey of agricultural pesticide applicators in the United States. However, by using a mixture of agricultural censuses and pesticide usage surveys, the Agency has developed an estimate of the approximate number of domestic aerial applicators and can identify the number of farms that receive agricultural

pesticide applications categorized by pesticide formulation, application method, and type of applicator. The Agency estimates that there are approximately 3,500 to 4,000 aerial applicators in the United States. Table 5-1 reports the approximate number of farms reporting pesticide applications categorized by formulation, application method, and type of applicator. The types of application methods and pesticide formulations match fairly well with PHED/AHETF scenarios.

Table 5-1. Approximate number of farms reporting the application of pesticides, categorized by formulation, application method, and type of applicator. Note that a given farm is counted multiple times in the column and row totals based on the unique combinations of formulation, application methods, and type of applicator reported on that farm. Data represent the annual number of farms (5-year average, 2001-2005).

Formulation	Application Method	Commercial Applicator	Private Applicator	Totals
Dry Flowable/WDG	Aerial	14,000		14,000
	Ground	97,000	160,000	300,000
	Spot	1,000	7,000	8,000
Granular	Aerial	2,000		2,000
	Ground	9,000	82,000	98,000
	Spot	<1,000	2,000	2,000
Liquid	Aerial	62,000		62,000
	Ground	340,000	600,000	1,000,000
	Spot	8,000	115,000	130,000
Wettable Powder	Aerial	10,000		10,000
	Ground	9,000	43,000	110,000
	Spot	<1,000	1,000	2,000
Totals		550,000	1,000,000	1,800,000

Note: Values in the above table are rounded and therefore the row and column totals do not sum. Further, the row totals include records where the type of applicator is unknown. These unclassified records can have a substantial impact on the row totals (e.g., wettable powder applied by ground). Chemigation data are incomplete and are not included. Spot includes spot treatment and trunk sprays. Ground includes broadcast, banded, in-row, and airblast methods of application.

The AHETF submitted a proposal for the number of samples to be collected for various agricultural handler scenarios as part of developing an exposure database, referred to as AHED (Agricultural Handlers Exposure Database). Table 5.2 provides a comparison of the AHETF-proposed sample sizes for the AHED scenarios and the samples sizes currently available to the Agency from the PHED. The proposed number of samples for each scenario will be re-evaluated as the AHETF proceeds with its project. Each scenario is meant to be representative of handlers wearing long pants, long-sleeved shirts, and chemical resistant gloves. The numerical scenario identifiers are based on the scenario numbering scheme presented in the Agency's *PHED Surrogate Exposure Guide* (see Section 2 above). The range of PHED sample sizes for a given scenario reflects the disparate number of body part exposure values available (e.g., for scenario #1 perhaps leg patches were only collected for 16 monitoring events, whereas arm patches were collected for 21 monitoring events). Unlike PHED, the AHETF-proposed sample sizes represent an individual's entire exposure since all studies to be included in the AHED will follow the

same monitoring and sample collection protocol, which include collecting exposure measurements for all body parts for each monitoring event.

Table 5-2: Proposed AHETF Sampling Plan By Scenario And Numbers of Monitoring Events		
Handler Scenario	**AHETF Proposed (n)**	**PHED (n)**
1: Open mix/load, dry flowables	25	16 - 21
2: Open mix/load, granules	16	33 - 78
3: Open mix/load, liquids	45	59 - 72
4. Open mix/load, wettable powder	25	22 - 45
5: Water Soluble Packets	16	6 -15
6: Closed System mix/load, liquids	40	16 – 31
6a: Closed System, load granules	16	none
7: Closed Cockpit, fixed-wing aerial application of liquids *To be combined with Scenario 9*	36	7 - 22
8: Closed Cockpit, fixed-wing aerial application of granules *to be combined with Scenario 9a.*	8	0 - 13
9: Closed Cockpit, rotary-wing aerial application of liquids *To be combined with Scenario 7*	10	3
9a: Closed Cockpit, rotary-wing aerial application of granules *To be combined with Scenario 8*	8	none
9b: Open Cockpit, rotary-wing aerial application of liquids	15	none
9c: Open Cockpit, rotary-wing aerial application of granules	15	none
11: Airblast, open cab	35	18 – 48
12: Airblast, closed cab	16	20 – 30
13: Ground boom, open cab, liquids	40	21 – 42
13a: Ground boom open cab, liquids with soil incorporation *To be combined with Scenario 13*	5	Included in Scenario 13
14: Ground boom, closed cab, liquids (with and without soil incorporation)	15	12 -31
15: Ground boom, open cab, granules *To be combined with Scenario 15b*	11	0 - 5
15b: Ground application, open cab, granules with soil incorporation *To be combined with Scenario 15*	5	2 – 30
16: Ground application, closed cab, granules with/without soil incorporation	Rely on Scenario 15	none
18: Low pressure hand-wand application of liquids	25	4 -13
19: High pressure hand-wand application of liquids	33	9 - 11
24: Rights-of-way application of liquids	15	4 - 20
30: Belly Grinder, mix/load/apply	15	20 – 45
34: Backpack, mix/load/apply liquids	40	9 – 11
34a: Backpack, mix/load/apply granules	40	none
40: Commercial Seed Treatment	60	0
41: On farm treatment, including planting treated seed	16	0
42: On farm treatment and planting, liquids	15	0
43: Planting Treated Seed	0 Rely on Scenario 41	0
44: Chemigation, mix/load	0	0

Table 5-2: Proposed AHETF Sampling Plan By Scenario And Numbers of Monitoring Events		
Handler Scenario	**AHETF Proposed (n)**	**PHED (n)**
	Rely on Scenario 6	Rely on Scenario 6

The sample plan submitted by AHETF includes justification for the numbers of samples per scenario and an analytical plan for testing the statistical power of each dataset (scenario). The AHETF sampling program places greater emphasis on scenarios that represent higher exposures or that represent a larger segment of the agrochemical market. Overall, the procedures for performing the studies reflect several years of multi- agency meetings with the task force representatives. It is anticipated for a variety of reasons that the information produced from these studies will be of a much higher quality than the PHED studies currently used.

The proposed AEATF exposure scenarios and corresponding numbers of monitoring events are presented in Table 5-3. The proposed number of samples to be collected for each exposure scenario is generally based on Series 875 Group A (i.e., 15 monitoring events). Some of the studies include monitoring workers at their place of work with minimal influence on work habits other then wearing of dosimeters (e.g., observational studies such as metal working fluid and pressure treatment of wood). Other studies will be performed in simulated circumstances (e.g., mopping floors, wiping walls at a rented reception hall). While other studies will be performed in a simulated room/chamber at a laboratory to control air exchange rates, etc. (e.g., aerosol sprays).

Table 5-3: Proposed AEATF Sampling Plan By Scenario And Numbers of Monitoring Events		
Handler Scenario	AEATF Proposed (n)	Existing Data
1: Mop Study	15	CMA
2: Wipe Study	15	CMA
3: Pour Solid Study	20	CMA
4. Pour Liquid Study	20	CMA
5: Aerosol Spray Study	15	PHED
6: Metal Working Fluid Study	15	Model
7: Brush/Roller Painting Study	20	PHED
8: Pump Liquid Study	15	CMA
9, 10, 11, 12: High/Low Pressure Spray (four studies total)	60	PHED/CMA
13: Airless Spray Study	15	PHED
14: Immersion/Dip/Soak Study	15	NA
15: Pressure Treatment Study (Wood Preservative)	20	Various
16: Place Solid Study	15	CMA
17: Fogging Study	15	Model

5.1 Within-worker and Between-worker Variability

To date, all regulatory agencies have assumed that all observed variability is between-handler variability. That is, repeated measurements on the same individual performing the same task would be considered as separate (different) individuals This *a priori* assumption has not been rigorously addressed in the literature with respect to mixer/loader applicators in agricultural settings (e.g., Nigg et al., 1986; Kromhout and Vermeulen, 2001). The studies comprising PHED contain exposure measurements for both the same worker performing the same task multiple times and for different workers performing the same task one time. Figure 5-1 below exhibits this feature of the data set.

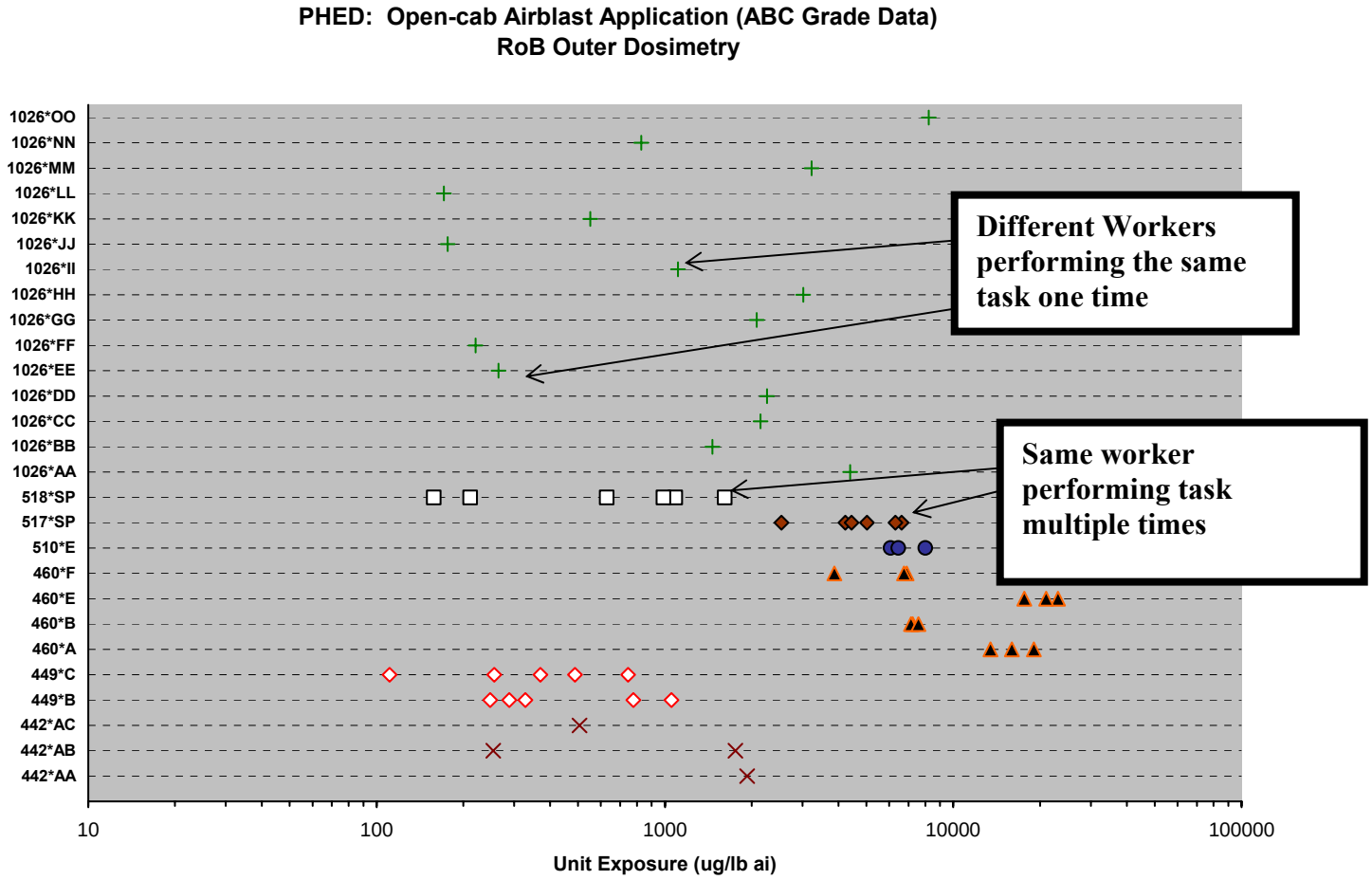


Figure 5-1

A corresponding plot(Figure 4.6) using the same color/character combinations in Section 4.1.3 presents the data only by study code – the number of separate individuals monitored within each study is presented here. Each data point on the plot represents one monitoring event whose value is the exposure normalized by the AaiH (i.e, . unit exposures). One can see that each monitoring event does not necessarily represent a separate individual each time. Currently, the Agency does not distinguish between the monitoring events in these studies based on whether they are repeat measurements of the same individual or of different individuals (i.e., within PHED each of these 56 monitoring events would be considered to represent 56 separate individuals).

The AHETF does not intend to make repeat measurements on individuals to evaluate within-worker variations (e.g., from day to day or site-to-site) The AHETF has performed a number of simulation exercises and contend that it is more effective from a statistical point of view to increase the number of clusters, or studies rather than the number of monitoring units within each study. The AHETF further asserts that resources would be better spent monitoring single handler-days and increasing the number of studies rather than focusing on intra-individual variability.

The AHETF submitted two critical documents that define proposed research plan and also illustrate the methods that are to be used to develop the scope of the plan. These are referenced in Section 6 as AHETFa&b, 2006. The Agency has evaluated these documents and identified a number of issues about which it will be requesting the Panel's assistance in addressing.

6. Bibliography

AHETFa, 2006. Agricultural Handlers Exposure Task Force (AHETF) Technical Summary Document For a Multi-Year Pesticide Handler Worker Exposure Monitoring Program (submitted to docket by Agricultural Handlers Exposure Task Force as background document for this meeting).

AHETFb, 2006. Procedures for Determining the Required Number of Clusters and Monitoring Units per Cluster to Achieve Benchmark Adequacy (submitted to docket by Agricultural Handlers Exposure Task Force as background document for this meeting).

AHETFc, 2006. Summary Comparative Evaluation of Absorbed Dose Estimates Derived From Passive Dosimetry Measurements With Those Derived From Biological Monitoring: Validation of Exposure Monitoring Methodologies (Sponsor AHETF).

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