Antimicrobial Exposure Assessment Task Force II (AEATF II)

VOLUME 5

Governing Document for a Multi-Year Antimicrobial Chemical Exposure Monitoring Program

Interim Draft Document

February 13, 2008

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1 Introduction

Microorganisms grow anywhere moisture and nutrients are available. Antimicrobial pesticides are essential to control microorganisms that otherwise would result in economic losses, wasted resources, and human and animal illness. Generally, U.S. Environmental Protection Agency (EPA) regulates as pesticides those antimicrobials that target microorganism growth on inanimate objects. Pesticides and pesticide products are defined by EPA in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA; EPA 1989), 40 CFR (Code of Federal Regulations), Section 2(u), Parts 152.3 and 152.15. Other categories of chemicals that control microorganisms used as drugs and in human and animal food and human personal care and cosmetic products are regulated by the U.S. Food and Drug Administration (FDA). Only those categories regulated by EPA are discussed here.

1.1 Overview of Antimicrobial Pesticides and Their Benefits

Antimicrobials are broadly grouped as “public health” or “nonpublic health” depending on whether or not claims are made to control microorganisms pathogenic to man and which occur on inanimate objects. However, that simple grouping does not adequately identify the uses or benefits of antimicrobial pesticides.

A. Public health antimicrobial pesticides are those that carry claims to control on environmental surfaces microorganisms that are pathogenic to man. Claims to sanitize, disinfect, or sterilize are considered *de facto* claims to control microorganisms pathogenic to man (including bacteria, fungi, and viruses). However, these products are used across a very broad range of use sites and applications, including everything from hospital surfaces to home bathrooms, from restaurant food processing and handling areas to the home kitchen, from municipal drinking water systems and municipal swimming pools to the backyard swimming pool, and from commercial or hospital laundries to everyday home laundry use. These products are regularly used in homes, offices, schools, hospitals, restaurants, food processing facilities, and a large variety of industrial facilities as well as farm and animal premises. These products also are used to help ensure that the water we drink is not contaminated by pathogenic microorganisms.

In order to obtain an EPA registration, all antimicrobial products that make a public health claim must submit efficacy data based on specific application instructions and conducted according to strict protocols and must document a very high level of performance under stringent conditions. Efficacy testing is a requirement and is defined under FIFRA in 40 CFR Part 158.640. These

products help to provide protection against food-borne diseases produced by Salmonella or E. coli, as well as against pathogens such as Staphylococcus, Norovirus, SARS, and HIV/AIDS virus.

These products include common and well-known chemicals such as hydrogen peroxide and sodium hypochlorite, as well as a large number of other compounds. The following is a partial list of sites where public health antimicrobial pesticides can be used:

- Hospitals, nursing homes, medical and dental offices, sick rooms, and hospices
- Homeless and emergency shelters, locker rooms, and communal living quarters
- Meat and poultry, seafood, processed food, beverage and dairy, and other food storage and processing facilities, agricultural premises, animal premises and farms
- Restaurants, cafeterias, and institutional food services industry
- Residences, schools, public facilities, senior and child day care facilities
- Public water treatment facilities, personal and emergency water treatments
- Swimming pools, hot tubs, whirlpools, and related facilities

B. Nonpublic health antimicrobial pesticides are all antimicrobial pesticides other than those that claim to control microorganisms pathogenic to man. These include antimicrobial pesticides to control, on environmental surfaces, diseases pathogenic to animals but not to man (such as hoof and mouth disease, bird flu in poultry houses, various diseases in kennels or veterinary facilities). However, this grouping also includes a diverse range of products that provide protection against microbial degradation, contamination or fouling to inanimate articles, substances, systems or processes. Essentially any organic system in the presence of moisture is subject to attack by microorganisms, and prevention of such attack helps preserve critical resources, extend the useful life of the items, minimize disposal, and improve the overall utility of those articles, substances, systems, and processes. In many cases, the use of an antimicrobial also can minimize or obviate the need for the use of other chemicals or treatments later on that can result in greater human or environmental exposure. These antimicrobials also are used to improve energy efficiency. Included within this category are the following types of antimicrobial pesticides:

1. Material preservatives: Virtually all water-based products are subject to microbial decay. If microbial growth is uncontrolled, the in-service or shelf life of manufactured goods is significantly reduced, resulting in economic losses and wasted resources. Following is a partial list of products that must be preserved to prevent premature deterioration and decay. The need to dispose of spoiled

products wastes resources and could increase substantially the burden on the environment.

Latex emulsions
Paints and coatings
Pigment dispersions
Slurries
Adhesives, caulks and joint compounds
Printing ink
Non-clothing textiles (e.g., fire hoses, tarpaulins, cordage, and canvas)
Leather and suede
Cotton and wool fabrics
Paper and package coatings and additives
Lumber, wood, plywood, particleboard, and other cellulose-derived materials
Plastics, vinyls and polyurethane
Polymer emulsions
Detergents, cleaners and other consumer products
Jet fuel and other petroleum-derived fuels
Concrete admixtures

Many of these products would be impractical without antimicrobials to preserve them. As an example, latex paints are easier to clean up, have lower odor and lower levels of volatile organic carbons than oil and solvent-based formulations. However, bacteria can proliferate in the water-based latex medium. Bacterial action produces enzymes which can destroy the thickeners in paint overnight. Gases resulting from bacterial metabolism not only result in foul odors, but also bursting cans, an obvious safety hazard. Incorporating an antimicrobial prevents bacterial growth in cans containing latex paint. In fact, antimicrobials made this product possible.

Similar situations exist for a wide variety of products, including water-based adhesives, latex emulsions, pigment dispersion, caulking compounds, and others. Spoilage of any of these products can result in gas formation, offensive odors, color changes, viscosity loss, and pH drift, any one of which may mean loss of functionality. These products, which along with paint represent nearly $20 billion to the US economy, require the use of antimicrobials.

2. Poultry houses, Egg Producing Facilities, Milking Houses and Other Agricultural Premises

Disinfectants, virucides, fungicides, and sanitizers control or eliminate animal pathogens. This has become increasingly important as increased international movement has led to the spread of devastating animal diseases such as foot and mouth disease, Newcastle disease, and avian flu.

3. Water Treatment

a. Comfort Cooling, HVAC, etc. – Water must be treated to control the growth of microorganisms that, left uncontrolled, could reduce efficiency and increase energy usage, pit and corrode equipment as well as causing fouling and malodors.

b. Cooling Water Systems -- Water is used for cooling industrial processes and as a means of heat exchange. Any industrial processor that produces heat, either incidentally, as in, nuclear power plants, other utilities, or those sites running heavy equipment, must use coolants to maintain desirable temperature ranges and prevent overheating. Otherwise, systems become fouled, equipment is damaged, energy consumption increases, and processes fail. For example, electrical utilities and many manufacturing facilities use water for process cooling. To minimize consumption, the water is cooled and re-circulated. If untreated, microbial deposits will form in the system resulting in reduced efficiency yielding increased production costs, increased energy consumption, and increased water requirements. In extreme cases, biological fouling can compromise the integrity of the industrial equipment due to the corrosivity of bacterial waste products.

c. Industrial Process Waters – Many processes depend upon water as a key component of processing (e.g., pulp and paper mills). Treatment is necessary to prevent odor, clogging and fouling of systems, protect equipment from corrosion, and reduce energy needs and treatment of water prior to discharge. Unrestrained microorganism growth in pulp and paper mills interferes with paper quality by degrading and staining pulps, causing transparent slime spots, decreasing durability, and chemically degrading fibers.

4. Marine Antifoulants

Any submerged surface is rapidly fouled with micro- and macro-organisms. On ships and boats, fouled bottoms decrease maneuverability and safety, increase energy consumption, while reducing speed and performance. Antifoulants dramatically decrease the growth of fouling organisms for up to five years. They also reduce the spread of invasive alien species, which can have highly detrimental economic and environmental impacts and also can pose threats to human, animal and plant life. When incorporated into paint on the hull of ships, antimicrobials prevent biological deposits. A slime layer only one millimeter thick on the hull can reduce speed by 15% and increase fuel costs by more than $1 million in a single year. Heavier deposits not only cause further speed reductions and loss of maneuverability, they can result in corrosion and limit the life of the coating, requiring premature dry-docking. With every six-month extension of the time between dry-docking for the world's fleet, the use of antimicrobials results in estimated annual cost savings of over $800 million.

5. Metalworking Fluids

Metalworking fluids are used at thousands of manufacturing facilities to cool and lubricate metal parts being drilled, milled, ground, or otherwise worked.

Functioning also to prevent corrosion and flush metal chips from the worksite, the fluids are particularly prone to microbial contamination. Microbial growth causes offensive odors and plugs equipment lines leading to corrosion and blemishes on the finished surfaces, loss of productivity from slowed equipment speeds and necessitating more frequent changes of fluid resulting in unnecessary fluid replacement costs as well as increased fluid disposal. Antimicrobials are essential for optimizing fluid life, fluid functionality, and worker comfort and productivity. While this is effectively a material preservative use, it is considered separately from the US EPA regulatory perspective.

6. Wood Treatment

Wood rots readily and its organic components provide all the nutrients that bacteria and fungi require for growth. Failure to control decay organisms will result in structural failure, reduced life cycle, and increased disposal requirements. The use of wood preservative chemicals protects a significant resource (wood) and can extend the useful life of wood products from just 2-5 years to more than 20 years, resulting in a significant protection of existing forests. Treatment with antimicrobials is vital for wood used structurally in buildings. Wood treatment chemicals also can be used to prevent growth of algae and molds on the surfaces of wood and to prevent the permanent staining of cut lumber by microorganisms, i.e., sapstain. Wood treatment antimicrobials are used on newly cut wood surfaces, kiln dried wood, milled wood and other building materials. A wide variety of seasoned/unseasoned, indoor/outdoor, and terrestrial/marine/aquatic wood items and surfaces are treated with wood preservatives. The types of wood products include fresh-cut logs or lumber, seasoned building materials, utility poles and fence posts and rails (prior to or after being placed in service), structural members, structures, dwellings, transportation vehicles, crop growing/harvesting/shipping/storage containers, lawn furniture, playground equipment, garden/landscape timbers, and log homes.

1.2 Regulatory Need for Estimation of Exposures to Antimicrobial Pesticides

EPA regulates pesticides under the statutory authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Currently, antimicrobials registered prior to November 1, 1984, are going through a re-registration process. Starting in 2007, all antimicrobials also will be reviewed on a 15-year cycle as part of EPA's "registration review" program. In both programs, EPA must determine whether, when used according to the labeled directions, there is a reasonable certainty of no harm to humans and no unreasonable risks to the environment. In addition, new products, new uses and major amendments to existing antimicrobial products must undergo similar review and determination. Antimicrobial pesticides are managed by the U.S. EPA's Office of Pesticide Programs (OPP), Antimicrobials Division.

EPA has typically based its exposure assessments for antimicrobials on rules of thumb, some based on registrant reports of industrial hygiene or other non-pesticide guideline exposure information and some based on EPA-derived information. Following passage of the Food Quality Protection Act of 1996, EPA produced a number of screening level occupational and residential risk assessment guidelines in the form of draft standard operating procedures. Although data exist, albeit with limitations, to estimate potential exposures to agricultural handlers, i.e., the Pesticide Handlers Exposure Database (PHED; EPA 1988), no such database exists for occupational subjects handling antimicrobials, outside of limited data (Popendorf et al., 1992) generated by the Chemical Manufacturers Association (CMA, now the American Chemistry Council or ACC). Further, only limited antimicrobial exposure monitoring data exist to support quantitative exposure analyses to this class of pesticides. In the past ten years, a few occupational exposure monitoring studies involving antimicrobials have been submitted to EPA; however, they have limited utility as they cover only certain use patterns. Some of the data generated from these studies have a high degree of uncertainty due to low numbers of samples for a particular use pattern or insufficient sensitivity in analytical detection. Because most antimicrobial pesticides are used in indoor environments, the potential exposure from the use of these products could be substantially different from handling agricultural pesticides outdoors. Thus, EPA must either to try to use agricultural exposure data for industrial and consumer antimicrobial-related assessments or use assumptions and predictive models that have not been validated to support their exposure assessments and related decision making processes.

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In 2001 (letter from Margaret Stasikowski, Director, Health Effects Division to Daniel Fay, Valent USA Corporation, 16 March 2001), EPA outlined its prospective plans regarding the existing agricultural exposure data contained in the Pesticide Handlers Exposure Database (PHED). The letter stated EPA's intention to drastically overhaul PHED version 1.1 because many of the existing exposure studies in the database were outdated or scientifically inadequate by "today's standards". In addition, many exposure scenarios that are being assessed by the Agency are under-represented in PHED version 1.1. This is particularly apparent with antimicrobial pesticides, where potential exposures are very different from those associated with agricultural pesticides. Thus, there is a clear need to generate better exposure data to improve the quality of human health risks assessments for antimicrobial products. That need has been repeatedly identified in regulatory decisions.

As key elements in the risk assessment process, exposure data allow for estimation of absorbed dose, which is then compared to a relevant toxicological endpoint from an animal dosing study. The algorithm to calculate the average daily dose to a worker is relatively simple. The inputs require an estimate of how much chemical is going to be handled during a work shift, a body weight, and a measure of exposure potential based upon the activity conducted by the worker

(by exposure route). Although there are ranges and uncertainties associated with each of these inputs, the measure of exposure for a particular job function or activity is where the greatest uncertainty lies.

The Agency has acknowledged that while the use of existing data and assumptions in its human health risk assessment process for antimicrobial products is necessary, it would also lead to overly protective labeling, a requirement for chemical companies to develop costly product-specific confirmatory exposure data, and even the suspension of certain uses. Thus, according to EPA, the creation of a consortium to develop generic exposure data on occupational activities would be a cost-effective means of generating a large amount of high quality credible data (Stasikowski 2001).

On November 1, 2004, the American Chemistry Council (ACC) Biocides Panel established the Antimicrobial Exposure Assessment Task Force II (AEATF II) to measure exposure of subjects in mixing and loading operations in industrial settings and professionals involved in application of products containing biocides in industrial, institutional and residential settings. The AEATF II currently consists of forty-three member companies. The purpose of this task force is to develop generic exposure data on a broad range of use pattern/application method combinations as well as specific post-application exposures (e.g., measurements of residue deposition on treated surfaces and the post-application transferability of these residues using EPA-recommended environmental sampling methods). Each specific set of related tasks, antimicrobial formulations, equipment, engineering controls, and worker and/or consumer practices considered by AEATF II is termed a **scenario**. These data obtained for each antimicrobial-handling scenario addressed by AEATF II will be used to support EPA registration and re-registration of most antimicrobial active ingredients in the future. The concept behind a group of companies working together to generate jointly-owned data is to reduce individual company's costs, generate more data than would be possible by a single company or even small group of companies alone, while providing consistency in design and execution, and obtaining coordinated scientific input from appropriate regulatory agencies (U.S. EPA, California Department of Pesticide Regulation or CDPR, Health Canada's Pest Management Regulatory Agency or PMRA, and European regulatory authorities).

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1.3 Purpose of the Governing Document

The purpose of this document is to provide the U.S. EPA, CDPR, PMRA and the Human Studies Review Board (HSRB) with a description of the overall scope of the AEATF II program, demonstrate the need for additional human exposure monitoring data, and explain the proposed methodology for the exposure monitoring studies proposed for conduct by the AEATF II. This document also describes the plans of the AEATF II to develop a generic database, i.e., the Biocide Handlers Exposure Database (BHED™). By providing this background

information, the AEATF II intends to present a scientifically valid basis for conducting the proposed human exposure monitoring studies.

This draft version of the "Governing Document" focuses on the technical and ethical aspects of the AEATF II program. The governing document is being submitted to EPA (and other regulatory agencies), and the HSRB, in conjunction with each specific study protocol for proposed AEATF II exposure monitoring studies. It is anticipated that future versions of this document will be issued to incorporate comments and guidance provided by the EPA's Office of Pesticide Programs (OPP) and the HSRB.

It is important to note that the scientific and ethical aspects of the AEATF II program are addressed, more specifically, as part of each proposed protocol being submitted to the EPA and HSRB. Thus, this document will be supplemented by important study protocol-specific scientific (e.g., study or scenario-specific study design and sample size determination) and ethical (e.g., how a particular AEATF II study will address recruitment, informing, seeking consent, and minimizing risks to study participants) considerations. The ethical components of the AEATF II program are based, in part, on recommendations made by the National Academy of Sciences Committee on the Use of Third Party Toxicity Research with Human Research Participants (e.g., demonstrated need for the knowledge to be obtained from intentional human dosing studies, justification and documentation of a research design and statistical analysis that are adequate to address an important scientific or policy question, an acceptable balance of risks and benefits and minimization of risks to participants, equitable selection of participants, free and informed consent of participants, review by an appropriately constituted IRB or its foreign equivalent) to ensure that AEATF II exposure studies, which are to be conducted under EPA Guideline 875 Series A, will meet the highest scientific and ethical standards.

The AEATF II program also addresses relevant feedback provided in the report of the HSRB meeting of June 27-30, 2006 (Fisher 2006) which discusses an initial review of five study protocols submitted by the Agricultural Handlers Exposure Task Force (AHETF), another multi-year exposure monitoring effort. The AEATF II program has also been informed by the recent April 18 – 20, 2007 HSRB meeting (http://www.epa.gov/osa/hsrb/apr-18-20-2007-public-meeting.htm) and EPA's "Draft Framework for Developing Best Practices for Recruiting, Screening, and Informing Human Subjects, and Obtaining Consent for Occupational Exposure Studies with Pesticides" presented at this meeting. Furthermore, the AEATF II program incorporates recent recommendations provided by the EPA's Science Advisory Panel (EPA 2007).

2 Specific Objectives of the AEATF II Monitoring Program

The primary objective of the AEATF II is to generate handler exposure monitoring studies to estimate characterize exposures distributions for a multitude of occupational / industrial and consumer exposure scenarios involving antimicrobial-containing products. The data from these studies will fill gaps in the current antimicrobial exposure dataset and allow for more precise estimations of potential dermal and inhalation occupational risks to workers and consumers handling products containing antimicrobial agents. The study results will be placed into a computer software database (i.e., the Biocide Handlers Exposure Database or BHED™) allowing the data to be used generically for risk assessments of all antimicrobial agents. The AEATF II will exercise the rights associated with submission of data under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) in connection with BHED™. The database will be available to both AEATF II company members and regulatory agencies for registration and re-registration purposes.

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The AEATF II study program has been designed to cover the most common types of occupational and residential handling scenarios involving antimicrobials. Initially, EPA identified application methods and use scenarios based on a review of antimicrobial product labels and/or Agency areas of interest, in conjunction with 12 “Use Site Groups” that EPA has used historically to delineate antimicrobials use sites. Some application methods have been combined and the following Use Site Groups and 14 application methods/use scenarios have been agreed upon by the EPA, Canadian, and California regulatory agencies and members of the AEATF II. The EPA Use Site Groups and Application Methods/Use scenarios include the following (see Appendices A and B for additional explanation and information):

EPA Use Site Groups

1. Agricultural Premises and Equipment
2. Food Handling/Storage Establishments Premises/Equipment
3. Commercial, Institutional & Industrial Premises/Equipment
4. Residential and Public Access Premises
5. Medical Premises and Equipment
6. Human Drinking Water Systems
7. Industrial Process Water Systems
8. Material Preservatives
9. Antifoulant Coatings
10. Wood Preservatives
11. Swimming Pools
12. Aquatic Areas

Application Methods/Use Scenarios

1. Aerosol Spray
2. High to Low Pressure Spray
3. Pour Liquid
4. Pump Liquid
5. Pour Solid
6. Place Solid
7. Mop
8. Wipe
9. Fog
10. Brush/Roll
11. Airless Spray
12. Immerse/Dip/Soak
13. Pressure Treat
14. Metalworking Fluid

Post-application scenarios are still under discussion, with the possibility of conducting two studies – one to evaluate exposure (e.g., transferable residue measurements) to antimicrobials on soft surfaces (such as carpet) and one to evaluate exposure to antimicrobials on hard surfaces (such as countertops or wood decking).

All human subject monitoring studies will be conducted using standard industrial hygiene passive dosimetry techniques, consisting of both dermal and inhalation monitoring. All Task Force studies will be conducted according to current EPA Office of Pesticide Programs' Harmonized Test Guidelines – Series 875 Occupational and Residential Exposure Test Guidelines (Series 875 A and B for handler and re-entry, respectively) and conducted under Good Laboratory Practice standards per 40 CFR Part 160. All monitoring studies will be conducted in compliance with all applicable provisions of EPA's regulations providing for the protection of human subjects of research, 40 CFR Part 26. The Task Force is designing study protocols that would allow study results to be broadly acceptable to both North American and European regulatory authorities.

Industry-wide generic task forces go through various defined stages, with the data generation phase of the task force typically lasting approximately eight years. The limit of expenditures for AEATF II is set at $9 million. This is based on the assumption that a total of 19 core studies will be conducted, with each study containing 15 to 25 sets of individual measurements. The support costs for doing this work, such as analytical method development, database construction, legal, task force management, etc., are included in the stated dollar amount. This sizeable investment by the antimicrobial industry confirms the commitment to generate the data needed to accurately assess risks to persons using antimicrobial products.

3 AEATF II and BHED™

The Antimicrobial Exposure Assessment Task Force II (AEATF II) was established to generate data for antimicrobial pesticide exposure scenarios to meet EPA data requirements for registration. AEATF II member companies have ongoing data requirements resulting from chemical and product-specific existing and announced data call-in notices, anticipated re-registration obligations via confirmatory data demands, prospective registration review obligations and requirements based on registration applications. The member companies agreed to jointly develop generic data in support of their respective registration obligations since existing data are not adequate.

The primary AEATF II goal is the collection of worker exposure monitoring data and its incorporation into a new generic database that can be used to estimate exposure distributions. The database will be a proprietary product of the Task Force and will be called BHED™ (Biocide Handlers Exposure Database). BHED™ will be submitted to EPA and other regulatory agencies, and used by those regulators to conduct detailed quantitative exposure assessments to support safety determinations for occupational pesticide uses.

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"What is the distribution of normalized personal exposures during each studied antimicrobial exposure scenario?"¶
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Generic databases were developed over the last twenty years in response to a regulatory need to assess the occupational risks associated with a wide range of pesticide handling situations. The concept was discussed first in an American Chemical Society Symposium in 1984 (Reinert and Severn, 1985; Hackathorn and Eberhart, 1985; Honeycutt, 1985) and its development encouraged by a FIFRA Scientific Advisory Panel in 1986. In 1992, the Pesticide Handlers Exposure Database (PHED) was first released following a joint effort by pesticide manufacturers, the EPA, and Canadian regulators (Honeycutt, 1986; Lunchick, 1994, Reinert, 1986, Leighton and Nielson 1995, Nielson et al. 1995). Since then, PHED has been used extensively in a generic manner and has successfully supported many occupational risk assessments. However, much of the data in PHED are derived from exposure studies that are considered outdated or scientifically inadequate by current standards (Stasikowski, 2001). In addition, many antimicrobial handler scenarios of interest to EPA are absent or under-represented in PHED. Other regulatory agencies have expressed similar dissatisfaction with the limitations of PHED data. A major purpose of BHED™ is to address deficiencies in existing data such as those included in PHED. And in 2007, EPA convened another Science Advisory Panel SAP (SAP) to discuss the need for new data to replace PHED and the panel agreed with EPA that "additional data could significantly improve the Agency's ability to assess worker exposure" (SAP, 2007). A major purpose of the BHED™ is to address PHED deficiencies (and limitations of other existing data sources).

Like PHED, BHED™ will be populated with exposure data for subjects who handle antimicrobial pesticides as part of their normal job (occupational) or task (consumer), so their participation as subjects in the studies underlying BHED™ will not add appreciably to their typical exposure from handling pesticides. All AEATF II studies are designed and conducted in accordance with the latest U.S. EPA guidelines for occupational exposure studies.

The development of BHED™ is funded and directed by the AEATF II. However, an AEATF II Regulatory Agency Advisory Committee (RAAC) has been established to promote active participation by interested regulatory agencies. The committee is comprised of representatives of the U.S. EPA, the Canadian Pest Management Regulatory Agency (PMRA), the California Department of Pesticide Regulation (CDPR), and European regulatory authorities. This committee meets on an ad hoc basis to review the program progress and provide technical input to the AEATF II.

4 Regulatory Need for Generic Exposure Data

FIFRA requires the U.S. Environmental Protection Agency to assure that any pesticide registered in the United States does not have unreasonable adverse effects on subjects handling that pesticide (http://www.epa.gov/pesticides/regulating/laws.htm). The Pest Control Products Act (PCPA; http://www.pmra-arla.gc.ca/english/legis/pcpa-e.html) requires a similar determination by Health Canada. This safety determination is generally made by means of quantitative risk assessment and risk management procedures. Risk assessments require a detailed evaluation of the toxicity of the pesticide and an estimation or measurement of the exposure potential for users (and/or amount of pesticide absorbed by the individual as a consequence of its use). Exposure or absorbed dose estimates are quantitatively compared to no-effect exposure levels (often from experimental animals) for hazards identified in standardized toxicology studies. During the risk evaluation, the likelihood of the expression of any toxicological effect on the subjects and a comparison of the risks and benefits are considered. This basic paradigm (hazard identification, dose-response assessment, exposure assessment, and risk characterization) was summarized by the National Academy of Sciences and has become the standard for risk assessment by regulatory agencies (NAS, 1983; NAS, 2006). More recently, the pesticide handler risk assessment process was fully described in a summary document prepared for an EPA SAP review of exposure methodologies (EPA 2007).

The AEATF II database, BHED™, is intended to provide the regulatory agencies with the handler potential exposure data necessary for them to perform the exposure assessment portion of safety determinations. Toxicology data and benefit information are product-specific and must be provided by individual pesticide product registrants.

When estimating exposure to persons who handle pesticides, a major challenge to overcome is that several parameters contribute to the likelihood and level of exposure. These include things such as handling liquids versus solids, how the product is packaged, using open versus closed systems, application with various equipment types, how much product is handled, whether or not personal protective equipment (PPE) is worn, and whether the worker mixes/loads or applies the product or does both. The number of combinations of these parameters makes it impossible to generate human exposure data for all situations, so a number of simplifying approaches have been adopted. These include:

1) Establishing various 'scenarios' (see Appendix A) that cover common combinations of these parameters and generating data for those scenarios;
2) Restricting some scenarios to include the higher exposure portions of them (e.g., professional janitorial personnel performing mopping tasks using higher exposure potential technologies such as string and bucket mop systems);
3) Generating data with subjects wearing minimal PPE;
4) Using data for one chemical/product as a surrogate for another (similar) product; and
5) Assembling data into a generic database (e.g., BHED) for use as surrogate data applicable to many products or for multiple job functions performed by one person.

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Since the early 1980's it has been the consensus of the scientific community that the amount of residue that contacts a worker's clothing and skin, and the amount of residue that is available for inhalation, are primarily a function of physical rather than chemical factors. That is, the chemical nature of the active ingredient in a pesticide product has little influence on the extent of exposure compared to physical parameters associated with the use of the product. The physical parameters include formulation type (e.g., liquid or granule product), method of application, and the way in which a person handles the pesticide during mixing, loading and application. Because of this, exposure potential is considered "generic" since it is independent of the specific active ingredient (Hackathorn, 1985; Honeycutt, 1985 and 1986; Reinert, 1985). Generic exposure data may therefore be used in lieu of product-specific data for most safety assessments. However, some situations, such as exposure to volatile compounds, (e.g., chlorine dioxide) require consideration of chemical-specific adjustment factors or modeling approaches (e.g., indoor air models).

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

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

Most of the pesticide exposure data available for inclusion in the initial 1992 version of PHED had been conducted by individual pesticide manufacturers who designed their studies to support the registration of a specific product or a group of similar products. It was very common for these companies to generate a set of exposure data that represented the worst case for exposure potential incorporating design features such as the maximum use rate, minimum PPE, and minimum engineering controls. If a risk assessment was acceptable for such a situation, then it was argued that lower use rates, additional PPE, and additional engineering controls would certainly also pass a risk assessment. However, this meant it was common for a study to involve 15 or more measurements of essentially the same situation where each person handled the same product, in the same packaging, in similar amounts, using the same equipment, and for similar periods of time. While these studies are useful for product-specific cases, they are not always generically useful. Nevertheless, many of these types of studies were assembled to form PHED and collectively the database did seem to improve the risk assessment process as regulators could often rely on larger data sets to estimate potential exposure.

However, the available studies for inclusion in the PHED, in hindsight, were not designed, *a priori*, to meet the needs of a generic database and thus, have some technical limitations. In addition, it is now an older database and many use practices have changed. Further, it has limited applicability to most antimicrobial pesticide uses. Exposure monitoring methods have also changed. The basic passive dosimetry methodology has long been accepted as a standard, reproducible procedure that provides accurate and reliable data that does not underestimate exposure (Ross et al., 2007). Even though the passive dosimetry methodology is still a very sound measure of exposure, there have been some improvements. In particular, much of the data in PHED are based on patch dosimetry and exposures were often not measured on all body areas for each monitoring unit or event, i.e., ME. However, PHED provided reasonable estimates of exposure based on the technology of the 1980's. Today, whole-body garment dosimetry is used instead of patches to improve the ability to estimate the distribution of total body exposure.

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There is general consensus among regulatory agencies that the most efficient means of generating handler exposure data is to pool technical resources and assemble a generic database. This consensus and the extremely limited availability of data for antimicrobial pesticides led to the formation of the AEATF II in November, 2004. The task force database, BHED™, will be designed to reflect a logical set of use scenarios with adequate data in each scenario to provide reliable estimates of exposure potential and its distribution. Individual measurements will involve separate subjects and more diversity in equipment and conditions than in PHED, especially for the amount of product handled.

5 Description of AEATF II Monitoring Program and Scenarios

The primary purpose of the AEATF II monitoring program is to develop a new generation of more accurate and useful information and data on worker and consumer exposures to antimicrobials. A secondary purpose is to incorporate these data into a generic database (BHED™). These data will consist of dermal and inhalation exposure estimates derived from monitoring subjects who handle pesticides under a variety of circumstances, using various pesticides and equipment types. AEATF II refers to each unique handling situation as a 'scenario' and anticipates the database will contain sufficient data to support exposure assessments for 14 distinct handling situations, or scenarios (see attached "AEATF II Scoping Document" provided as Appendix A; Appendix B provides a detailed description of each use site identified in the Scoping Document; Appendix C provides a glossary of terms).

In general, each An antimicrobial scenario is defined as a set of related tasks, pesticide formulations, equipment, engineering controls, and worker and/or consumer practices. For example, two scenarios of interest are "mopping application" and "wiping application." The scenarios of interest to the Task Force fall into two general categories:

1. Scenarios that are addressed by simulated-condition studies based on discrete or segmented tasks (mixing, loading and application methods) that can used, separately or in combination, to estimate exposures occurring in a variety of use conditions; and
2. Complex and/or multi-task scenarios that are addressed using *in situ* (e.g., on-site, observational) studies.

The basic element in both simulated-condition and *in situ* studies is the monitoring unit or monitoring event (ME). Each ME will consist of measuring dermal and inhalation exposure potential for a single subject for a time period that represents a typical workday. The general approach is to obtain, for each scenario, a variety of MEs using different subjects and a diverse set of conditions that will reflect current and projected antimicrobial mixing/loading and application practices in North America. Diversity in characteristics that are either known or assumed to be exposure-related will be emphasized. The measured exposures from each scenario-specific set of MEs can then be used to represent the future handler-day exposures to arbitrary (i.e. generic) antimicrobial compounds. For each scenario, the basic objective always is that the set of MEs adequately characterize both the typical and the more extreme exposures expected for a single workday. The design of scenario-specific studies and the construction of MEs are described in Section 16 and in Appendix E.

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A single scenario, such as "mopping", may be defined as a specific task, i.e., the mop-based application of a label-specified end-use formulation containing an antimicrobial chemical. It is common in institutional settings today that automated dispensing systems provide the applicator with ready-to-use mop solutions, and the applicator does not mix and load the end-use mop solution in a bucket. Therefore, the applicator's exposure during a single workday in these conditions would arise only from the task of application and intermittent disposing or emptying the dirty mop bucket solution. The distribution of daily exposures under the "mopping" scenario would then adequately describe the handler's daily exposure to the antimicrobial. In other circumstances, however, a mop applicator could also be manually mixing and loading the mop solution, i.e., preparing the end-use dilution by adding a concentrate to water in a bucket. In these cases, the daily exposure for an antimicrobial handler would arise from two discrete tasks, i.e., mopping (including dirty mop solution disposal) and mixing/loading of mop solution. To provide da ... [1]

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Collectively, all scenario-specific studies that generate MEs to be included in BHED™ are referred to as the AEATF II monitoring (or testing) program. BHED™ will be used to support North American registrations for existing and new pesticide products as required by FIFRA in the United States and the Pest Control Products Act (PCPA) in Canada.

An AEATF II scenario represented by the set MEs in BHED™ may or may not correspond exactly to set of antimicrobial-handling tasks being considered for regulatory evaluation. Scenarios that are complex and consist of multiple non-separable tasks will be addressed by in situ (observational) studies. The MEs from these studies can be used directly for regulatory evaluation. In some situations, however, the number of possible combinations of tasks would too large to address each by a separate scenario. As a result, some AEATF II scenarios correspond to single discrete tasks (e.g. mopping, wiping, mixing, etc.) that will be addressed by simulated-condition studies. When regulatory interest is only in the discrete task (e.g., mopping only) then the scenario in BHET™ is directly applicable. However, when interest is in a combination of these tasks (e.g. mixing plus mopping) then results from several AEATF II scenarios must be combined.

A single scenario, such as “mopping”, may be defined as a specific task, i.e., the mop-based application of a label-specified end-use formulation containing an antimicrobial chemical. It is common in institutional settings today that automated dispensing systems provide the applicator with ready-to-use mop solutions, and the applicator does not mix and load the end-use mop solution in a bucket. Therefore, the applicator’s exposure during a single workday in these conditions would arise only from the task of application and intermittent disposing or emptying the dirty mop bucket solution. The distribution of daily exposures under the “mopping” scenario would then adequately describe the handler’s daily exposure to the antimicrobial. In other circumstances, however, a mop applicator could also be manually mixing and loading the mop solution, i.e., preparing the end-use dilution by adding a concentrate to water in a bucket. In these cases, the daily exposure for an antimicrobial handler would arise from two discrete tasks, i.e., mopping (including dirty mop solution disposal) and mixing/loading of mop solution. To provide data for regulatory agencies to address the addition of this discrete task (mixing and loading), the AEATF II will conduct separate studies of mop application (which would include discrete measurement of exposures associated with mopping and dirty mop bucket solution emptying) and of mixing and loading via open pouring of liquids.

At times, user’s of the BHED™ data may need to consider the distribution of a combined exposure from multiple tasks represented by separate scenarios. The arithmetic mean of a combined single-day exposure is simply the sum of the arithmetic means for each separate task. However, other aspects of the combined distribution depend on how exposures for the same individual from different tasks are correlated. If the exposures are perfectly correlated (i.e. the

correlation is 1) then any percentile of the combined distribution is the sum of the percentiles for each task separately. If the same-person-different-task exposures are independent, however, then the combined percentiles are less extreme than the sum of the separate percentiles. This 'shrinkage' of the combined distribution is rather minimal and is practically non-detectable if one task's mean exposure is much larger than any of the other tasks mean values. Thus, unless a separate estimate of the between-task correlation is available, a practical recommendation for most BHED™ users would be to simply assume that the tasks are maximally correlated and add all percentiles. This approach would likely be acceptable in the context of regulatory-decision making when relying upon BHED™, given the overestimation (more conservative) bias associated with summed upper-percentiles. More importantly, the development of normalized exposure data for discrete tasks provides the flexibility to construct or assemble and assess multi-task exposures and thus, greater utility for a generic exposure database.

In some instances, there may exist, a discrete task or set of tasks that falls outside all the scenarios for which monitoring is planned. This is most often because the task is rare or would be expected to give non-detectable exposure levels. When reasonable, users of BHED™ might choose to ignore the task or use another scenario as a surrogate for the missing task. For example, in the case of mop application, in some cases, a person may pour a concentrated formulation containing an antimicrobial into a mop bucket containing water to create a label-specified end-use dilution. The exposures (dermal and inhalation) that may occur during this liquid pouring task can be addressed with the separate "open liquid pouring" study data. The "open liquid pouring" data could be used directly as a conservative surrogate for pouring a concentrate into a mop bucket. In this example, it is important to adjust the surrogate exposures distribution for the amount of active ingredient handled in the specific mop bucket pouring situation being assessed.

6 Limitations of Existing Data and Justification for Supplemental or Confirmatory Data

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

By 2000, the U.S. Environmental Protection Agency began evaluating alternatives to PHED. The EPA has outlined its intentions regarding PHED (Letter from Margaret Stasikowski, Director, Office of Pesticide Programs, Health Effects Division, to Daniel Fay, Valent USA Corporation, 16 March 2001). EPA has acknowledged the need to "overhaul" PHED version 1.1 because many of the existing exposure studies in the database are outdated or scientifically inadequate by "today's standards". In addition, many antimicrobial pesticide exposure scenarios that are being assessed by the Agency are under-represented or not even included in PHED version 1.1.

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

- Inadequate number of measurements for one or more body areas;
- Inadequate quality assurance or quality control data;
- Use of patch dosimeters instead of whole-body dosimeters;
- Lack of whole body dermal estimates for subjects (i.e., not all body parts monitored for dermal exposure in most studies);
- Many (>70%) non-quantifiable residues on inner dosimeters;
- Lack of diversity for test conditions (e.g., same subjects used repeatedly or all subjects handling the same amount of product); and
- Lack of representativeness of test conditions (e.g., equipment or procedures that are no longer in common use).

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

For reference, PHED confidence ratings can be summarized as:

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

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

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

Therefore, PHED can have low confidence for one clothing/PPE situation and high confidence for another within an exposure scenario. While protection or penetration factors can be used to estimate protected exposure from non-protected exposure results, or vice versa, this may create additional uncertainty for exposure estimates and may not be appropriate for all risk assessments. PHED data with potential relevance to antimicrobial scenarios are as follows:

PHED Scenario (#)	Comments re: PHED Scenario	AEATF II Application Method
Liquid (3)	Mixing/Loading (M/L); open mixing	Pour Liquid
Pump Liquid (6)	M/L; closed mixing	Pump Liquid
Paintbrush/Roller (22)	Brush application only	Brush / Roll
Aerosol Spray (10)	Application only	Aerosol Spray
High Pressure Spray (19)	Application only	High Pressure Spray
High Pressure Spray (35)	M/L, Liquid, open pouring; and application	Pour Liquid and High Pressure Spray
Lo Pressure Spray (32)	M/L; Liquid; open pouring; and application	Pour Liquid and Low Pressure Spray
Low Pressure Spray (33)	M/L; Wettable Powder; and application	Pour Solid and Low Pressure Spray
Low Pressure Spray (18)	Application only; handwand equipment	Low Pressure Spray
Airless Spray (23)	Application only; house stain	Airless Spray
Pour Solid (1)	M/L; Dry flowable; open mixing	Pour Solid
Pour Solid (2)	M/L; Granular; open mixing	Pour Solid
Pour Solid (4)	M/L; Wettable powder; open bag	Pour Solid

In addition to data available in PHED, another source of existing data being used by regulatory agencies in the case of antimicrobials is that represented by an exposure monitoring program conducted by the CMA (Popendorf et al. 1992). On 4 March 1987, a Data Call-In Notice was issued for submission of data for antimicrobial pesticide active ingredients. In response, the CMA developed a generic biocide exposure assessment protocol and conducted a study, *Chemical Manufacturers Association Antimicrobial Exposure Assessment Study* (conducted by Dr. William Popendorf at the University of Iowa; Popendorf et al. 1992) based on the protocol. The CMA effort originally considered a list of ten pesticide active ingredients. This list was reduced to 9, considering several criteria. Exposures to seven of these nine chemicals were assessed, as well as exposure to zinc chloride, which was used as a surrogate tracer for a process and chemical which could not otherwise be assessed. In total, 88 separate MEs were obtained for six end-use settings and nine application methods (pour liquid, pump, pour solid, place solid, aerosol spray, high pressure spray, low pressure spray, mop and wipe) to assess both dermal and inhalation exposures.

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Based on EPA's review (Mostaghimi 1995), CMA's study met some requirements, but was lacking in other areas. Specifically, areas in which the Amended Report complied with the procedures specified by the EPA's dermal and inhalation exposure guidelines included the following:

1. Most of the dermal samples had detection limits low enough to allow accurate reporting of the sample, according to EPA guidelines.

2. Some of the field recovery data were acceptable; five chemicals had acceptable recoveries from gloves, and two chemicals had acceptable recoveries from air, and the results were corrected for losses in the field using correction factors determined from the recovery data.
3. The materials used in the analyses were acceptable in most cases and were adequate for further analysis. To assess dermal exposure, gauze pads were used for dry residues, cotton gloves were used for assessing exposure to hands, and placement of dermal pads was found to be acceptable. For inhalation exposure, standard flow rates were used for air impingers and personal sampling pumps, standard NIOSH factors were applied to respirators to estimate reduction of exposure inside the respirators; and
4. Documentation of data collected during laboratory and field operations was adequate based on both CMA's description of their data gathering efforts and presentation of data provided in Appendix C of CMA's Amended Report (Popendorf et al. 1992). In addition, replicate-specific notes were provided for any unusual problems that may have contributed to error.

However, the following areas were found to be lacking:

1. Good Laboratory Practices, especially in the area of providing quality assurance, must be followed more closely;
2. A majority of extraction efficiencies were below the minimum level suggested in the guidelines. Perhaps more importantly, the percent field recoveries (which represent the amount recovered under actual conditions encountered in the study) of many of the chemicals were lower than the minimum needed to assess exposure. Therefore, either different active ingredients would need to be used in future studies, or new analytical methods to increase recoveries should be employed.
3. A significant proportion of air monitoring samples were lower than the detection limit; and
4. None of the application method/end use settings had the minimum number of replicates (i.e., 15) recommended in EPA's guidelines.

The limited number of MEs combined with poor recovery data severely limits the conclusions that can be drawn from CMA's study. Therefore, the EPA and other regulatory agency reviews indicated that additional data for all application method/use setting combinations should be obtained to support more confident inferences about exposures in a variety of settings.

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The deficiencies identified by EPA in CMA's report were corroborated by other reviewers. First, the California Department of Pesticide Regulation (CA DPR) notes that the exposure data cannot be used as generic data for all antimicrobials because recoveries were low, precision of the measurements were

not established, and CMA did not establish the validity of generalizing the information among applications and end-use settings (Powell et al., 1995). Canada also reviewed the study and made similar conclusions (Worgan and Rozario, 1993).

In summary, in order to assess potential risks from exposure to antimicrobials, EPA has extremely limited data on which to rely. In fact, EPA has repeatedly identified that data as inadequate.

In each of the following example Re-registration Eligibility Decisions issued during 2005 and 2006, EPA has stated that "the risk assessment noted deficiencies in the surrogate dermal and inhalation exposure data available from the Chemical Manufacturers Association (CMA) data base. Therefore, the Agency is requiring confirmatory data to support the uses assessed with the CMA exposure data within this risk assessment."

- PHMB. September 2005. EPA739-R-05-003
- Benzisothiazoline-3-one. September 2005. EPA739-R-05-007
- Para-Tertiary-Amylphenol, Potassium Sodium Salt. January 2005. EPA738-R-05-001
- Azadioxabicyclooctane. September 2005. EPA739-R-05-010
- Chlorine Dioxide and Sodium Chlorite. August 2006. EPA738-R-06-007
- Pine Oil. September 2006. (publication number unavailable)
- Aliphatic Alkyl Quaternaries (DDAC). August 2006. EPA739-R-06-008
- Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC). August 2006. EPA7389-R-06-009

The above list is not exhaustive but is intended to point out that the Agency has clearly and repeatedly required additional exposure data for assessing risks from occupational and residential uses of antimicrobial pesticides.

7 Alternatives to Additional Human Monitoring

Regulatory agencies are charged with assuring that registered uses of a pesticide will not cause unreasonable adverse effects to pesticide handlers. As part of such determinations, regulators and risk assessors must be able to estimate with confidence likely levels of occupational exposure. Excluding new human monitoring studies, the information available to make reliable approximations of exposure currently comes primarily from generic data contained in PHED and CMA data (Popendorf, 1992), but also from pesticide-specific exposure studies, modeling, and published literature. There is a general paucity of published literature relevant to antimicrobial exposure; and the few relevant publications were not conducted under GLP, did not typically measure whole body exposure, and the raw data for verifying results is generally not available. Further, there are no known reliable (validated) models to estimate dermal exposure to antimicrobial users. The use of animal data is obviously not an option for studies that monitor occupational exposure to individuals engaged in their normal work activities.

Therefore, the only alternative to the conduct of new human monitoring studies appears to be:

- The continued use of the existing information sources (PHED and Popendorf et al. 1992, other published literature, and predictive modeling); and
- The acquisitions of additional handler exposure data from other existing product-specific studies that meet established acceptance criteria and that have generic applicability.

The limitations of PHED and the other current sources of exposure assessment data have been discussed briefly above. The limitations of existing data are being evaluated by AEATF II on a scenario-by-scenario basis using acceptance criteria (see Appendix D) developed via a consensus process with regulatory agencies (U.S. EPA, Health Canada and California EPA). Existing data can also inform the design and sample size (see Appendix E for the AEATF II general study design approach) for proposed studies, where additional data are determined to be needed. Appendix F provides an example evaluation in the case of applicator dermal and inhalation exposure data available in PHED for hand-held aerosols. This example includes a comparison of the PHED data to key acceptance criteria adopted by the AEATF II (see Appendix D).

Under the first stage of the AEATF II program, and prior to the conduct of scenario-specific exposure monitoring studies with human volunteers, the AEATF II reviews existing handler exposure data from various sources and considers acquiring data that meet established acceptance criteria. A recent SAP (2007) evaluated the AEATF II acceptance criteria and concluded:

> The Panel viewed the selection criteria proposed by AHETF and AEATF II to be reasonable for generating exposure data for using in exposure assessments, with the following caveats. The monitoring duration requirement may be too stringent. Some provision to allow the inclusion of data from settings where only short-term uses are the norm may need to be added.

Although some useful worker exposure studies may be acquired by AEATF II, most of the existing data are not sufficient to meet the generic data needs identified in advance by the AEATF II and the Regulatory Agency Advisory Committee. While there may be other data that have been submitted to EPA and may be suitable for a generic data base, they are proprietary and AEATF II does not have access to them. Consequently, at this point, no viable alternatives to performing additional human monitoring studies exist for most scenarios.

It should also be pointed out that pre-requisite studies for AEATF II testing do not require research with human subjects. These pre-requisite studies include analytical method validations, field recovery validations, and toxicity studies that support the registrations of the test materials used. Therefore, the exposure measurements (monitoring units or events, i.e., MEs) proposed by this document reflect the entirety of human participation.

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8 Ethical Considerations

All AEATF II studies will be conducted in compliance with the applicable requirements of 40 CFR Part 26, EPA's regulations for "Protections for Human Subjects of Research", and, if they are conducted in California, with the applicable requirements of California Code of Regulations Title 3 Section 6710. Ethical considerations are scenario and study protocol-specific, however, general considerations are discussed below.

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8.1 Subject Recruitment Process

AEATF II studies require IRB, EPA/HSRB and sometimes CDPR approval of the protocol and process before subjects are recruited and the worker exposure monitoring study is initiated. The subject recruitment process must be tailored to each scenario-specific study. AEATF II studies will typically incorporate the elements described in the section as components of the recruitment process.

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Recruitment is conducted by selecting trained or experienced antimicrobial chemical handlers from subjects (workers or consumers, depending on the scenario and products being studied) identified by personal contact through local

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service businesses or research organizations. Recruitment materials such as advertisements or fliers may be used. The Principal Investigator (Study Director) approves the selection of all study sites and subjects, generally after visiting the proposed sites and talking to potential volunteers. Informed consent discussions are conducted by the Principal Investigator, generally shortly before study initiation.

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8.1.1 Identification and Recruitment of Potential Subjects

It is important to acknowledge that each study protocol must include specifically defined processes for the identification and recruitment of potential subjects. This protocol specificity includes for example, eligibility criteria.

Population Base

In general, AEATF II proposed studies will involve adult subjects that meet specified inclusion/exclusion criteria and who will be recruited from the professional handler and/or consumer user population in defined geographic locations within the United States (U.S.), Canada and possibly, for a few studies, from European countries, and defined geographic locations therein. Persons with professional training and/or experience will be initially contacted by the Field Coordinator using a phone interview script. Recruitment of subjects will be through a) word-of-mouth and telephone contact, b) relevant service companies or recruitment agencies that have been provided with a flyer that describes the study and contains a phone number and name of an AEATF II study contact person; or c) direct contact with service providers who are asked if AEATF II may have their permission to ask their employees if they might be interested in participating in the study independently from their employer where AEATF II provides the chemical and use equipment, or at the employer's place of business, if the employer is providing the antimicrobial and use equipment. Interested subjects should contact the Field Coordinator directly.

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Enrollment of Alternate Subjects

Alternate subjects will be enrolled into each study and the number of alternates enrolled will depend on an individual study's objective regarding the number of monitoring units (or monitoring events, i.e., MEs). Typically, enrollment of three to six alternative subjects is anticipated. All subjects will be informed during the interview process that a small number of subjects will be designated as alternates and are expected to be present at the test site on a given day, but might not participate in that day's activity. An alternate will be monitored if the assigned subject does not present or if the assigned subject drops out for any reason. If a subject begins monitoring but stops less than a specified time period into a given study, the dosimetry from that subject will not be analyzed and the alternate will be used. Dosimetry from any subject that complete a minimum specified duration (to be specified in each study protocol) or more will be

analyzed and the results assigned to the nearest target task duration interval, i.e., subjects who completed as least 20 minutes of a given task (e.g., surface wiping), would be assigned to a pre-specified 30 minute target task duration group. The alternate subjects not tested the first day will be asked if they are available to fully participate the next day. Alternate subjects will be compensated for coming to the test site. Alternate subjects will serve as back-up for any enrolled subjects who fail to appear on a given day, for subjects that decide to withdraw prior or during the test, for female subjects testing positive in the pregnancy test, or for any other personal circumstance.

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Inclusion and Exclusion Criteria

The Principal Investigator is responsible for ensuring that study-specific inclusion criteria are met when participants are recruited. The subjects will be asked to fill out a demographic questionnaire and asked health-related questions. Females will be asked to take a pregnancy test. The responses and results will provide the basis for inclusion or exclusion from the study.

Inclusion

- Males or females, 18 to 65 years of age
- In good health
- Willingness to sign the Informed Consent Form
- Speak and read English or Spanish (or, if feasible, another predominant language selected for a specific study based on the associated potential subjects' demographics)

Exclusion Criteria

- Skin conditions on the palmar surface of the hands (e.g., psoriasis, eczema, cuts or abrasions)
- Pregnancy, as shown by a urine pregnancy test
- Lactation
- Allergies to household chemical-based products, soaps or isopropyl alcohol
- Declines to sign the Informed Consent Form or the Health Questionnaire
- Does not read and understand English or Spanish (or, if feasible, another predominant language selected for a specific study based on the associated potential subject's demographics)
- Is less than 18 or more than 65 years old
- Is not in generally good health
- Severe respiratory disorders (e.g., moderate or severe asthma, emphysema)
- Cardiovascular disease (e.g., history of myocardial infarcts, stroke, congestive heart failure or uncontrolled high blood pressure)

- Is an employee of the contract laboratories conducting the study, or is related by blood or marriage to personnel in the contract laboratories.

Willingness to Participate
Participants must be freely willing to participate in a study of this type and have no interest in the conduct or outcome of the study (e.g., they cannot work for a pesticide manufacturer who is a member of AEATF II, or for the Principal Investigator or any other sub-investigator, or for any party with a substantial or contractual interest in the research, nor can they be relatives of any investigators).

Experience
Most AEATF II studies will involve only professional workers (e.g., janitorial professionals, wood treatment facility workers, machinists at metal working shops) with experience specific to the tasks being investigated. This will ensure, in the case of subjects, that they have met basic safety trained requirements, as dictated by their employer, prior to handling pesticides. Further, if professional pesticide products are used in the study, only professional subjects would be involved in the study. In some studies, products that could be used by workers or consumers will be involved; thus, potential subjects could include consumers with relevant experience in performing a scenario-specific task

Age
All monitored subjects will be at least 18 years of age, and no older than 65. Subjects will be asked for a Government-issued photo-ID to confirm their age.

Health Status of Participants
Only subjects who consider themselves to be in good health will be eligible. This will be affirmed by the subject's responses to the health-related questions. The subject-provided responses and information help the Study Director to exclude subjects who are not in good general health, allergic, mentally ill, cognitively impaired, chronically ill, or terminally ill. This will help limit the risks of adverse effects due to pesticide handling.

Work Periods
All monitoring periods will be designed to represent the typical duration of the specific task or activity being monitored during a normal workday. Generally, this will involve monitoring periods from 30 minutes to eight hours in length, since most AEATF II scenario-specific activities are performed intermittently during the work day. Data sources will be identified and evaluated regarding product use/usage information to inform study designs with respect to product application sites and surfaces, application methods, amounts handled, and duration of tasks or work periods. An example source of publicly available professional "habits and practices" information is that from the International Sanitary Supply Association (ISSA; www.issa.com). ISSA is the leading international trade

association for the cleaning industry. ISSA's worldwide membership includes more than 4,800 distributors, manufacturer, building service contractor and in-house service provider members. ISSA cleaning operations observational survey data (time and motion studies) were used to inform AEATF II study designs, e.g., predominant mop technology, cleaning task durations, for the mop and wipe applicator exposure studies. Another example source of product use information, including task duration or work periods, is a proprietary survey conducted by the Chemical Specialty Products Association (www.cspa.org), Antimicrobial Exposure Joint Venture (AEJV), which has collected data focusing on consumer antimicrobial cleaning product use in residential settings.

Product Label Non-Conformance

All subjects will be required to perform pesticide handling tasks in conformance with the label requirements. BHED® is designed to reflect exposure to workers and/or consumers who follow legal and proper handling of pesticides and not who misuse the product or otherwise violate the label. In particular, subjects must wear the Personal Protective Equipment (PPE) required by the label and researchers will remind participants to use that PPE should they be observed not wearing the PPE during exposure monitoring. Any subjects who will not follow the label requirements during the study will be asked to discontinue their participation and their exposure samples will not be collected. A subject will be reminded once if found not wearing PPE. A second infraction is grounds for subject removal from the study.

Pregnant or Nursing

The pregnancy status of all potential female participants will be ascertained through the use of a supervised over-the-counter urine pregnancy test conducted within 24 hours prior to the initiation of monitoring. Any pregnant subjects will be excluded from the study. In addition, women who are nursing will be excluded.

Speak and Read either English or Spanish

English and Spanish are by far the most common languages used by occupational pesticide handlers in North America. Translators for other languages are often difficult to locate where antimicrobial products are used, making it difficult to ensure fully informed and fully voluntary consent for speakers of other languages. Thus, AEATF II anticipates that it will not enroll participants who are not fluent in either English or Spanish. If a language other than English or Spanish has high incidence (>15%) amongst potential subjects for a specific study, translation of study materials, the availability of translators, and the additional language-speaking technical staff person (e.g., present during the study's field phase) will be considered by AEATF II.

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8.1.2 Exclusion of Vulnerable Group(s)

AEATF II prohibits most of the vulnerable groups as participants, including: people who are ill, cognitively impaired, pregnant, minors, employees or relatives of the Principal Investigator, etc. As described above, local site coordinators are generally used to locate suitable sites and potential participants – they are identified as a research site in applications to IIRB. AEATF II will occasionally allow a local site coordinator, or an employee of the site coordinator, to be a participant in a study. In this case, the subject must meet all of the criteria listed above, including the requirement that he/she be experienced in the particular task being monitored. AEATF II will only use such research staff if they also have experience handling pesticides in a commercial environment, for example as the owner of a separate commercial facility or in a previous job. This group (i.e., employees of research site) may be vulnerable to coercion since the local site coordinator receives the benefit of payment for his services.

However, as described in the next section, AEATF II takes special care to prevent coercion of these subjects by having their supervisor/employer confirm they won't be coerced and that their participation decision will have no impact on their employment or work opportunities.

AEATF II does not intend to recruit limited or non-readers, however, a fair percentage of the workforce (and consumer population) has Spanish as their primary language. When AEATF II knows in advance that a Spanish speaker may be recruited for a particular study, this potentially vulnerable category will be identified in the application to IIRB. AEATF II has procedures in place to deal with candidates and subjects who prefer to use Spanish. These procedures are discussed in the following section.

Another potentially vulnerable group that might be part of the target population is poor/uninsured (health care insurance) subjects. AEATF II does not intentionally recruit these individuals and will not inquire as to the economic or insurance status (health care insurance) of potential study participants. Therefore, this category will not be identified to the IRB as one that is intended to be recruited. As discussed below, the remuneration being offered (generally for just one day of participation) is believed to be not high enough to induce otherwise reluctant subjects to participate, so the economic status of participants in these studies is not a concern. The level of remuneration will be consistent with pay in a particular region of the country if there are obvious differences in wages between regions. In addition, AEATF II will cover all costs of injury or illness that subjects experience because of participating in the study (that are not covered by the subject's or their employer's insurance).

Another potentially vulnerable group that might be part of the target population is illegal workers. For example, illegal workers may feel obligated to participate (e.g., in order to protect their job) or be reluctant to accept medical treatment. Federal laws give employers the responsibility for ensuring their workers are legal, but AEATF II does not employ subjects. AEATF II will therefore assume workers are legal and will not ask about their status. In addition, should researchers become aware of an illegal worker they will not share that information. Workers who might be illegal will be protected from coercion primarily via the mechanism described below where the Study Director will discuss the voluntary nature of study participation with the worker's supervisor/employer.

8.2 Informed Consent Process

Two fundamentally different recruitment situations may occur. If a study is being conducted on an active worksite where subjects are normally employed to do their job, the following preliminaries occur before subjects meet the Principal Investigator for studies that occur at normal worksites. When potential sites have been selected and potential participants have been identified by the Field Coordinator, a flyer describing the study is distributed to potential participants. Before any contact with potential subjects the Principal Investigator has a discussion with the direct supervisor of each potential participant to ensure that the supervisor has no interest in whether the subjects do or do not choose to participate, and further, that the supervisor understands that subjects should not feel any coercion to participate in the study. The supervisor must confirm there will be no adverse impact on a worker who does not volunteer, or withdraws from the study, for any reason. This extra care to prevent coercion from employers will be documented on a form which the supervisor, business owner, or commercial applicator must sign. Prospective volunteers are introduced to the Principal Investigator, and their language of choice is determined. Then, each volunteer is provided with the supervisor's signed form, the IRB-approved consent form, and a full explanation of the study, its requirements, and any potential risks as discussed below for studies conducted away from subjects' normal worksite. This occurs during a confidential and private discussion with the Principal Investigator at the worker's location if the study is being conducted at a work site under the worker's supervisor's control.

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If subjects are recruited to work at a site not under their supervisor's control, i.e., away from their normal worksite, and not under their supervisor, another paradigm is used. The Field Coordinator will be contacted by individuals that have been made aware of the study by a flyer posted at their place of employment. Using an IRB-approved phone script, the language preference of the subject will be identified, and interested potential subjects will be scheduled for a meeting with the Principal Investigator or foreign language-speaking designee.

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Interested volunteers will be screened and enrolled into the study based on one-on-one conversation held at the office of the Principal Investigator. A Spanish-speaking technical designee will be available to ensure communication with anyone preferring Spanish over English. The Principal Investigator will share information on the study design with interested participants, and provide them with copies of the IRB approved Informed Consent Form and answer their questions. The Principal Investigator will describe the study to the volunteer in great detail and encourage each potential subject to ask questions and request clarification at any time during this process as well as in all activities that follow. The Principal Investigator will provide each potential subject with a copy of the product label and MSDS and answer any questions regarding the product to be tested. The Principal Investigator will go over the Inclusion and Exclusion Criteria for the study and answer any questions that the potential subjects have. They will be provided with copies of the Informed Consent Form, the Subject Self-Reporting Demographic Form and the State of California Department of Pesticide Regulation "Experimental Subject's Bill of Rights" and encouraged to take them home with them to discuss with family and friends.

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The Principal Investigator will explain to potential subjects wishing to remain in consideration that they may withdraw from the research study at any time without penalty to their compensation. The Principal Investigator will then read the "Experimental Subject's Bill of Rights" to the potential subjects. The amount and form of compensation, the potential risks and discomforts and treatment, and compensation for injury will be more fully explained and potential subjects encouraged to ask questions. If the potential subjects do not have any questions and are interested in participating in this research study, they will then be asked to sign the Informed Consent Form and then fill out the Subject Self-Reporting Demographic Form. The Principal Investigator will check the potential subject's driver license or state-issued identification card to verify age to exclude minors, and identity as required by California DPR, and review the package of information provided for completeness against the protocol's inclusion/exclusion criteria. The Principal Investigator will retain the final right to refuse participation to any potential subject; however, following signing the informed consent form, any potential subject not actually monitored will be given the minimum compensation. For female subjects, final eligibility will be determined on each study day following a pregnancy test.

Volunteers are advised of their right to withdraw from the study at any time and for any reason without jeopardizing their position with their employer. Volunteers are also informed during the confidential consenting process that they will receive compensation after they volunteer to participate in the study, even if they withdraw for any reason or the sponsor does not use them for any reason.

AEATF II consent forms are unique to individual studies, but all have very similar structure and contain the following:

- Study title
- Protocol number
- Study sponsor
- Investigator name
- Study site(s)
- Study-related phone number(s)
- Sub-investigators
- Statement of the purpose of the study
- List of procedures involving the subjects
- Detailed list of risks and discomforts
- Statement regarding disclosure of new findings
- Statement of benefits of participation
- Statement of no cost to the subjects for participation
- Statement of payment for participation
- Statement of alternatives indicating this is not a medical treatment study and the alternative is to not participate in this study
- Full explanation of confidentiality of worker information
- Statement of compensation for injury
- Source of funding
- Voluntary participation and withdrawal
- List of resources who may be contacted to obtain answers to questions
- A section for signatures of the participant and the person conducting the informed consent discussion

During the discussions between potential participants and the Principal Investigator, ample time is provided for questions and the Principal Investigator will provide any additional information or clarification that is requested. These discussions typically take place at the worker's location, in a private setting, generally in a meeting room of a facility or commercial application company. Consent is generally obtained within one to three days of actual study conduct, but sometimes earlier. If the worker agrees to participate he/she is asked to sign and date the informed consent form and the Principal Investigator provides a copy of the signed form to the worker. Within 24 hours prior to participation, any women who are selected to participate will be asked to take a urine pregnancy test (over the counter variety) and will be allowed to participate only if the test is negative. This test will be supervised by a female researcher. To protect the privacy of the worker, the test results are not revealed to the employer or co-subjects. If the worker chooses to proceed with the study then a female researcher will confirm the test is negative and record this in the study raw data. No positive test results will be documented and the worker will be allowed to withdraw from the study without stating a reason (and still receive appropriate remuneration).

For subjects whose preferred reading language is Spanish, AEATF II obtains an IRB-approved translation of the consent form and ensures that a Spanish-speaker familiar with the study protocol is present during the informed consent process and during study conduct. In all cases, the Principal Investigator will conduct discussions in English, but the participant will sign the version of the consent form in his preferred reading language. The Spanish speaker may be an employee at the study site, but more typically will be supplied by the Principal Investigator and will be brought into the discussion if the subject's preferred language is not English. A Spanish-speaker familiar with the study protocol will also be utilized during the study should any issues arise which can't be resolved directly with the worker.

Deleted: For subjects whose preferred reading language is Spanish, AEATF II obtains an IRB-approved translation of the consent form and ensures that a translator is present during the informed consent process and during study conduct. In all cases, the Principal Investigator will conduct discussions in English, but the participant will sign the version of the consent form in his preferred reading language. The translator may be an employee at the study site, but more typically will be supplied by the Principal Investigator and will be brought into the discussion if the subject's preferred language is not English. Translators will also be utilized during the study should any issues arise which can't be resolved directly with the worker. ¶

In all situations, if the Principal Investigator is not comfortable that the worker fully understands the discussions and the contents of the consent form, the worker will be excluded from consideration to participate in the study. This will be ascertained by providing repeated opportunities to ask questions and by asking questions of the potential volunteers that would require a response that indicates understanding of key issues. For example:

- Q: When can you withdraw from the study?
  A: Whenever I want.
- Q: What will your supervisor have you do if you don't volunteer?
  A: My regular job.
- Q: What will you wear so we can measure inhalation exposure?
  A: An air pump on my belt.
- Q: Will researchers tell you how to do your job?
  A: No.

Subjects' ability to read and understand either English or Spanish will be confirmed by their answers to the Subject Self-Reporting Demographic Form. The process for obtaining informed consent is fully documented in each AEATF II study protocol.

8.3 Subject Remuneration

In almost all cases, AEATF II is studying the potential exposure to pesticides for subjects who are performing their usual activities. This would be generally true for both scripted and non-scripted activities. Thus, pesticide handling would be conducted even if they weren't participating in the study.

AEATF II has selected a standard remuneration amount for all AEATF II studies and participants since the inconvenience involved is essentially the same for participants in all studies. In addition, AEATF II chooses not to offer an hourly rate since it prefers that subjects perform their typical tasks and wants to avoid

any incentive for subjects to choose a particular task since they could “earn more money”. The researchers utilized by AEATF II all have experience in dressing and undressing subjects and the complete process takes only about 20 to 30 minutes throughout the work day. This represents the primary inconvenience associated with participation in an AEATF II study.

While any standard amount of remuneration could represent a very different proportion of various subjects’ typical daily pay, fairness suggests that each worker should receive the same amount of remuneration since the amount of inconvenience is essentially the same.

AEATF II selected the amount of $100 at the outset of the task force project and still believes this is an appropriate amount, although compensation may be varied if the local economy requires more or less for cost of living. This is equivalent to approximately $15/hour for a full day’s work which is similar to other amounts from other studies that have recently been approved by HSRB. AEATF II believes that $100 is not sufficiently high as to create undue influence to participate in the study, especially since subjects are generally limited to one day of study participation.

Individuals that are not tested including anyone signing the informed consent form but not subsequently being monitored will be compensated for their time and inconvenience at the rate of $50 per day. Subjects participating in the study will be compensated $100 for the single day that they are monitored. The values for compensation are based roughly on a day’s wage of $100 and represents potential lost time from work, travel time and incidental expenses incurred in study participation. Compensation will be in the form of cash at the completion of participation.

Generally, a particular person will be allowed to participate in the study only one time. This study design principal provides data for separate exposure measurements that reflect different subjects in order to capture variability between subjects. However, the same worker could participate more than once in a study (or in two studies) as long as the worker performs a different task. For example, one person could be monitored for exposure as a mixer/loader on one day and as an applicator on another day (assuming the experience and other criteria are met). In this case, that person would receive a $100 payment on each of those two days.

It is important to note that subjects who are professional workers and who are participating in any AEATF II studies that are being conducted “in situ” (i.e., exposure monitoring studies at workplaces such as a metal working shop) are “on the job” and will receive their normal salary and all other compensation they are due, including compensation for any overtime worked according to local laws. This compensation is the responsibility of the worker’s employer and not AEATF II.

In addition to their normal compensation, AEATF II will provide a payment of $100 (U.S. dollars if in the United States or comparable compensation if in Canada or Europe) to each worker who volunteers to be monitored for exposure. This payment is in appreciation for the extra effort and inconvenience associated with subjects participating in the study which includes wearing the inner dosimeter (long underwear, requires undressing in a private area); allowing researchers to wash their hands and wipe their faces; allowing researchers to remove the inner dosimeters at the end of the monitoring period; and wearing a personal air sampling pump throughout the workday.

8.4 IRB Review Process

AEATF II generally uses the Independent Institutional Review Board (IIRB) in Plantation, Florida (www.iirb.com) to review each of its study protocols for ethical compliance. Initial review submissions from AEATF II to IIRB typically include the following:

- The submission package to the IRB includes the study protocol and appendices including, test substance MSDS, summary of toxicology information and estimated risk for exposure anticipated in that study based on U.S. EPA's Registration Eligibility Decision documents (REDs). Additionally it includes experimental subjects' bill of rights, subjects self-reporting demographic form, flyers soliciting prospective subjects and scripts used to verbally describe the study to prospective subjects. All documents provided to subjects will be translated into another language if the subject demographics warrant, i.e., if >15% of the population uses another language in any study region.
- Initial Review Submission Form (IIRB form revised 01-2006; this is part of the IRB correspondence file required by 40 CFR 26.1125).

The IIRB form identifies AEATF II as the sponsor and the Study Director as the Principal Investigator. It also identifies study site(s) (generally local site coordinator research facilities) and provides details about subject recruitment, consent, and payment. Hospitalization procedures are also provided which identify the nearest emergency medical facility to the study site(s) and indicate that 911 (or other local emergency number) will be used as the primary method for obtaining medical attention should any worker experience adverse effects during a study. IIRB also maintains files containing the Principal Investigator's curricula vitae and documentation of human subjects training which support the submission.

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IIRB will review all new study protocols at regular convened meetings. When studies are to be conducted in California, AEATF II will also submit study protocols and related information to the California Department of Pesticide Regulation (CDPR) for their review and approval under CCR Title 3 Section

6710. Any changes required by CDPR will be incorporated into the study protocol, which will then be reviewed and approved by IIRB. Only upon receipt of IIRB-approved protocol and consent forms will CDPR grant final approval for the study to be conducted in California. Further changes in the protocol and associated materials may also be required by EPA, and would also lead to re-review by the IIRB.

All protocol changes (amendments and deviations) shall be reported to the IIRB in writing by letter, fax or email. Proposed changes (amendments) deemed necessary to eliminate apparent immediate hazards to the human subjects may be implemented without prior IIRB approval. All other amendments must be reviewed and approved by the IIRB prior to implementation, or as specifically instructed by IIRB policy in this regard. Approval will be granted in accordance with IIRB policy and procedures, and may be granted by telephone provided it is documented in writing in the study raw data. The IIRB may provide expedited review of minor changes as defined by 40 CFR Part 26.1110 at its discretion.

Unplanned changes (deviations) which occur during conduct of the study cannot, by definition, be reviewed and approved by the IIRB prior to implementation. Deviations will be reported in writing by letter, fax or email as soon as possible following the change. The Principal Investigator shall follow written instructions provided by the IIRB for prompt reporting to the IIRB, appropriate institutional officials, and the EPA of unanticipated problems involving risks to human subjects or others.

8.5 Additional Efforts to Protect Human Subjects

The AEATF II takes many steps to ensure the safety of the subjects being monitored. As outlined above, protocols and consent forms are approved by an IRB (and DPR, if needed), informed consent is obtained for all study participants, consent is obtained in writing in the worker's preferred language, certain vulnerable groups are not recruited, pregnant and nursing women are excluded, and participants are informed they may withdraw at any time. Other steps that AEATF II takes to ensure the safety of study participants are summarized below; each study protocol will define "stop criteria" and medical management procedures.

The objective of the AEATF II is to generate data collected under actual use conditions and following all label requirements. Subjects are never asked to wear less protective clothing than they would ordinarily wear, even if the clothing is not required on the product label. In cases where a worker normally wears PPE not required by the label, the AEATF II either allows them to wear the extra clothing (or equipment) or they are excused from the study, depending on the specific goals of the study. The AEATF II may also provide some PPE items required on the product label (e.g., protective eyewear) to ensure they meet requirements.

Copies of the material safety data sheet (MSDS) and product label are made available to members of the study team and study participants. During the consent process, the Principal Investigator will provide these documents for review to potential volunteers and will discuss the possible acute toxicity effects associated with the pesticide product in the study. AEATF II study participants will also be reminded of standard practices that should be followed to reduce exposure to pesticides. For example, label-required PPE such as the requirement to wear protective eyewear and to remove clothing that get drenched with chemical from an accidental spill.

During study conduct, researchers will ensure compliance with safety requirements on the product label. For example, subjects will be reminded to use the label-specified PPE and to follow use directions on the label. Each worker will be observed by a researcher during the entire monitoring period and the Principal Investigator will be present on all days of monitoring. All researchers who have interactions with the subjects have completed a course in The Protection of Human Research Subjects, e.g., Certified Investigator Training Initiative (CITI), which reinforces the ethical requirements of conducting studies involving human participants.

Study participants are asked to wear an extra layer of clothing (whole body inner dosimeter) under their normal work attire. Efforts are made to schedule studies

during cooler times of the year and/or indoors as much as practical to help minimize potential for heat stress. The informed consent form identifies heat-related illness as a potential health hazard that may be associated with participating in the study, so AEATF II is very careful to prevent such illness. First, the Principal Investigators and study observers are trained to recognize symptoms of possible heat stress. Second, researchers always have plenty of water and sports drinks on hand for the subjects who are encouraged to drink liquids during the monitoring period. Third, a poster "Controlling Heat Stress Made Simple" will be prominently displayed at the study site. Most importantly, environmental conditions (temperature and humidity) are continually monitored and operating procedures are in place to reduce the possibility that participants are subject to heat stress.

Finally, the Principal Investigators know in advance where to take subjects who might be overheated or who have other medical concerns. If any participant is injured or experiences illness as a result of being in a study, medical treatment will be available at a nearby health care facility. If necessary, AEATF II will arrange transportation to receive medical attention. AEATF II will cover the costs of reasonable and appropriate medical attention that are not covered by the participant's own insurance or by a third party. Treatment records will not become part of the research records for this study.

9 Study Benefits

A critical principle of ethical research is that the risks to the subjects must be outweighed by the benefits to the subject and to society. To approve proposed research with human subjects, an Institutional Review Board must determine that "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" (40 CFR §26.1111(a)(2)). The low incremental risk anticipated for pesticide handlers participating as subjects in the AEATF II monitoring program are outweighed by the societal benefits expected to be gained from increased knowledge of typical exposure levels in representative antimicrobial chemical use scenarios.

A critical principle of ethical research is that the risks to the subjects must be outweighed by the benefits of the research to the subjects and to society. The Common Rule codifies this principle: "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" (DHHS, 2001). If the benefits of monitoring pesticide exposure in the field to subjects do not outweigh the risks, then the program should not be conducted. AEATF II argues that the risks involved with pesticide handlers participating in the monitoring program, who expose themselves to pesticides as part of their daily lives, are minimal and are

outweighed by the societal benefits gained by knowledge of expected exposure levels and by the eventual benefits of safe pesticide use.

9.1 Benefits to Subjects

None of the studies in the AEATF II monitoring program will provide direct benefits to the study participants. Information from this monitoring program will be used to estimate the exposure and health risk to handlers (workers, or for some scenarios, consumers) who are involved in mixing, loading and applying antimicrobial chemical products. This may lead to safer pesticide handling practices that indirectly benefit the participants and other antimicrobial pesticide handlers. Individual workers may request their exposure results relative to the average and extremes observed in the study. This information may inform them that their work practices produce more or less exposure than average and may inspire them to modify behavior to reduce their exposure.

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9.2 Benefits to Society

The AEATF II exposure monitoring program will significantly improve the ability of EPA and other regulatory agencies to estimate the risks to professional pesticide handlers from handling antimicrobial pesticides. Knowledge gained from the monitoring program will be applicable to a variety of antimicrobial pesticides, and will be used to assess risks of new pesticides and new uses of registered pesticides. Knowledge gained from the monitoring program could also be used by EPA to impose stricter safety standards on currently used pesticides, when appropriate (Resnick, 2005).

The data developed in the AEATF II monitoring program will improve the scientific basis for EPA's occupational risk assessments. Worker exposures will be measured under realistic conditions. The data collection parameters will reflect current antimicrobial practices, equipment, and techniques. Monitoring techniques are of high quality and have been standardized for use across the AEATF II monitoring program. BHED™ will become the best available data to support assessments of antimicrobial pesticide handler exposure.

BHED™ will not repeat the limitations of PHED. In particular, BHED™ will include all data on each individual sampled, not just data on individual body parts. Improved estimates of whole-worker exposure, including estimates of the potential distribution between subjects, will now be possible.

To the extent the generic database approach proves successful, it may reduce the need for product-specific worker exposure studies conducted by individual registrants for new products and uses.

9.3 Likelihood of Realization of Benefits

The collection of worker exposure data that can address the data needs of the regulatory community and membership of the AEATF II is considered extremely likely. It is also highly likely that regulators and risk assessors will use these data extensively. This has been the case for previous FIFRA joint data development task forces of many types, including those developing data for generic exposure assessment. Regulatory agencies are strongly committed to using generic exposure databases as an important component of risk assessments. The use of worker exposure data in a generic manner has been generally accepted since the concept was discussed and supported by a FIFRA Scientific Advisory Panel in 1986. In addition, the successful development and release of PHED in 1992 and its subsequent use by regulators to support many occupational risk assessments strongly suggests that the BHED™ database will find even greater use and its benefit realized.

10 Study Risks

Most of the studies designed within the AEATF II program are intended to reflect what would be considered "normal" activity patterns for many subjects and individuals handling biocidal products. There are some situations in which an activity is semi-scripted, within the range of expected practices, to provide diversity in parameters that may be related to exposure including the amount of active ingredient handled and the duration of tasks. However, in each of the proposed studies, careful consideration is given to the potential study-specific risks to the individuals involved and what specific efforts will be made to minimize or eliminate these risks. General risk considerations are presented in this section. Each proposed study protocol will indicate study-specific risk considerations and communication of those risks to potential study subjects as part of the informed consent process. If a subject is injured as a result of being in an AEATF II study, medical treatment will be available from a near-by health care facility that knows about the study. The study sponsors (i.e., AEATF II) will cover any cost associated with a subject's medical treatment that is not covered by their own insurance or by a third party.

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10.1 Description of Potential Risks to Subjects

The risks of the study can be broadly separated into two general categories, those due to potential exposure to an active ingredient and those due to physical stress that may arise from certain activities. Each must be considered to determine what can be done to avoid unnecessary risks.

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Physical risks can arise from climatic conditions, extra clothing (in the form of wearing two complete layers of clothing, the inner and outer dosimeters), and exaggerations of normal activities. Some of these aspects can be controlled by

location and ventilation, yet other aspects are directly a result of the study design and cannot be easily altered without invalidating the data collected. However, those aspects that cannot be easily altered should be carefully evaluated, based on existing data (e.g., habits and practices or product use survey data) and expert opinion, to minimize the exaggeration of activity (e.g., upper-bound for total time spent performing a given tasks, such as surface wiping associated with cleaning activities during a day) without compromising the study results. The exaggeration of activity patterns can lead to concerns related to potential ergonomic issues (e.g., fatigue and heat stress). These need to be considered on a case by case basis for the application method / study scenario.

The other aspect of risk is chemical resulting from exposure to an active ingredient or solvent used to remove the chemical from skin. This can be controlled to some extent by selecting active ingredients that have less toxic profiles and have already been evaluated and approved for the application being investigated. In addition, preference is for actives that have been evaluated and do not require personal protective equipment for their usage in the application. This criterion generally assures that the product has been evaluated with very health protective assumptions and is approved already for this application. The counter to this is that some exaggeration of usage may be required to obtain detection of the active ingredient on the dosimeters. An example of this is pouring liquids; typically a pouring event is 1 to 5 minutes and the circumstances are such that detection of the active ingredient on a dermal dosimeter is unlikely, even with extremely low detection limits. Hence to be sure that exposure is actually being measured, it is necessary to increase the amount of product poured and the length of time that the activity is carried out. For the evaluation it may be necessary to pour liquids from several consecutive containers for an extended time period. Based on the results of existing studies, it is anticipated that the time and amount poured can be scaled to obtain detection on dosimeters, but avoid unnecessary potential for exposure.

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10.2 Risks of Heat-Related Illness

Heat stress is the build-up in the body of heat generated by the muscles during work and heat coming from the environment. Heat illness (e.g., heat exhaustion and heat stroke) can result when the body is subjected to more heat than it can accommodate. Weather, workload, clothing/PPE, and lack of worker conditioning can increase the risk of a worker experiencing heat-induced illnesses. In addition to causing serious physiological conditions, early symptoms of heat illness such as dizziness and confusion can lead to an increased risk of occupational accidents above that which is already present. Therefore, AEATF II takes special care to monitor subjects for signs of heat stress. All study observers are trained to recognize signs and symptoms of heat stress, and the Principal Investigator (Study Director) and all observers promote drinking water

and taking rest breaks. Researchers will stop study participation for subjects who experience heat-related illness.

10.3 Risks of Exposure to Surrogate Antimicrobial Pesticides

Toxicology Hazard to Subjects

For each specific active ingredient chosen, AEATF II reviews the available toxicology data to assure no undue hazard. Government-authored summaries of the data are given to an IRB as part of the review package. The surrogate chemical / active ingredient selection criteria include selection of active ingredients that have low toxicity profiles, with good warning properties and reversible effects. This selection process, however, is limited by the fact that the active ingredient and the specific product used need to be approved for the application method by the US EPA. By making this restriction, there is assurance that the product has had at least a screening-level risk assessment completed in the past.

Likelihood of Serious or Irreversible Effects

All of the applications being evaluated by AEATF II involve short-term exposures, in most cases an exposure period of less than 8 hours. Hence, the main concerns will be for acute exposure potential. As a result AEATF II focuses on reviewing the likely exposures to the active ingredient and assures there is no undue risk from acute exposure. Further, constant monitoring of the exposure scenario and options for immediate termination by the participant or the study observer are included, and every effort is made to avoid injury or over-exposure. The subjects selected to participate in a study will be experienced in the use of the equipment and types of products involved in that particular study. Any subject with known allergic reaction to the product and specific pesticide used in the study will be excluded from participating. At high concentration some antimicrobial chemicals can produce dermal irritation, but this is not commonly seen at the end-use dilutions being handled in AEATF II studies. Any severe dermatitis or allergic reactions would result in stopping a subject's participation in the study and providing access to any necessary medical treatment, including transportation, if needed, to local medical care facility(ies) identified prior to a study's initiation.

10.4 Risks of Exposure to Face/Neck and Hand Wash Solution

Risk from irritation due to exposure to the washing solution (e.g., 50% isopropyl alcohol and water) used on the face/neck and hands can occur if the subjects have existing abrasions. Subjects will be informed prior to the study that the washing solution (e.g., alcohol/water mixture) used to rinse their hands and wipe

their face and neck may sting, if they have any cuts or abrasions on their hands or face.

At breaks during AEATF II studies and at the termination of the study, the subjects will have their hands washed by study personnel using a washing solution (e.g., 50% isopropyl alcohol/water). Further, at the end of the study after the final wash solution samples are collected, subjects will proceed to wash their hands thoroughly with soap and water.

The Principal Investigator (or designee) will examine subject's hands at the time of each sampling event and note any observed irritation to the skin. Any subject showing an adverse skin reaction will be asked to immediately stop further participation. The subject's exposed skin will be gently washed with clean water and mild soap to remove the test product, and the area will be gently dried with a clean towel.

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10.5 Psychological Risks

Study subjects may find it embarrassing to have a researcher present with them while they change from their clothes into and out of the cotton inner and outer dermal dosimetry (work) clothing provided by AEATF II. This is necessary to make sure that the special dosimeter underwear fits properly, and that it and the outer dosimetry clothing doesn't get contaminated when the test is over. The researcher who helps will be of the same sex, and will be the only other person with the subject. The subjects will be wearing their own underwear all the time. Embarrassment risk from disrobing is expected to be low because the researchers are same-sex, and experienced.

If the subject is female, they might be surprised to learn the results of the required pregnancy test on the day of the research. No one but them and one female researcher will know those results, and they will not be recorded.

11 Procedures for Monitoring and Preventing Risk to Subjects

During all AEATF II studies, the Study Director (Principal Investigator) and the field investigators share the responsibility for awareness of heat illness and toxic responses in study participants. All such researchers are required to complete training on the ethical treatment of test subjects. Prior to study conduct, the Principal Investigator will assess the availability of medical assistance in the locality of the study and identify appropriate emergency medical facilities that may be utilized. This information is included in the Institutional Review Board (IRB) application. IRB protocol and consent form approvals are prerequisites to submission to EPA or HSRB. During each study, every participant will always have a researcher assigned to observe his/her handling practices and this "observer" will have the primary responsibility for detecting adverse effects. Typically this observer is close enough to the worker to have a conversation. Observers are trained to recognize heat stress and are informed of the most likely acute effects of overexposure to the pesticide being used in the study. Should an adverse reaction occur during an AEATF II study, emergency procedures will be implemented. These procedures typically include halting subject participation, removing the subject from the offending environment, and calling 911 for medical assistance if needed. In addition, AEATF II has an adverse effects reporting policy in place to notify EPA of potential new findings as required by FIFRA Section 6(a)(2).

As mentioned above, the primary means of preventing toxic effects is to require subjects to wear appropriate clothing and all required PPE. During study conduct, observers will remind subjects that PPE must be properly worn when handling the pesticide. Non-compliance on the part of the worker will result in discontinuing the monitoring for that worker.

For heat stress, the following procedures will be followed by researchers to prevent illness in study participants:

- Ensure plenty of water and sports drinks are available for the subjects.
- During worker orientation, remind the subjects of the risk of heat stress, suggest they drink some water before they start work, and let them know how/where they can get water during the monitoring period.
- Urge subjects to drink water during the monitoring period and remind them that thirst does not give a good indication of how much water a person needs to drink. There is no need to take hand washes or stop inhalation monitoring during a water break.

- Observe subjects during the monitoring period and be aware of the signs and symptoms listed below.
- Require subjects to take rest breaks when early signs or symptoms of heat illness are present (e.g., headaches, dizziness, fainting, weakness and moist skin, mood changes, mental confusion, upset stomach or vomiting; for example, http://www.osha.gov/Publications/osha3154.pdf.
- Regularly monitor temperature and relative humidity.
- Stop the monitoring as discussed below.

11.1 Medical Management and Stop Rule

The subjects will be checked for allergic and irritant skin reactions, particularly redness, eczema, itching or pain. The subjects will be asked to immediately report any adverse effect including skin reaction to the Principal Investigator (or designee). Any subject showing an adverse skin reaction will be asked to immediately stop further participation. As noted previously, the subject's exposed skin will be gently washed with clean water and mild soap to remove the test product, and the area will be gently dried with a clean towel.

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Since subjects will wear an extra layer of clothing, the risk of heat related illness may be increased. The Principal Investigator will discuss the symptoms of heat stress with the subjects. Study personnel will monitor subjects for symptoms and signs of heat stress, and will monitor the ambient temperature, relative humidity, and heat index (HI). Generally, if the HI exceeds 95 degrees Fahrenheit (F) the research will be discontinued.

Study personnel will be instructed to inform the Principal Investigator immediately of any skin reactions, heat stress, or other unanticipated adverse effects observed or reported during conduct of the study. The medical management procedures set forth in AEATF SOP # AEATF 11.C will be implemented for any instance where the subject's work is halted for medical reasons (other than solely because of a heat stress index above 95), and for any post-study reports of illness, skin reactions or other unanticipated adverse effects. If two or more subjects withdraw or are withdrawn from the study for the same medical reasons, the study will be suspended until the cause of the withdrawal is fully investigated and determined. If two or more subjects develop an adverse skin reaction after they leave the study site, all subjects will be contacted by the Principal Investigator to determine whether further medical management is appropriate.

The Principal Investigator will maintain a record of adverse health observations and reports, and follow Sponsor, IIRB, EPA and California DPR policies for medical event reporting. Sufficient personnel will be present at the study site to maintain an appropriate level of technical support, scientific supervision and observations relevant to the safety of test subjects.

11.2 Additional Procedures for Monitoring or Preventing Risk to Subjects

If an OSHA permissible exposure level exists for an inactive ingredient, an evaluation will conducted by AEATF II to assure exposure during the study is less than the limit. In addition the aim is to keep exposures as low as possible while getting less than 40% of measurements below the detection limit (so that a majority of measurements are above the detection limit for statistical inferences and exposure assessment). This specific aspect is what drives the need for preliminary evaluation of existing data to determine adequacy of detection limits.

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Each protocol will address emergency procedures if an adverse reaction occurs. Where the study is conducted and what the application method is will influence this to a certain degree, but the objective is to have the needed assistance available during the conduct of the study. This would include evaluating potential physical hazards (i.e., ergonomic concerns) throughout the study as well as potential exposures to active ingredients.

As noted earlier each principal investigator assesses the availability of medical assistance in the locality of the study. For example there are certain local regulations and practices that need to be accounted for in designing these studies as a few of the AEATF II studies could be conducted outside of the US. For example, the conduct of an indoor “pour liquid” study is being evaluated for conduct in the Netherlands at a contract laboratory facility. Open pouring of liquids in indoor settings represents an exposure scenario that could be realistically simulated in a laboratory setting. In some cases AEATF II must meet local regulations that do not always allow AEATF II to be completely consistent across various studies. However, the same objective always exists, to collect useful, scientifically defensible data of the highest quality possible, while minimizing exposure and protecting subjects.

As discussed later in this document, scripting in AEATF II studies will be minimized and will primarily involve design features that ensure monitoring intervals that represent a typical day’s duration (i.e., not excessively short or long) and coverage of the practical range for amount of product handled within each use scenario. However, study participants will be using familiar equipment in a manner that is typical for them. Therefore, AEATF II believes the increased risk of heat-related illness in certain conditions is the only added risk that study participants will likely encounter.

12 Risk Assessment for Anticipated Exposures to Proposed Surrogate Chemicals

AEATF II monitors exposure to subjects who handle commercially available antimicrobial pesticide products. In general, useful surrogate chemicals [e.g., didecyl dimethyl ammonium chloride (DDAC), CAS No. 7173-51-5] have multiple uses (e.g., multiple use sites and application methods), formulation types, minimal PPE requirements (i.e., low acute toxicity), and reliable and validated analytical methods. AEATF II will utilize extant risk assessments conducted by EPA for the antimicrobial pesticide to be used in each study to inform the potential for excessive antimicrobial pesticide risk that subjects may experience as a result of participation in an AEATF II exposure monitoring study. If a risk assessment does not exist for the exposure scenario with that chemical, AEATF II will conduct an assessment using EPA-recommended methods.

13 Risk Versus Benefit Comparison

By monitoring exposure to professional antimicrobial handlers (or consumers) who follow their normal practices, but wear an additional layer of clothing (as an inner dosimeter which traps chemical that penetrates the work clothing), AEATF II's monitoring program generally presents a reduced risk to subjects. The risk of dermal toxicity is actually reduced and the added risk of heat illness is mitigated by a medical management program which emphasizes measures to prevent heat-related illness. The potential benefits to antimicrobial workers as a whole and to consumers and society in general, for example, in the form of more accurate measurements of potential exposure to antimicrobial pesticides to inform safety evaluations, versus study-specific risks, will be included in the discussion of each study protocol.

Against the slight risks are balanced substantial benefits. Products containing antimicrobial chemicals are used extensively in hospitals, schools, homes, etc. to control pathogenic bacteria and viruses known to produce increased morbidity and mortality in humans, domestic animals and pets. Measuring exposure of subjects in this research study will produce reliable data about the dermal and inhalation exposure of subjects and the general population performing these tasks. The resulting data will improve the completeness and accuracy of the database used by the EPA to assess exposure to these chemicals. The ability to accurately predict risk may allow other chemical classes of antimicrobials to also be registered based on exposure estimates generated from the data to be produced by this study.

14 Characterization of Potential Study Participants, Exposure Monitoring Methods and Ancillary Information

Appendix A identifies the antimicrobial pesticide handler scenarios that will be covered by AEATF II's generic exposure database, BHED™. However, it is important to point out several restrictions that will be placed on the subjects to be included in those scenarios.

14.1 Subject Characteristics

Age of Subjects

For ethical reasons, all study participants must be at least 18 years of age.

Health Status of Subjects

Only subjects who consider themselves to be in good health will be considered for participation in AEATF II studies.

Reproductive Status of Female Subjects

Women who are nursing or pregnant will be excluded from the study. Non-pregnancy will be confirmed by an over-the-counter urine test just prior to women participating as study subjects for studies involving intentional exposure

Experience of Subjects

Only subjects who have experience performing the particular task will be allowed to participate.

Monitoring Period Duration

All monitoring events (MEs) will be designed to represent a normal workday for the particular task being monitored. Generally, this will involve monitoring periods of at least half of a normal work day to overcome the criticism of early exposure studies where many of the sampling regimes monitored subjects for only a few minutes. Avoiding very short monitoring intervals will ensure that daily exposure estimates are not biased by unusual conditions during that short interval. Some work tasks (e.g., mopping) are performed intermittently through a work day. When monitoring exposure for such tasks, the work schedule will be compressed to obtain the typical duration of exposure or amount of active ingredient handled in a normal work day.

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Product Label Conformance

All subjects will be required to perform pesticide handling tasks in conformance with the label requirements. BHED is designed to reflect exposure to subjects who follow legal and proper handling of pesticides and do not misuse the product or otherwise violate the label procedures. In particular, subjects must wear the PPE required by the label and researchers will remind participants to use that PPE should they be observed not wearing the PPE during exposure monitoring. If there are any special cases where it is proposed that an AEATF II study data set is developed using measurements for a non-pesticidal surrogate chemical, all handling will be based on OSHA-specified PPE as identified on the Material Safety Data Sheet and/or other workplace safety requirements.

14.2 Exposure Monitoring Techniques

Techniques to monitor pesticide handler exposure fall into three main categories. These are area (environmental or industrial hygiene) monitoring, passive dosimetry measures taken on the individual, and biomonitoring taken from individuals.

Area Monitoring
The oldest and least accurate exposure monitoring technique to estimate individual exposure is area monitoring. This monitoring primarily consists of air monitoring in the general vicinity of subjects and sometimes surface monitoring of the pesticide in the workplace. This technique is a traditional industrial hygiene measure and can be used to monitor the pesticide manufacturing workplace to ensure that environmental levels are controlled, but it is not particularly useful in quantifying total worker exposure. This method may give a reasonable approximation of inhalation exposure potential, but does not allow a quantification of dermal exposure. Past monitoring studies have consistently demonstrated that the dermal route is the most significant route of exposure to pesticide handlers (Wolfe, 1976).

Passive Dosimetry
Passive dermal dosimetry taken on subjects consists of (1) patch (*e.g.*, gauze pad) dosimetry; (2) whole body garment dosimetry and, (3) hand/face dosimetry techniques. Hand washes and patch dosimetry, or the use of whole body dosimeters are methods for quantifying the amount of pesticide that contacts the skin or clothing of a worker, and provides a measure of external (dermal) exposure. The use of whole body dosimeters, which are usually sectioned into standard body part areas (*e.g.*, upper arms, lower arms, upper legs, lower legs, front and rear torso) prior to extraction and analysis, prevents the need to extrapolate from a small patch size to the whole body part. Personal air monitoring devices have been used to characterize exposures via the inhalation

route by collecting a known volume of air in the breathing zone of the worker and analyzing for the mass of pesticide of interest present.

1. Patch Dosimetry

Patch dosimetry was first utilized in the mid 1950s for pesticides. With patch dosimetry the potential exposure of the subjects' skin and clothing is measured using a number of absorbent cloth or paper patches, attached to body regions, inside and outside clothing. Placement of patches to represent the entire body (head/face/neck, upper and lower arms and legs, and front and rear torso) are needed on each individual monitored. The surface area covered by the patches represents <10% of the total body surface area. After a defined period of exposure, the patches are removed and analyzed for pesticide content. The quantity of a pesticide on a patch of known area is then related to the area of body region on the assumption of uniformity of deposition over that area. Body part surface areas can be obtained from standard reference texts and exposure guidance documents (EPA 1999).

The assumption of uniform deposition is probably the principal disadvantage of the patch technique. This is illustrated by the extrapolation of the value given by half the limit of quantification (LOQ) to the total body part; this may give a substantial under or over-estimate of exposure. The patch method may give significant under- or over-estimates of exposure, depending on whether the patches have captured the non-uniform, random deposition of concentrate splashes or spray droplets. Individual body region exposure values are then added to give a total potential exposure expressed in mg/hour or mg/lb of product handled or applied.

2. Whole Body Dosimetry

The whole body dosimeter method came into use during the late 1970s/early 1980s (Abbott et al., 1987). The method involves the use of clothing, usually two layers of cotton or cotton/blend material, which act as the pesticide collection media. The outer layer of clothing should be representative of what the subjects normally wear. The inner layer, usually ‘long johns’, represents the skin. The method overcame one of the inherent problems of the patch method, i.e. the assumption of uniformity of pesticide deposition on the skin and clothing. Exposure of the head is assessed by use of a hood or hat preferably made of the same material, or a patch attached to a hat. A face wipe technique can also be used, in which the skin of the face and anterior and posterior neck is wiped with cotton swabs containing a suitable solvent to remove the pesticide residues.

PPE required by the product label are worn over the sampling clothing. The selection of sampling clothing should err on the cautious side by

utilizing the minimum clothing that might be worn under the prevailing conditions. The use of the whole body method overcomes the perceived problem of non-uniformity of deposition. Furthermore, extrapolation from small target areas to larger body regions is not necessary. For these reasons, the method is believed to give a more accurate estimate of potential and actual dermal exposure.

3. Hand Wash

EPA (1996) reviewed the literature on studies that had included hand exposure measurements and concluded that their contribution to total exposure ranged from around 40% to 98%, depending upon the application method. The methods for measuring hand exposure include lightweight absorbent gloves, and swabbing or rinsing the hands in various solvents (EPA 1996). Mild detergent solutions can be used in the handwash technique, for example 'Aerosol' OT. However, AEATF II intends to use a wash solution that will have a high solubility for the test material. This may result in varying the solvent from study to study. For example, in the first 2 studies proposed by AEATF II, 50% isopropanol/water will be used to remove a quaternary ammonium compound from the skin. All these methods have their advantages and limitations and it is difficult to evaluate the accuracy of any procedure.

The generally held view is that the use of gloves results in a significant over-estimation of total dermal exposure, owing to the retention of more of the pesticide than would otherwise be retained by the skin. Gloves also contain foreign materials such as sizing, which may be co-extracted with the pesticide. At low levels of contamination this may cause analytical difficulties. However, glove contamination with dirt and grease arising from the worker's activities are a more likely cause of analytical problems. It is important to use a solvent that adequately solvates the active ingredient. This can be deduced from water and solvent solubility. Inevitably there is a loss of standardization of the intervals at which hand wash samples are taken. However, it does give some information on the extent of hand exposure that might be of value in overall data interpretation.

Measurement of hand exposure through hand washes has become standard in exposure monitoring because it is consistent and mimics the method of hand decontamination under normal work conditions. Hand washing not only provides the best measurement of exposure, it is also more accurate than using collection media like cotton gloves. In monitoring via hand washes, residue only accumulates on the skin surface (as in the real world), rather than on a multi-layer porous medium that, due to the permeable nature of the surface, has a far greater capacity to accumulate and store residues. However, even hand washes can significantly overestimate exposure because most of the residue measured as exposure should actually slough off or be washed off the skin surface following normal hygiene (washing) during and at the end of a

work shift. Further, several lines of evidence suggest that material washed from hands is not all bioavailable: 1) The amount washed off in well controlled rat dermal absorption studies shows that for most compounds the percentage taken into skin does not change from 1–8 hours post application (Thongsinthusak *et al.*, 1999); 2) Only a fraction of the amount applied is dermally absorbed, with an average dermal absorption of about 10% for pesticides applied in solution to humans (Ross *et al.*, 2000); 3) Much of the pesticide to which subjects are exposed can be adsorbed to dust, and in this form it is not as available to skin for absorption, thereby further reducing availability (Driver *et al.*, 1989); 4) Hand washes are taken before breaks, before meals, and at the end of shifts so that material washed off early in the day has no opportunity for absorption throughout the work day but is counted as part of the exposure; and, 5) If gloves are not worn, hands frequently receive the highest dose density, and percent dermal absorption is typically inversely proportional to dose density (Ross et al., 2001).

Inhalation Monitoring

For pesticides that are poorly absorbed via the skin, the inhalation route can become the most important route of absorption. An important review of personal sampling methodology for field monitoring of airborne pesticides was published by Lewis (1976). A personal air sampling method is the most appropriate for the determination of potential inhalation exposure of subjects. Several techniques are available such as solid adsorbents for vapors and sizing and filter cassettes for particles, all attached to battery powered personal sampling pumps. A personal sampling technique involving sampling devices located in the breathing zone and sampling pumps is preferred, because it is a practical way to get a representative sample. Breathing rates for the calculation of inhalation exposure from airborne concentration data can be obtained from standard reference texts such as EPA's Exposure Factors Handbook (1999).

The inhalable fraction (all material capable of being drawn into the nose and mouth) is the most biologically relevant fraction to measure. An example of a suitable device is the Institute of Occupational Medicine (IOM) personal sampling head designed specifically to collect this fraction (Vincent and Mark, 1987). For use of this device, a sampling flow rate of 2 L/min is a specific requirement.

Examples of suitable adsorbent materials for some volatile compounds are activated charcoal, `Tenax' and XAD-2 resins mounted in stainless steel or glass tubes. The choice of material should be determined by analytical retention (trapping efficiency) and extractability studies. Concurrent sampling for particulates and vapor can be achieved by mounting the filter sampling head in front of the vapor trap in a 'sampling train'. This train allows retention of any vapor stripped off the filter on the resin. The material on the filter can be analyzed both gravimetrically and/or chemically and an estimate made of the pesticide content of the particulate sample. Where use of such a sampling train is needed, laboratory validation of the sampling efficacy, particularly of the adsorbent resin, is necessary owing to the possibility of stripping material from the resin by the relatively high flow rate of 2 L/min.

Biomonitoring

Biomonitoring, also known as biological monitoring, typically uses the amount of pesticide (or its metabolites) detected in the urine of exposed individuals to obtain an accurate measurement of the total amount of pesticide actually absorbed by the worker via all routes (inhalation, dermal, and incidental oral ingestion). In order to use biomonitoring quantitatively, one must have primate (preferably human) pharmacokinetic data. Although biomonitoring provides total absorbed doses (i.e., pesticide levels in the body), it does not explain the contributions of each specific exposure pathway, i.e., biomonitoring data cannot generally be used generically. However, biomonitoring data prevent the need to extrapolate from external dosimetry to internal dose, and can serve as valuable validation tools for passive dosimetry.

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Nature of Testing Guidelines

Regulatory agencies frequently collaborate to make exposure monitoring guidelines harmonized. A good example is the Series 875 guidelines of US EPA that were designed with multinational input starting with a meeting in The Hague in 1992 and punctuated with meetings in Ottawa, Toronto, and Washington, DC that culminated with the issuance of OECD and EPA guidelines that are very similar (OECD, 1997; EPA, 1997).

Justification for Passive Dosimetry

Because it is difficult to isolate and validate particular dermal dosimetry methods, the best validation is a comparison of the sum of passive dosimetry methods against the biomonitored dose. The data examined in a recent review of both proprietary and published studies demonstrated an excellent correlation between passive dosimetry and biomonitoring (Ross et al., 2007). Passive dosimetry as a measure of dosage appears to be consistent with biomonitoring with no bias, i.e., there is no tendency to over or under estimate exposure. This evaluation demonstrated that the total absorbed dose (or daily dosage) estimated using passive dosimetry for important handler and reentry scenarios is generally similar to the measurements for those same scenarios made using human urinary biomonitoring methods. Further, this is strongly supported by statistical analysis of individual worker passive dosimetry: biomonitoring ratio and variance within and between studies. The passive dosimetry techniques currently employed yield a reproducible, standard methodology that accurately and reliably quantifies exposure and does not underestimate daily absorbed dose.

14.3 Role of Ancillary Study Information

Every exposure monitoring study collects data that characterizes the environmental conditions and behaviors that may have some influence on worker

exposure. The environmental data includes temperature, humidity, airflow or wind speed and directionality, light levels, detailed descriptions of the equipment used to mix/load or apply the chemical, measurements of the amount of chemical used dilution rates, water source, chemical source, etc. Behavior of each individual monitored including work rate, personal hygiene, neatness or attention to detail, personal habits e.g., tobacco, chewing gum, method of using gloves, evidence of fatigue, etc. are all recorded either with field notes and/or with photography including video. Although most of this information cannot be used to quantify individual exposure, it can be extremely useful in understanding how conditions/behaviors observed during the study compare with "normal" conditions or behaviors, and how any unusual conditions may have contributed to differences in exposure.

15 Incorporation of Existing Data into BHED™

To establish the need for additional exposure monitoring data involving human subjects, AEATF II conducted a systematic review of all available, relevant data for each scenario proposed for inclusion in the multi-year program. This process included publicly available data (e.g., specific data subsets from PHED) and proprietary data sources (e.g., CMA study). Each of potential data source has the potential to provide scenario-specific exposure data (MEs) and associated supporting information for inclusion in BHED™. A data evaluation process was developed for the evaluation of existing data sources and involves the following steps:

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- ***Development of data acceptability criteria***: The existing data acceptability criteria addressed general study design and exposure monitoring techniques, including the analytical and quality control aspects of the studies. They are detailed in Appendix D.
- ***Primary review***: A process that involved the screening of handler exposure data from PHED version 1.1, publicly available data, and compensable data owned by AEATF II members.
- ***Secondary review***: A detailed evaluation of data that passed the screening process for acceptability under the acceptance criteria with decision records for each study review.
- ***Final review***: A process that involved guidance by regulatory agencies including the U.S. EPA, Health Canada, and California EPA, on acceptance of the data for use within BHED™.

Much of the existing data are deemed unsuitable for a generic database due to poor QA/QC (generally low or insufficient field fortification recoveries), a preponderance of non-quantifiable residues, or the use of testing conditions that do not represent current pesticide handling practices in North America. Another key technical issue that eliminated some existing data was the decision to exclude exposure data for subjects who wore more than a single layer of

clothing. This decision was discussed with the Regulatory Agency Advisory Committee who agreed that a modern generic database would be most useful if it contained exposure data for minimal clothing and PPE situations. Regulators prefer to estimate protected exposures (e.g., dermal exposure under coveralls plus normal clothing) from unprotected exposure measurements (e.g., dermal exposure under just one layer of normal clothing) than vice versa. Therefore, BHED™ has been designed so that clothing/PPE protection factors can be estimated by a user from the two dosimetry clothing layers in order to estimate protected exposures (typically workers), or consumer (unprotected) exposures.

16 Monitoring Event Selection

Each AEATF II antimicrobial-handling scenario will be addressed by one (or possibly more than one) study. The purpose of each study is to obtain monitoring events (ME) for incorporation into BHEDTM. The specific details of a study design will necessarily differ from scenario to scenario. The scenario design documents and study protocols will provide the rationale and description of the specific ME selection procedures. This section summarizes those aspects of the ME design common to all scenarios. Appendix E provides a more extensive description of the concepts and procedures for selection and construction of monitoring events.

16.1 Predicting Future Generic Exposures with Monitoring Events

For the purposes of the AEATF II monitoring program, the basic element of a scenario is considered to be the handler-day (HD). Each handler-day corresponds to a particular worker and the scenario-related activities that he performs during a single work day. Regulatory interest for each antimicrobial-handling scenario is centered on predicting occupational exposure under a specific set of generic future handler-day conditions. In particular, it is desired to characterize exposures resulting from the future use of an arbitrary (and perhaps currently non-existent) antimicrobial active ingredient at some arbitrary, but quantifiable, amount of active ingredient contact.

An ME is the basic tool used by the AEATF II Monitoring Program to predict exposures. Each ME is a set of scenario-specific handler-day (HD) conditions that have been experimentally selected (i.e., chosen, simulated, or constructed) to represent expected future HD conditions. Every ME is also monitored to obtain a measurement of the actual exposure resulting from the simulated or selected HD conditions.

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An important aspect of the scenario target population is that it consists of both those handler-days that use the AEATF II's surrogate chemical and those that use other chemicals. Thus, many of the handler-days in the target population cannot be directly monitored for exposure. It is very unlikely that the handler-days associated with a surrogate chemical will have the same conditions in the same proportions as handler-days with other chemicals. Thus, the subset of surrogate-using handler-days is unrepresentative of the full target population. This disparity complicates the sampling process considerably: In effect, the AEATF II monitoring program obtains a sample of the conditions of all handler-days in the scenario target population, but evaluates exposure for those conditions with handler-days that use a surrogate chemical. This is reasonable under the assumption that under the same conditions, exposure is independent of the particular active ingredient used. ¶
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Appendix E describes the target population and discusses, in greater detail, the complexity and design limitations resulting from the need to use surrogate chemicals and volunteer subjects.

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An ME can predict future exposure only if the handling conditions of the ME represent future HD conditions. Because each ME is expensive, it will be possible in practice to construct only a small number (N) of MEs. Obviously, a set of only N MEs cannot predict every possible future HD condition. The successful use of a small set of MEs to represent the diversity expected among future handler-days is aided by three factors:

1. Dermal and inhalation exposure to the chemicals are considered generic (i.e., independent of the particular active ingredient used). This *generic principle* permits use of a small set of surrogate active ingredients to predict exposure from other active ingredients.
2. Exposure is considered to be *proportional* to the true amount of active ingredient contacted by the antimicrobial handler. The exposures obtained from MEs are expressed relative to a measurable normalizing factor (NF) is expected to be proportional to amount of active ingredient contact. Then exposures for any future NF level of interest can be predicted by multiplying the normalized exposures by this future level.
3. *Expert knowledge* of possible handler conditions expected throughout the scenario if obtainable. This permits construction of MEs from HD conditions selected (i.e., simulated or chosen) to represent a diverse set of future handler-day conditions.

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If the ME conditions can be appropriately chosen then a useful set of MEs can be constructed and used as a predictor of future HD exposure in an aggregate sense.

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An exposure distribution is a reasonable aggregate description of future handler-day exposures for a scenario. The future HD distribution describes the likely exposure that would result if one were to randomly pick a future HD among those using ai X when the level of the normalizing factor is HX. There are actually a series of predicted exposure distributions, one for each possible value of HX. However, since any predicted exposure can be computed from the normalized exposure, it is simpler to focus only on the distribution of normalized exposure.

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The complete normalized exposure distribution is rarely needed. Regulatory interest most often focused on just two general aspects of this distribution:

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- The **middle values** such as the arithmetic mean or the median. These exposure values tend to characterize average or 'typical' exposure levels.

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- The **larger values** of exposure possible, such as the 95th percentile of the distribution. This aspect better characterize the extreme, one-time, worker exposures.

It is desired that the set of predicted exposures obtained from the set of MEs adequately characterize the middle and larger values of the future HD distribution. Technically, a set of constructed MEs cannot be a random sample from a distribution of future HD conditions. But some random sampling interpretation might still be a convenient and reasonable model for how the set of predicted exposures from the MEs relate to the future (normalized) exposures for an arbitrary antimicrobial. This permits the use of conventional statistics, such as means and percentiles, calculated from the observed ME exposures to approximate the 'middle' and 'larger' exposures expected in future HDs. For the AEATF II Monitoring Program, confidence in this approximation is improved by using a reasonable reference random sampling model (16.2.2) rather than assuming just simple random sampling. In addition, diversity selection (16.3), using both purposive and random components, is used whenever possible. Diversity selection is an attempt to obtain, as much as is practical for small sample sizes, a diversity of conditions that are expected to influence exposure, either directly or indirectly. This increases the likelihood that the range of conditions in the future HD population expected to impact exposure is reflected in the 'pseudo-sample' of MEs as well.

16.2 Determining the Number of Monitoring Events

16.2.1 The Two-Stage ME Selection Process

Although the details of will vary from scenario to scenario, the ME selection process will always have the same general two-stage structure. The first stage consists of selecting or constructing specific locations and specifying a range of dates for monitoring at each location. Each such local area and range of potential monitoring dates is termed a monitoring site.

The second stage consists of selecting one or more subjects and handling conditions within each site and constructing the MEs. For simulated condition studies the MEs are created by assigning appropriate subjects to scenario tasks under conditions that are expected to exist in the future HD population. For in situ studies, appropriate handler-days are selected from among existing subjects and conditions that are expected to represent future HD conditions.

In general, N_C sites are selected at the first stage and N_M monitoring events (MEs) will be obtained within each site at the second stage. When N_M is greater than one, the set of MEs at the same site is termed a cluster. In general, MEs in the same cluster are expected to be more similar than those in different clusters. This correlation usually means that the smallest total sample sizes (i.e. total

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number of MEs) are attainable when there is only a single ME per site. On the other hand, there are often substantial overhead costs per site that make multi-ME sites more efficient.

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16.2.2 The Two-Stage Random Sampling Reference Model

In the strictest sense, sample sizes can only be determined using statistical theory alone when either

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1. There is assumed random, representative sampling from a population and the goal is to estimate some characteristic of that population; or
2. There is assumed randomization of experimental units to treatments and the goal is only to compare or to contrast treatments in some manner.

Only in these two situations will statistical theory predict how increasing sample size decreases estimation error. In other experimental situations, sample size must be determined using one of the two 'random' situations above as a reference model. The random reference model is constructed so that it reflects the actual situation (i.e., a mixture of random and non-random selection) as closely as is practical.

The sample size that is appropriate for the reference model is then used for the actual study design. In a real sense, then, the reference random sampling model is used to establish benchmark sample sizes that can satisfy benchmark objectives. Although rarely stated explicitly, the use of reference sampling models and benchmark objectives are quite common.

Because all AEATF II scenarios have a two-stage selection structure, they will all use the same reference sampling model. For each scenario, two-stage random nested (or cluster) sampling is the reference model used for the combination of purposive and random two-stage diversity selection that actually occurs. This reference model assumes that:

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1. Exposure, normalized by the potential active ingredient contact factor, is lognormally distributed with geometric standard deviation GSD.
2. There are N_C clusters (i.e. sites) and N_M MEs per cluster. The total number of MEs in a scenario is, therefore, $N = N_C \times N_M$.
3. The within cluster (i.e., within-site) correlation of (log) normalized exposure is equal to ICC.

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The reference sampling model incorporates a two-stage selection structure and the potential for correlation within clusters, but ignores any effects of diversity selection. The ICC is irrelevant to the future distribution of normalized exposure, per se. However, this intra-cluster correlation is a necessary part of the

reference sampling model because the MEs are obtained in clusters (i.e. there are multiple MEs per site).

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16.2.3 Benchmark Objective

The benchmark objective for all AEATF II monitoring program scenarios will have the general form:

> ***If there are N_C clusters and N_M MEs per cluster and the underlying lognormal two-stage reference sampling model were actually true, then selected parameter estimates will be within K-fold of the true values at least 95% of the time.***

If the true parameter of the sampling model is denoted by θ and its sample estimate by T, then T is within K-fold of θ whenever

(1) $$fRA = \text{Max}\left(T/\theta,\ \theta/T \right) \le K$$

The quantity *fRA* is called the fold relative accuracy of T. To satisfy the condition (1) above 95% of the time requires that the 95th percentile of *fRA*, fRA_{95}, be no greater than K. If the 2.5th and 97.5th percentiles of the sampling distribution of T are denoted $T_{2.5}$ and $T_{97.5}$, respectively, then this benchmark objective can also be stated as:

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(2) $$fRA_{95} = \text{Max}\left(T_{97.5}/\theta,\ \theta/T_{2.5} \right) \le K$$

EPA provides guidance to AEATF II on the minimum degree of benchmark accuracy needed for regulatory use in particular scenarios. The current consensus is that estimates of the geometric mean, the arithmetic mean, and the 95th percentile should be accurate to within approximately 3-fold of their true value.

It should always be kept in mind, however, that this objective is specified in terms of the reference random sampling model. This reference sampling model does have the same two-stage nesting structure as the actual ME selection approach. The lognormal distribution assumption is also reasonable, robust, and consistent with existing data. However, the reference distribution assumes simple random sampling at each stage. It does not, and cannot, incorporate the combination of purposive and random diversity sampling actually used. As discussed in Appendix E, the consequence of diversity sampling is expected to be a tendency for the sampling variation of normalized exposure to be overestimated. The sample should over-represent extremes and under-represent the more common values. Such diversity-oriented data collected for this scenario, but analyzed with respect to the two-stage reference distribution, is expected to have minimal bias for central tendency. In contrast, upper percentiles of exposure are expected to

be, on the average, too large. There is no way to determine the actual magnitude of such overestimation. In this case, overestimation of upper percentiles is of minimal concern: for practical exposure assessments, overestimation of exposures is a conservative practice utilized by regulatory agencies. A tendency to both consider and even overestimate upper percentiles is consistent with this practice.

16.2.4 Sample Size

Under the reference two-stage random sampling model described above, the only quantities needed to determine relative accuracy of population parameter estimates are reasonable values for GSD_{nE} and ICC. Such values could be based on existing exposure data for scenario-specific tasks, surrogate exposure data from similar tasks, and/or reasonable assumptions based on subject-matter expertise.

Given values for GSD_{nE} and ICC, fRA_{95}, can be computed for any combination of N_C and N_M and compared with K. Calculation of the 95% percentile of fold relative accuracy is complex, however, and is usually best accomplished using Monte Carlo simulation methods. When the number of MEs per cluster, N_m, is the same for all clusters, a straightforward simulation approach can be used to determine fRA_{95}. This procedure is:

1. Simulate a set of normalized exposure data for N_c clusters and N_m monitoring events per cluster using the two-stage reference sampling model.
2. From each set of simulated data, calculate T, the estimate of θ
3. Repeat steps 1 and 2 above M times to get M values of the estimate T
4. From these M T-values calculate $T_{2.5}$ and $T_{97.5}$, the 2.5th and 97.5th percentiles of T, respectively.
5. Calculate the 95th percentile of fold relative accuracy, fRA_{95}, using formula (2) above.

The number of simulations, M, should be some large number such as 1,000 or 10,000. This process can be continued until a combination of N_C and N_M are found that satisfy to benchmark objective.

16.3 General Diversity Selection Guidelines

In general, the objective of diversity selection is simply to obtain a diverse set of handler-day conditions from among those conditions possible in when an

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¶
For various reasons, a set of handler conditions (i.e., tasks or activities), although technically part of the scenario, may be excluded from the sampling process. This may occur, for example, if the conditions excluded are extremely rare or even obsolete. Such restrictions could also occasionally occur if AEATF II, in an effort to reduce the total number of MUs in the monitoring program, restricts it's testing to certain conditions believed to result in slightly higher exposure. For example, mixer/loader MUs will always involve preparation of multiple loads since this probably leads to higher exposure potential than preparing just a single load (involving an equal amount of pesticide). In another example, the mopping scenario is restricted to the mop application technology with the highest likely exposure potential, (i.e., string mops, versus lower exposure potential technologies such as ready-to-use mop systems). When such restrictions are necessary, the scenario will be explicitly redefi ... [2]

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arbitrary ai is used in future scenario-related tasks. These selected HD conditions are then used to construct monitoring events. Diversity selection is conducted independently at each of the two stages of selection. Thus, a diverse set of sites is selected followed by a diverse set of ME conditions within each site.

In the AEATF II Monitoring Program, the term diversity selection is preferred in lieu of the phrase diversity sampling. This is to emphasize the fact that the future HD conditions used for MEs are selected from either existing or from synthesized conditions (or from both). This selection of conditions can employ both purposive and random elements. When there are multiple diverse configurations available, random selection from among such configurations can reduce the likelihood of intentional selection bias. On the other hand, when some possible ME configurations are more diverse or more cost effective than others, it might be preferable to select these purposively.

Diversity should always be with respect to characteristics that are expected to impact exposure. Diversity selection attempts to create a sample that contains as many of the different conditions as possible that exist in the population. If the diversifying conditions are associated with exposure, then a diversity sample will tend to be more variable with respect to exposure than would a same-sized representative sample. In effect it will be analogous to representative sampling from a distribution that is more diverse than the actual future one.

Whenever possible, the characteristics used should be meta-factors. Meta-factors are characteristics that indirectly influence a number of other characteristics. For example, a worker is a meta-factor because substituting one worker for another alters a number of factors (e.g., behavior, physical appearance, stamina) that might affect exposure. Other common meta-factors are geographic location and time-of-year. Not every characteristic that may impact exposure can be, or even should be, considered in diversity selection. The number of possible combinations of factors that may impact exposure will always greatly exceed the number of planned MEs. Consequently, only a few characteristics, preferably meta-factors, can be used effectively in diversity selection.

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16.3.1 Stratified Diversity Selection

As discussed in Appendix E, there are a number of acceptable approaches that can be used to achieve diversity among ME handler-day conditions. Among the formal methods, stratified diversity selection is often the simplest to implement. In this approach available selectable units (e.g., sites, MEs) are partitioned into strata based on characteristics likely to impact exposure. Each possible selection unit must belong to one and only one stratum. The number of strata must be at least as large as the number of units that will be selected. (For

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example, if there are three units to be selected, then there should be at least three strata.) Diversity could be achieved by selecting (purposively or randomly) no more than one unit from each stratum. If there are more strata than units to be selected, then a subset of the strata should be selected first. This could be either purposively (to increase diversity) or randomly (to reduce intentional selection bias).

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16.3.2 Diversity Selection of First-Stage Units

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At the first stage of ME selection sites are the 'selectable' units. Diversity selection of sites means obtaining sites that are different from each other, on the average, with respect to some characteristic(s) expected to impact exposure. If sites are constructed environments, then they can be built to be different from each other with respect to important characteristic(s). If there are a number of possible sites available and a set is to be selected (randomly or purposively), then stratified diversity selection of sites, based on the important characteristic(s), is a feasible approach

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16.3.3 Diversity Selection of Second-Stage Units

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The second stage selection units are the final MEs. The MEs should be diversified independently within each selected site. In most cases within-site diversity selection of MEs focuses only on two characteristics: subject and normalizing factor.

Handling-day exposures for the same individual (on different days) are expected to be correlated since worker characteristics and behaviors are repeated. This is not true for different workers. Worker behaviors are expected to have great impact on exposure. Consequently, diversity is always increased by simply requiring that each ME be constructed using a different individual.

MEs should also be diverse with respect to the normalization factor that is deemed appropriate for the scenario. One feasible approach is to partition the possible levels of NF into N_M strata and construct one ME from each stratum. In some cases (e.g. simulated-condition studies) there is a pool of available workers that can be assigned to any NF stratum. If all possible configurations of assignment are equivalent, then workers could be randomly allocated to strata. If some allocations are non-equivalent (e.g. more cost effective or there are scheduling issues) then a purposive assignment of individuals to NF levels might be preferable.

In other cases (e.g. In Situ/observational studies) worker availability depends on the particular NF level chosen. Some individuals may only work with higher NF levels and some with only lower NF, say. Selection of workers could still be

random, although random choice would be within each NF stratum. However, when such associations between subject and NF levels exist, purposive allocation might result in a more cost effective and practical configuration.

17 Description and Role of AEATF II Studies

In the context of the BHED™ exposure monitoring program a 'study' takes on a specialized role. It is that component of the program actually conducting MEs in accordance with the spirit of Good Laboratory Practice (GLP) standards issued by EPA (40 CFR 160). AEATF II studies meet the definition of study in the GLPs at 40 CFR §160.3, which reads in pertinent part: "Study means any experiment at one or more test sites, in which a test substance is studied in a test system under laboratory conditions or in the environment to determine or help predict its effects . . . or other characteristics in humans . . . or media." Each AEATF II study will involve conducting MEs under one or a number of scenarios. For example, a study might be designed primarily for mopping application, but exposure of the mixer/loaders who prepare the mop liquid mixture will be a different study. Because it has a very restricted, albeit important, function within the BHED™ program, the study protocol need not contain extensive program information that is not relevant to the conduct of its particular MEs. However, each study protocol will reference the AEATF II program "governing document."

In most cases, AEATF II study timing and location are not dictated by the seasonality of work to be performed. However, finding sites and making arrangements for the studies is often challenging, particularly in observational studies (e.g., subjects at a wood preservative treatment facility) where no scripting of subjects' activities while handling pesticides would be allowed. Further, the AEATF II must identify sufficient usage to define and follow a representative day of the specific pesticide handling activity for each participant (or monitoring unit or event, i.e. ME). Since some studies consist of monitoring participants performing activities that are governed by variable schedules, etc., it is nearly impossible to provide full protocol details (e.g., specific site, surrogate compound, application rate) required by the Good Laboratory Practices regulations and still satisfy the review schedule of U.S. EPA and the HSRB, which must be done many months before a study can be conducted. In contrast, for studies that can be conducted in an experimental manner, wherein a surrogate environment (e.g., experimental chamber) can be used and various parameters controlled, a more definitive protocol design can be provided.

All MEs required by the sampling design for most use scenarios can be collected in a single study, and most individual AEATF II study protocols will describe a single-study and single-year monitoring program designed to generate a range of exposure monitoring data for all discrete activities associated with that use scenario. An individual protocol typically represents a single, stand-alone study, representing MEs performing a single activity. In some cases data from more than one study will be combined for a given scenario.

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<#>Sample Size Determination¶
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The AEATF II monitoring program is not an experimental study whose purpose is to test hypotheses about the distribution of exposure or about potential determinants of exposure. Rather, its purpose is to collect sufficient data for each handler scenario to meet a specific minimum or 'benchmark' adequacy requirement. These data, possibly augmented by additional exposure data from other sources, will then be used for a variety of regulatory purposes. Benchmark adequacy requirements, based on discussion with the Regulatory Agency Advisory Committee, may differ from one scenario to another. ¶
¶
<#>Benchmark Objective¶
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The benchmark objective for each scenario is that estimates for selected exposure distribution measures expressed as normalized exposure (e.g., by pounds of active handled) be accurate to within K-fold at least 95% of the time. This specified relative accuracy level, K, could be scenario-specific. Currently, however, there is a general consensus that, for regulatory purposes, 3-fold relative accuracy (i.e., K=3) is a reasonable default for all scenarios. The standard distribution measures considered for the primary benchmark are the arithmetic mean and the 95th percentile. A more detailed discussion of benchmark adequacy and its statistical implications are provided in AHETF 2007, Appendix C. ¶
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For this objective, accuracy is determined assuming cluster sampling from a lognormal distribution as a surrogate model for the actual purposive MU sampling. As described in Appendix E, the BHED™ purposive sampling recognizes larger sampling units referred to as clusters. For the mop and wipe scenarios, for example, clusters are different buildings and time periods located in the same general geographic area. ¶
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Each exposure study is performed in accordance with long-standing EPA guidelines for conducting occupational and consumer exposure studies (Durham, 1962; Wolfe, 1967; WHO, 1975 and 1982, OECD, 1981; NACA, 1985; Chester, 1993; Worgan, 1995) as described in Series 875: Occupational and Residential Exposure Test Guidelines (U.S. EPA, 1986 and 1996) and in accordance with U.S. EPA FIFRA Good Laboratory Practice Standards (GLPs), 40 CFR, Part 160 (U.S. EPA, 1989). These guidelines are consistent with guidelines used in other countries such as Canada, Australia, and members of the European Union.

All of the individual study protocols will have many elements in common (albeit with scenario- and study-specific aspects) in order to have consistency and uniformity in the data sets. Exposure monitoring protocols differ mainly in the specific product used, equipment used, timing of the study, location and activity performed.

18 Documentation Procedures

Exposure monitoring studies conducted by the AEATF II are designed to measure potential exposure to subjects as they perform specific antimicrobial pesticide handling activities. As specified in AEATF II Standard Operating Procedures (SOPs; see current master list in Appendix G) and each study protocol (and as required by GLPs) all aspects of study conduct are fully documented. Most of the information collected during each study is entered by hand on paper by researchers on standard data forms provided by AEATF II. Much of the information that is collected during the study is also entered into the generic database, BHED™, for use in data analysis and for examination by database users in conjunction with data from other AEATF II studies. Information about subjects will be recorded under their unique ID code, and not in connection with their name or any other identifying information.

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

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

19 Quality Assurance Procedures

GLPs require rigorous quality assurance procedures to assure the quality and integrity of the data. All aspects of the studies are monitored by appropriate quality assurance units (QAUs) while studies are in progress to ensure compliance with FIFRA GLP regulations (40 CFR Part 160) and adherence to the protocol and relevant Standard Operating Procedures. This generally involves three different QAUs: one from the exposure monitoring contractor that conducts the study, one from the analytical laboratory that determines the level of antimicrobial pesticide residues in samples, and one from AEATF II (the sponsor). For each study, the following specific activities, among others, are conducted by these QAUs:

- AEATF II QAU inspects all contract research organizations and laboratories prior to use in a study to ensure that those researchers operate in compliance with GLPs
- AEATF II, Field Contractor and Analytical Contractor QAUs each review protocols prior to finalization
- AEATF II QAU performs periodic study inspections, while contractor QAUs perform periodic study inspections of their respective (analytical or field) portions
- Field Contractor QAU audits the raw data file in the field and Field Report
- Analytical Contractor QAU audits the raw analytical data and Analytical Report
- AEATF II QAU reviews and audits the final report which includes the Field Report and Analytical Report as appendices

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

20 Quality Control Procedures

In addition to the formal quality assurance efforts discussed above, there are a number of important quality control procedures which are followed in order to assure that exposure measurements are accurate and precise and to define what those exposure measurements represent. These include complete validation of all analytical methods; extensive documentation of exactly what the subject does while handling the antimicrobial pesticide product; field fortification and control samples designed to estimate stability of chemical residues during sampling, transit, and storage; laboratory fortification and control samples designed to establish efficiency of the analytical methods on a day-to-day basis; and detailed

guidelines on the use of calibration curves to determine chemical residues found on all sample matrices.

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

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

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

Similar quality control procedures are followed in the laboratory, including control and fortification samples which are designed to detect background residues, monitor the performance of the method, and detect matrix or reagent interferences which may be present. These samples serve as a form of positive

and negative controls. In addition to the detailed analytical methods for each surrogate and each matrix, all analyses must follow detailed AEATF II analytical guidelines which specify procedures related to standard curves, extract handling, documentation, etc. These procedures are specified in OPPTS Guideline Series 875.

21 Reporting Process

A detailed report is generated for each study, a “final report” in GLP terminology. These reports include a text and tabular summary, and detailed appendices including a Field Report and an Analytical Report. These reports are formally submitted to EPA, CDPR, and PMRA as they are completed. In general, these reports detail exactly what was done in the study, the results of analysis of residues, and what information will be entered into BHED™. However, individual study reports which do not represent data for a complete scenario will not include an analysis or interpretation of the exposure data generated.

Field reports document the conduct of exposure monitoring, including:

- Identification of the location of the study, and the environmental conditions during the exposure monitoring period(s)
- Descriptions of the subjects in the study
- Description of the test substance and packaging
- A record of the mixing, loading, and/or application, including a description of the subjects, equipment, and worker activities
- A summary of worker observations identifying any specific occurrences that may contribute to unusual worker exposure
- Descriptions of the work clothing and personal protective equipment worn by each worker
- A detailed summary of the amount of test substance handled or applied for each worker
- A detailed summary of the length of time each worker was monitored
- A complete description of the field recovery evaluation with a summary of specific handling and weathering of all field samples
- A complete description of collection, handling, storage, and shipping of samples.
- A complete description of the ethical conduct of the field study, including all elements required by 40 CFR 26.1303

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

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

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

22 Scenario Monographs

As part of the documentation supporting BHED™, AEATF II will generate scenario monographs for the benefit of regulators and other potential database users. Each monograph will include a description of the scenario as well as an assessment of the data adequacy within that scenario. More specifically, the monograph for each scenario will include:

- Detail definition of the scenario, including any restrictions.
- Representative use information for AEATF II member products to define application methods, rates, use sites, etc.
- Information about the diversity of work practices (equipment and procedures) currently in use in North America
- Summary of any existing data acquired by AEATF II
- Scenario design summaries for AEATF II studies
- Data tables presenting the monitoring data collected for each ME
- Statistical evaluation of the adequacy of ME data with respect to the benchmark objective

AEATF II may also include in the monograph additional recommendations concerning the use of the ME data. Scenario monographs will also be formally

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submitted to the regulatory agencies when AEATF II determines the data collection for a particular scenario is complete.

23 Evaluation of Data Adequacy for Completed BHED™ Scenarios

The ultimate purpose of the monitoring program is to make the individual ME exposure data from all scenarios available to users of BHED™, i.e., to provide a generic pesticide handler exposure database. AEATF II will not analyze the scenario data for the purposes of exposure characterization or risk assessment as part of this data development program. Regulators and other potential users of the generic database will conduct such analyses. However, as part of the generic database development and documentation activities, AEATF II will evaluate how well the collected data meet the pre-specified benchmark adequacy objective. In addition, the AEATF II will quantify the impact of ignoring clusters and treating the data as a simple random sample. The results of this evaluation will be included in the scenario monograph (see section 22). Whenever appropriate, AEATF II will include in the monograph additional recommendations concerning the use of the ME data.

23.1 Benchmark Adequacy of the Completed Scenario

As defined in Section 16.2.3, the benchmark objective for each scenario is that selected lognormal-based estimates of the normalized single-day exposure reference distribution be accurate to within K-fold, at least 95% of the time. The benchmark estimates of interest are the arithmetic mean and the 95th percentile. In principle, the value of K could be scenario-specific although the current consensus is that for regulatory purposes K=3 is an acceptable default for all scenarios. In each scenario design plan will be a brief discussion of why K=3 is appropriate for that scenario, or alternatively the rationale for choosing another value of K.

As emphasized in section 16.2 above, it important to keep in mind that, like the sample size determination, this statistical adequacy benchmark is relevant only within the context of the reference random sampling model defined in Section 16.2.2. In particular, the monitoring data will be treated as if it were collected as a two-stage random sample from an infinite lognormal population. Technically, there is no statistical theory that can be applied to non-random samples (or even to random samples for which the probability structure is unspecified). Nearly all monitoring data used for regulatory purposes is of this type. As has always been the case, statistical conclusions based on such data imply the qualification: "to the extent that the data can be viewed as deriving from a true random sample." As pointed out in 16.2 above, diversity selection is expected to yield MEs that

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This benchmark is necessarily based on pre-data assumptions about the true nature of the exposure variation. It would be unlikely for all assumptions to be exactly satisfied for every scenario. Although slight deviations will have little or no impact, large deviations from the assumptions might result in data that deviate too far from the benchmark objective. Consequently, it is also of value to assess the benchmark requirement using the data actually obtained.¶
¶
The K-fold benchmark above is specified in terms of the true variation structure and the resulting probability that certain characteristics would be observed in the data. Once the data are available, however, such probability statements are less relevant than confidence statements calculated from the actual data. Consequently, evaluation of the benchmark objectives will be based solely on confidence intervals. ¶
¶
To assess this benchmark goal, a 95 percent bound on relative accuracy will be calculated from confidence intervals for the arithmetic mean and the 95th percentile. For a particular parameter, θ, let T denote its estimate calculated from the fit of a cluster sampling (variance component) model to the normalized exposure data. Further, let θ_a and θ_b denote the upper and lower limits, respectively, of a 95% confidence interval for θ. In most cases, the confidence interval, (θ_a, θ_b), will be a parametric bootstrap percentile interval obtained by resampling from a lognormal cluster sampling model. The 95 percent upper confiden ... [5]

tend to overestimate the true variation among future exposures. This suggests that the estimates of upper percentiles will tend to be overestimated (and lower percentiles underestimated) in the resulting monitoring data. With the small sample sizes used in this scenario, however, such estimation bias is probably trivial relative to ordinary uncertainties due to sampling, whether random or purposive.

This benchmark is also necessarily based on pre-data assumptions about the true nature of the exposure variation. It would be unlikely for all these assumptions to be exactly satisfied for every scenario. Although slight deviations will have little or no impact, large deviations from the assumptions might result in data that deviate too far from the benchmark objective. Consequently, it is also of value to assess the benchmark requirement using the ME data actually obtained. The K-fold benchmark above is specified in terms of the true variation structure and the resulting probability that certain characteristics would be observed in the data. Once the data are available, however, such probability statements are less relevant than confidence statements calculated from the actual data. Consequently, evaluation of the benchmark objectives will be based solely on confidence intervals.

To assess this benchmark goal, a 95 percent bound on relative accuracy will be calculated from confidence intervals for the arithmetic mean and the 95th percentile. For a particular parameter, θ, let T denote its estimate calculated from the fit of a cluster sampling (variance component) model to the normalized exposure data. Further, let θ_a and θ_b denote the upper and lower limits, respectively, of a 95% confidence interval for θ. In most cases, the confidence interval, (θ_a, θ_b), will be a parametric bootstrap percentile interval obtained by resampling from a lognormal cluster sampling model. The 95 percent upper confidence bound on realized fold relative accuracy (*fRA*) is then calculated as:

$$UCL_{95}(fRA) = \text{Max}\left(T / \theta_a,\ \theta_b / T \right)$$

The values of $UCL_{95}(fRA)$ will then be compared with the pre-specified relative accuracy benchmark objective, K.

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23.2 The Impact of Ignoring Clusters

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As described in Section 16 and Appendix E, the AEATF II monitoring design involves selecting MEs in two-stages: N_C Sites are selected in the first stage and a cluster of N_M MEs are selected in the second stage. Thus, a cluster is a set of MEs obtained in a single study at a particular geographic location (e.g., building) over a limited period of time (e.g. several days). Clusters are not a property of the future handler-day exposure distribution, *per se*, but merely necessary artifacts of the sampling process. Exposures for MEs in the same cluster are likely correlated to some degree. If so, then estimates of parameters should

accommodate this correlation. If a user ignores clusters (i.e., assumes the data are a simple random sample), then some parameter estimates may be biased and the confidence intervals may be too small. On the other hand, for the MEs of a particular scenario, such biases may be small and of little practical importance. When this is the case, analyses of the data can be simplified considerably. As an aid to regulators and other potential BHED™ users, the impact of ignoring clusters will be examined.

Estimates and confidence intervals for parameters of the normalized exposure distribution will be calculated using a model containing random cluster effects. From this analysis the variance components and intraclass correlation (ICC) and their confidence intervals will be estimated. In addition, the parameter estimates will be calculated assuming no cluster effect (i.e., assuming simple random sampling). These simplified estimates will be compared to those obtained under the cluster-sampling model. The differences, if any, obtained by ignoring clusters will then be summarized for the benefit of BHED™ users.

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Appendix A: AEATF II Scoping Document:

American Chemistry Council
Antimicrobials Exposure Assessment Task Force II (AEATF II)

Background and Scoping Summary

April 23, 2007

INTRODUCTION

On November 1, 2004, the American Chemistry Council Biocides Panel established an Antimicrobial Exposure Assessment Task Force II (AEATF II or Task Force) to conduct exposure monitoring studies involving the mixing, loading and application of products containing antimicrobials or industrial biocides.[1] The Task Force also has planned to develop methodologies to assess post-application exposure to applied products containing biocides, and will continue to work with EPA, CDPR and PMRA to determine the most useful approach, based on current regulatory needs. The Task Force aims to design study protocols that will make study results broadly acceptable to both North American and European regulatory authorities. The Task Force currently consists of 43 companies.

The AEATF II will generate generic exposure data on a broad range of use pattern/application methods to support the Registration, Reregistration and Registration Review of most antimicrobial active ingredients. Regulatory agencies now conduct most risk assessments for antimicrobial uses employing the stringent risk assessment criteria evolved from implementing the Food Quality Protection Act of 1996 (FQPA). There is a very limited amount of empirical exposure data for antimicrobial uses and EPA and other regulators routinely have used highly conservative estimates of exposures to assess antimicrobial risks.

Given the wide use of antimicrobials, developing generic exposure data is the most cost-effective and efficient approach to the needs of this industry. Moreover, given the highly segmented markets and diverse users of the same or similar antimicrobial products, a generic approach is the only practical way that data of the quality required by EPA can be generated. To this end, many of the studies are being designed to collect generic data that can be applied to the widest possible range of use scenarios.

Following is a brief overview of the range of antimicrobial use sites, as identified by EPA and adopted by the AEATF II, and of the application methods, segmented into separate

[1] The general terms “antimicrobials and “biocides” are used interchangeably in this document.

tasks to the extent possible, identified by the AEATF II with the concurrence of EPA, PMRA and CDPR.

EPA ANTIMICROBIAL USE SITE GROUPS

During preliminary discussions on the conduct of antimicrobial exposure assessment studies with EPA, a range of application methods were identified as appropriate for covering the 12 broad antimicrobial Use Site Groups that have been used traditionally by EPA's Office of Pesticide Programs (OPP) in regulating antimicrobials. The EPA Use Site Groups are set forth in Table 1.

EPA relies on these groupings to determine data requirements for various antimicrobials based on use. To this end, EPA further subdivides the groupings into food and non-food categories and indoor and outdoor categories in order to determine mammalian toxicity and environmental and ecological toxicity data required to support various uses. The Use Site Groups are a helpful way to identify the range of uses for which antimicrobials are employed and, in fact, have been used by North American regulators and the Task Force to define the scope of the Task Force's work. There are multiple sites within each grouping. Attachment B to this Governing Document is the 1997 listing of individual use sites in each EPA Use Site Group. This is the most recent list of use sites that has been made available by EPA.

APPLICATION METHODS FOR STUDIES

The application methods selected for the studies are the most common methods and include the following: pump liquid, pour liquid; pour solid; place solid (collectively referred to as mixer/loader activities by EPA); mop, wipe, aerosol spray, spray, soak/immerse, fog, brush and roll, airless spray, and pressure treat. These application methods are described in detail in Attachment 2, Glossary.

Table 1 includes a listing of the Use Site Groups and the application methods typically associated with each.

Table1.

USE SITE GROUPS	APPLICATION METHODS
Agricultural Premises and Equipment	pump, pour liquid, aerosol spray, spray, mop, wipe, fog, soak/immerse
Food Handling/Storage Establishments spray, Premises and Equipment	pump, pour liquid, aerosol spray, mop, wipe, fog, soak/immerse
Commercial, Institutional & Industrial spray, Premises and Equipment	pump, pour liquid, aerosol spray, soak/immerse, mop, wipe, fog,
Residential and Public Access Premises	pump, pour liquid, aerosol spray, spray, mop, wipe, fog, soak/immerse
Medical Premises and Equipment	aerosol spray, spray, mop, wipe, fog, soak/immerse
Human Drinking Water Systems	pump
Industrial Process Water Systems	pump, pour liquid
Material Preservatives	pump, pour liquid, pour solid, place solid, spray, soak/immersion, airless spray, brush/roll
Antifoulant Coatings	airless spray, brush/roll
Wood Preservatives	pressure treatment, soak/immersion, brush/roll, spray
Swimming Pools	pump, pour liquid, pour solid, place solid
Aquatic Areas	pump, pour liquid, pour solid, place solid

TWO MAJOR GROUPINGS FOR AEATF II STUDIES

The studies planned by the Task Force fall into two general categories: (1) simulated studies based on discrete or segmented tasks (mixing, loading and application methods) that can used to estimate exposures occurring in a variety of use scenarios; (2) in situ (e.g., on-site, observational) studies for complex and/or multi-task scenarios.

Studies Based on Segmented Tasks/Application Methods

AEATF II believes that by reasonably segmenting tasks involved in the application of antimicrobials, it will be possible to combine separate tasks as appropriate for various determining exposures in a variety of use scenarios. These studies will involve indoor, scripted scenarios. This approach will make the generic unit exposure data collected by the Task Force useful over the range of antimicrobial use sites and more flexible in utility to potentially changing use patterns. To this end, users of the AEATF II study results can use information from published and proprietary sources to establish values for other exposure factors or variables (e.g., the amount of time spent in a particular task in various occupational settings and residences, the average amount (or range) of a given product applied) in conjunction with the monitoring data to estimate typical exposures. Then the segmented exposure value associated with one discrete task can be combined with the values for other tasks that occur in a particular scenario to further estimate the exposure that could occur during a typical work day.

In Situ (Observational) Studies for Complex or Multi-Task Scenarios

Four of the AEATF II studies are being proposed for conduct in situ, as observational studies, given the complex combination of tasks, functions, etc. The unit exposure data collected from these studies are not intended to be combined, but instead will be representative of similar use scenarios.

List of AEATF II Planned Studies

Table 2 includes a list of the studies that the AEATF II plans to conduct, in the order of priority currently anticipated. Many of these studies will be conducted with simulated exposures. Those that are expected to be conducted as observational studies are so noted in the following table.

Table 2.

AEATF II PROPOSED LIST OF STUDIES IN ORDER OF PRIORITY

A. APPLICATOR/BYSTANDER EXPOSURE RESEARCH

Mop Study
Wipe Study
Wood Pressure Treatment Study (observational)
Aerosol Spray Study
Pour Liquid Study
Metal Working Fluid Study (observational)
Pour Solid Study
Brush/Roller Study (observational)
Airless Spray Study (observational)
High Pressure to Low Pressure Spray Studies
Immersion/Dip/Soak Study
Pump Liquid Study
Place Solid Study
Fogging Study

B. POST-APPLICATION EXPOSURE RESEARCH (approach to be determined)

Hard Surface
Soft Surface

STUDY DESCRIPTIONS

The following studies are discussed in the order of priority, as currently determined by AEATF II in conjunction with US EPA, PMRA and CDPR.

Mop

Mopping involves the application of a diluted or ready-to-use antimicrobial solution to a floor for disinfection or sanitization.[2] Mopping occurs in the five EPA Use Site Groups that involve application of disinfectants and sanitizers to inanimate surfaces: agricultural premises and equipment, food handling/storage establishment premises and equipment, commercial/institutional/industrial premises and equipment, residential/public access premises, medical premises and equipment. The mopping data represent a single or discrete task that can be combined with other segments or tasks to estimate exposures from combinations of activities that represent typical work days in a variety of occupation settings or typical residential use events. The Task Force will simulate mopping

[2] The terms "disinfect" and "sanitize" and variations of these terms are used as used by EPA in regulating antimicrobial pesticides. Each implies a specific level of antimicrobial efficacy, depending on the type of application method, and disinfect typically indicates a higher level of antimicrobial efficacy than sanitize. These terms do not have the same meanings in other regulatory or non-regulatory contexts.

activities, as it will be necessary to establish mopping times sufficient to obtain data, while limiting activity to the single task of mopping. This would be impossible in the vast majority of real-life occupational settings. Moreover, many of the facilities where extensive mopping might occur have legal and ethical considerations that would limit availability to the facility to researchers and associated monitors (e.g., food processing facilities and hospitals).

There are numerous types of mopping equipment, including for example, string mops used in conjunction with various types of wringer equipment, sponge mops, ready-to-use systems with disposable, impregnated mop cloths, etc. AEATF II, based on an evaluation of equipment, has concluded that string mops represent a reasonable worst case and will use this equipment along with buckets with hand-activated mechanical wringers.

There are data available estimating the amount of time spent mopping in various occupational settings (e.g., hospitals, hotels, homes), as well as the amount of time spent wiping, spraying, etc. These data can be used to aggregate exposures from various functions involving the application of antimicrobials in different occupational and residential settings to determine estimated total exposures covering a typical work day or residential usage event.

Wipe

Wiping involves the application of diluted antimicrobial products to surfaces other than floors in the five EPA Use Site Groups involving use of sanitizers and disinfectants on inanimate surfaces: agricultural premises and equipment, food handling/storage establishment premises and equipment, commercial/institutional/industrial premises and equipment, residential/public access premises, medical premises and equipment. The primary contact during use of wipes is dermally to the hand. Wiping can occur after trigger-spray application, wipe after dipping a wipe, sponge or other material in a container, or ready-to-use wipes impregnated with antimicrobial. AEATF II currently is planning to conduct two sets of MEs in simulated environments, one covering the use of pre-impregnated wipes and another involving use of a trigger spray followed by wiping with a dry cotton cloth. Use of wipes in conjunction with full-hand immersion will not be employed in this study, because full-hand immersion will be monitored in the dip/immersion study.

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As previously noted, the AEATF II will use data from published and proprietary sources to establish the amount of time spent in wiping activities in various occupational settings and residences in conjunction with the monitoring data to estimate typical exposures. The segmented exposure associated with wiping activity can be combined with others to further estimate the exposure that could occur during a typical work day in a variety of occupational settings.

Aerosol Spray

Aerosol spray is another application method employed in the five Use Site Groupings where there is application of sanitizers and disinfectants to inanimate surfaces: agricultural premises and equipment, food handling/storage establishment premises and equipment, commercial/institutional/industrial premises and equipment, residential/public access premises, medical premises and equipment. This study under simulated

conditions will monitor exposures resulting from spraying from aerosol cans onto surfaces, but will not include any wiping activities. To the extent that wiping can occur in conjunction with an aerosol product, the AEATF II believes that it will have sufficient data from the wipe study to combine with the aerosol study data to estimate exposures from such combined activities. These data can be used along with data on work day segments to estimate total exposures for various occupational settings and residential use scenarios, as needed.

Whether the aerosol generator is prepackaged in a pressurized can or a refillable can with a separate pressurized air supply makes no difference for purposes of monitoring exposure, because both systems are producing aerosols using the same principle of physics. Only the amount of chemical handled varies by packaging. Thus, refillable containers with separate pressurized air supply, which are the higher volume use method of application, should be employed for an exposure monitoring study. The distance that aerosol generation occurs from the body and the aerosol particle size are probably more important determinants of exposure than whether the aerosol is dispensed from a can or remotely. Key parameters that are likely to affect exposure (e.g., amount of product sprayed, air exchange rate) will be carefully recorded so that there is a basis for extrapolating from one use method to another.

Pressure Treatment of Wood

This study is not based on an application method, but rather is one type of treatment cover by the EPA Use Site Group "Wood Preservation." In contrast to the majority of studies to be conducted by the AEATF II, the data derived from the study of pressure treatment of wood cannot be used in conjunction with data from any other Task Force study in order to estimate exposure. The data derived from this study will be stand-alone data applicable only to wood pressure treatment use scenarios. This study is being proposed for conduct as an observational exposure monitoring study. Wood treatment *immersion* will not be studied by the AEATF II because the only exposure expected would be industrial bystander exposure. Industrial bystander exposure will be addressed or characterized in the wood pressure treatment and metalworking fluid preservation studies.

There are at least four GLP-compliant, EPA-accepted studies on pressure treatment of wood with the three "heavy duty wood treatment compounds" (chromated copper arsenate or CCA, creosote and pentachlorophenol). EPA's continuing interest in exposures resulting from this scenario probably is best explained by the estimate that 40 percent or more of the annual US volume of pesticide production is consumed in the pressure treatment of wood. EPA, therefore, has again requested that industry provide these data.

The AEATF II will rely on the North American regulators to identify tasks of special interest for study. Most of the tasks to be monitored are not directly involved in the application of the pesticide compounds, but instead involve secondary exposures associated with the treatment activities. Active ingredients have not yet been finally selected, but likely will reflect the new generation of wood treatment compounds that combine organic and metal-based components.

Pour Liquid

Pour liquid data to cover the pouring of registered pesticide products could be used in conjunction with the data from a number of other application studies, including: mop, wipe, spray, immerse/dip, pump and fog. There are two general types of containers now used for pesticides: “glug” and “no-glug”. There are data that suggest “no-glug” containers (those with an air bypass that prevents “glugging” and concomitant backsplash) produce significantly less exposure to the pourer than do containers without this feature, which led EPA to issue its recent regulation requiring certain pesticides to be sold in no-glug containers. The AEATF II study intends to generate data comparing no-glug containers as a supplement to the existing studies on open pour exposures in the PHED database. Moreover, the AEATF II data will cover smaller sized containers that are frequently used for antimicrobials, but are not well represented in the PHED data.

Metalworking Fluid Preservative

EPA has singled out this material preservative use for study because of the Agency’s contention that exposures to the preservatives used in MWFs are among the highest of all occupational exposures to biocides. A great deal of information exists in the public literature with regard to ambient levels of MWFs, but not to the preservatives in the fluid. There also are limited data on dermal exposures. Occupational exposures also are regulated by the Occupational Safety and Health Administration (OSHA) and have been well studied by numerous government and private organizations. However, there are no EPA guideline-responsive, GLP data on this particular use. Dermal and inhalation exposures will be monitored in the new study for machine operators using the preserved fluids, and may also be monitored for others present in the facility (i.e., bystanders).

This study, therefore, may be used to provide surrogate data to cover a range of industrial bystander exposure scenarios, e.g., pulp and paper mills, drift from cooling water installations, etc. Size of the aerosol and distance from the source probably could determine exposure to persons in the vicinity, and these data will be recorded. It is AEATF II’s belief that many of the secondary applicator exposure scenarios will be addressed with data generated from the primary applicator exposure studies. Uses such as paint, adhesives, caulking, etc. produce exposure to dilute concentrations of antimicrobial, and with judgment one can compare the unit exposure from the appropriate primary applicator scenario to many of these secondary applicator scenarios, i.e., exposure measured where the product makes a pesticidal claim can be applied to products that do not.

Pour Solid

PHED data clearly show that exposure (both dermal and inhalation) is inversely proportional to the particle size (and resulting surface area) of the solid being handled. PHED lists results for wettable powders (also applicable to dusts), dry flowables, and granulars that are all different solid formulations with increasing particle size and decreasing unit exposure in the order listed. The AEATF II expects to conduct a study using a dust or wettable powder and a granular formulation to bracket the range of particle sizes and resulting exposures currently in PHED.

Further, consideration may be given to observations of Heitbrink et al., (1992) regarding generation of aerosols during pouring of powders. Pour solid data could be combined with data from other application methods, as appropriate to estimate exposures in various occupational settings.

Brush and Roller

One of the most common applications for industrial biocides is for preservation of paints, coatings, caulks, adhesives and similar materials. EPA has historically used exposure to paints as the reasonable worst case for exposures to these and similar items. The vast majority of these paints and other materials are not themselves pesticides, that is, they do make any pesticidal claims. However, some paints and coatings are registered pesticides in that they claim to protect the substrates to which they are applied from microbial deterioration, e.g., antifoulant coatings and wood stains.

The Task Force plans to monitor the application of preserved paint where interior spaces are being painted. Rollers cover more surface area in a given time period than brushes and regulatory agencies assume exposure per unit applied is the same as brushes. Published data are currently inadequate to characterize exposure potential from roller application, but suggest exposure may be lower than brush application. A combination observational study (including both brush and roller methods) is therefore being proposed, because typically both methods are used during a typical or normal day of paint product use.

Airless Spray

Airless spray is used in the application of antifoulant paints, wood preservatives, and preserved paints. In fact, the use of airless spray equipment (e.g., Wagner) is growing rapidly in the application of paints in many interior commercial and even residential settings. The Task Force is proposing to conduct an observational study to monitor interior painting events using airless spray equipment. It is important to note that this study may differ significantly than others planned by the Task Force because it likely will involve the use of both respiratory and dermal personal protective equipment, as specified by either or both the spray equipment manufacturer and paint manufacturer (of a non-pesticidal paint).

High Pressure to Low Pressure Spray

Although distinctions are sometimes made between high and low pressure spraying, two variables affect spray particle size: pressure and orifice size. Small particle sizes (<30 microns mass median diameter) tend to produce higher exposure than larger particles because they stay suspended longer in the air and can be produced even with low pressure. A nomogram describing the pressure/orifice relationship to particle size would be useful and may be prepared during this work. A good deal of the equipment used for spray application is hand-held. Thus, another critical determinant of exposure is whether the spray emits above or below the shoulder.

Higher-pressure spray is used with material preservative, wood preservative and antifoulant coating uses. Lower pressure spray also may be indicated for these uses, is one of the most widely used application methods for sanitizers and disinfectants, and includes applications as diverse as trigger sprays and foam generators. However, there

are no commonly accepted parameters for what constitutes high or low-pressure sprays. Therefore, a large indoor, scripted-activity study (minimum 60 MEs) will be designed to account for the range of equipment types typically used in various applications and use sites and the range of typical particle sizes that might be generated. The distance from the generation source is likely also to be a critical determinant of exposure.

Data from this work will be used for estimating non-aerosol spray exposures to sanitizers and disinfectants in agricultural premises and equipment, food handling/storage establishment premises and equipment, commercial/institutional/industrial premises and equipment, residential/public access premises, and medical premises and equipment. Exposure from non-aerosol spray activity may be combined with exposure from other scripted tasks, as appropriate, to estimate total occupational or non-occupational exposure for a particular use scenario. The data also will be used for preserved paint, antifoulant coatings and wood preservative applications for spray uses that do not employ airless spray equipment. Such exposures will not be combined with other exposures from other tasks, but instead will be used to estimate typical occupational or non-occupational use scenarios.

Soak and Immerse

The terms soak and immerse can be used in a variety of contexts for antimicrobial application. There are industrial uses involving soaking or immersion (various types of wood and anti-sapstain treatment) that are mechanized and may use large volumes of antimicrobial but present only a potential for exposure to subjects as bystanders. On the other hand, low volume uses, such as dish sanitizers in restaurants and bars, commercial or institutional laundry sanitizers, disinfectants for halters and other stable or livestock equipment, etc. that are non-mechanized and involve repeated hand immersion, may offer more potential for exposure. The latter types of exposure will be monitored in a scripted study. The unit exposure data derived from this study may be combined with data from other discrete tasks to estimate total workday exposures for the agricultural premises and equipment, food handling/storage establishment premises and equipment, commercial/institutional/industrial premises and equipment, residential/public access premises, and medical premises and equipment Use Site Groups. Use in the wood treatment industry that involves primarily bystander exposure could be addressed by either the metal working fluid study or some subset of the monitoring units (or monitoring events) from the wood pressure treatment study.

Pump Liquid

Some of the largest volume uses of antimicrobials involve use of pump systems, e.g., application in oilfield and municipal water treatment facilities. However, these systems are closed metering systems using dry lock connections, with virtually no opportunity for worker exposure. Other examples of closed pump systems include tank truck unloading, automatic dispensing systems, metering pump systems for totes and drums, and tubeset pumps. Data on these various systems have been shared with EPA, to support the AEATF II position that additional data should not be required by EPA for pump liquid applications. In any case, there are probably sufficient data in the PHED database to cover all antimicrobial use patterns and all product types where closed or similar systems are not in place to eliminate or mitigate exposure. An analysis will be performed by the AEATF II to further assess the adequacy of the available data. In addition, a final decision in part depends on the EPA and the other North American

regulators' final position on whether occupational risk assessments will be required for subjects that use closed pump systems. Pump liquid data, if required, could be combined with data from other application methods, as appropriate to estimate exposures in various occupational settings.

Place Solid

Registrants have developed various "place solid" products to reduce the potential for exposure to dry flowable products. The most common "solid" delivery systems are powders/granulars in sealed, water-soluble bags and "tablets." EPA is requesting data because it has only one data record in the PHED database. However, the AEATF II believes that it is unnecessary to require a study with this application method. One of the most common antimicrobial pesticide uses employing tablets is application of sanitizers or algaecides to swimming pools. To the extent that a home owner might apply a single tablet on a weekly or semi-weekly basis, EPA has conceded that exposure is likely to be non-detectable. When a professional pool treater or other occupational applicator uses tablets, multiple tables may be applied over the course of the day. The AEATF II believes in such cases it is appropriate to require occupational users to wear chemical-resistant gloves, which again would reduce exposures to non-detect levels. There should be no need for these data and no need to do an occupational risk assessment if the requirement for gloves for occupational users appears on product labels. Place solid data, if required, could be combined with data from other application methods, as appropriate to estimate occupational exposure.

Fog

Fogging is used to treat large or irregularly shaped areas. Most fogging is done using remote operation, where applicator exposure is negligible. However, there are backpacks sold for occupational, indoor antimicrobial fogging applications, and EPA has requested data for fogging data using antimicrobials. However, the AEATF II believes that to the extent fogging is done using handheld equipment, respiratory and dermal PPE should be a standard requirement. Therefore, in either the case of remotely controlled foggers or hand-held fogging with PPE requirements, the potential for occupational exposure would be negligible. Further, there are no registered residential uses for antimicrobial foggers. As a result, the AEATF II believes that the requirement for fogging data for antimicrobials should be eliminated. Fogging data, if required, could be used for the following EPA Use Site Groups: agricultural premises and equipment, food handling/storage establishment premises and equipment, commercial/institutional/industrial premises and equipment, residential/public access premises, and medical premises and equipment.

POST-APPLICATION EXPOSURE STUDIES

Currently EPA uses the Residential Exposure Assessment Standard Operating Procedures (SOPs) as codified in SOP 12 (Smegal et al., 2001) and incorporated into software tools such as (REx – available at www.infoscientific.com and PIRAT – available from http://epa.gov/opptintr/exposure/pubs/piratdl.htm) to estimate potential reentry exposures. Dependent on the toxicity of the antimicrobial, use of default exposure estimates for post application exposure may be adequate.

The typical primary route of post-application exposure is dermal. It is possible to generate generic post-application dermal exposure data that would be generally applicable to a range of possible exposure scenarios (e.g., dermal contact with sanitized floor surfaces; incidental dermal contact with disinfected work surfaces; dermal contact with treated articles). Other task forces have developed data to evaluate post-application exposure (also known as reentry exposure) for environmental surfaces such as turf (Outdoor Residential Exposure Task Force; ORETF), and plant foliage surfaces (Agricultural Reentry Task Force; ARTF). Post-application exposure monitoring studies typically involve concurrent measurement of residues transferred from a treated surface as a function of time using a non-human transfer medium (discussed in the following paragraph) and the quantity of chemical transferred to full body dosimetry garments worn by individuals contacting a treated surface with a known intensity, for specific time duration. The dermal exposure rate (e.g., mg/hr) measured using dosimetry garments is divided by the concurrently measured surface transferable residues (e.g., mg/cm^2) to achieve a generic transfer coefficient (TC). This coefficient, which is also referred to as a "contact rate," is typically expressed in units of cm^2/hr.

In conjunction with measuring human dermal exposure following contact with a treated surface, a post-application exposure study also determines temporal transferable residue (measurements taken across time) from the treated surface using a generic method (a roller was used by ORETF and leaf washes were used by the ARTF). The AEATF II will need to develop or adapt an existing method for measuring transferable residues. Transferable residues are chemical-specific (due to different adsorption and dissipation characteristics that are unique to each chemical used on a matrix). Therefore, chemical-specific transferable residues must be generated by the individual registrant. These studies cost approximately 5 to 10% of what a human exposure monitoring study costs.

The AEATF II initially proposed to develop TCs by conducting one study with hard surfaces (e.g., floor or countertop) and one with soft surfaces (e.g., textile such as carpet or upholstery). EPA has requested that the Task Force defer any further work on post-application exposures until it has conferred with other North American regulators to more clearly determine how it will assess post-application exposures in the future.

REFERENCES

AEATF II (2004a). American Chemistry Council Antimicrobial Exposure Assessment Task Force II. Glossary of Terms: Application Methods and Use Patterns.

AEATF II (2004b). American Chemistry Council Antimicrobial Exposure Assessment Task Force II. Justification for Changes to EPA's Initial List of Application Methods.

AEATF II (2004c). American Chemistry Council Antimicrobial Exposure Assessment Task Force II. Mixer/Loader (Preparation Worker) and Applicator Exposure Monitoring Study Design Parameters.

AEATF II (2004d). American Chemistry Council Antimicrobial Exposure Assessment Task Force II. Post Application Exposure Estimates: AEATF II Data Development Needs.

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Appendix B. Antimicrobial Product Use Sites and Categories

I. Agricultural premises and equipment
II. Food handling/storage establishment premises and equipment
III. Commercial, institutional and industrial premises and equipment
IV. Residential and public access premises
V. Medical premises and equipment
VI. Human drinking water systems
VII. Materials preservatives
VIII. Industrial processes and water systems
IX. Antifouling coatings
X. Wood preservatives
XI. Swimming Pools
XII. Aquatic areas

I. Agricultural premises and equipment

a. Food area premises and equipment - indirect food contact *

AGRICULTURAL/FARM PREMISES	INDOOR FOOD, TERRESTRIAL FOOD
AGRICULTURAL/FARM STRUCTURES/BUILDINGS AND EQUIPMENT	INDOOR FOOD, TERRESTRIAL FOOD
BARNS/BARNYARDS/AUCTION BARNS	INDOOR FOOD
BEEF/RANGE/FEEDER CATTLE (MEAT)	INDOOR FOOD
BEEHIVES/BEE COLONY (DISEASED/NUISANCE)	INDOOR FOOD
BEEHIVES-EMPTY	INDOOR FOOD
CALVES (MEAT)	INDOOR FOOD
DAIRY CATTLE (LACTATING OR UNSPECIFIED)	INDOOR FOOD
DAIRY CATTLE (NON-LACTATING)	INDOOR FOOD
DAIRY FARM MILK HANDLING FACILITIES/EQUIPMENT	INDOOR FOOD
DAIRY FARM MILK STORAGE ROOMS/HOUSES/SHEDS	INDOOR FOOD

DAIRY FARM MILKING EQUIPMENT	INDOOR FOOD
DAIRY FARM MILKING STALLS/PARLORS	INDOOR FOOD
DAIRY GOATS (LACTATING OR UNSPECIFIED)	INDOOR FOOD
DAIRY GOATS (NON-LACTATING)	INDOOR FOOD
EMPTY CONTAINERS TO BE USED FOR RAW AGRICULTURAL COMMODITIES	INDOOR FOOD
FISH, FRESHWATER (MEAT)	INDOOR FOOD
FISH, SALTWATER (MEAT)	INDOOR FOOD
FISH HATCHERY BUILDINGS/AREAS (NON-AQUATIC)	INDOOR FOOD
FISH ROE (CAVIAR)(MEAT)	INDOOR FOOD
GAME ANIMAL (MEAT)	INDOOR FOOD
GOATS (MEAT)	INDOOR FOOD
HOG/PIG/SWINE (MEAT)	INDOOR FOOD
KIDS (MEAT)	INDOOR FOOD
LAMB (MEAT)	INDOOR FOOD
LIVESTOCK	INDOOR FOOD
MUSHROOM HOUSES-EMPTY PREMISES/EQUIPMENT	GREENHOUSE FOOD, INDOOR NON-FOOD
POTATO SEED PIECE STORAGE PREMISES/EQUIPMENT	INDOOR FOOD, TERRESTRIAL FEED
POULTRY (EGG/MEAT)	INDOOR FOOD
POULTRY (MEAT)	INDOOR FOOD
RABBITS (MEAT)	INDOOR FOOD
SEED HOUSES/STORES/STORAGE AREAS/WAREHOUSES	INDOOR FOOD
SHEEP (MEAT)	INDOOR FOOD
SHELLFISH (MEAT)	INDOOR FOOD

b. Direct food contact

ANIMAL DRINKING WATER	INDOOR FOOD
POULTRY DRINKING WATER	INDOOR FOOD

c. Nonfood area premises and equipment

AGRICULTURAL/FARM EQUIPMENT/SHOE BATHS	INDOOR NON-FOOD
EGG HANDLING EQUIPMENT (HATCHING)	INDOOR NON-FOOD
EGG HANDLING ROOMS (HATCHING)	INDOOR NON-FOOD
EGG PLANTS/HATCHERIES/BROODER ROOMS/SHOE BATHS (HATCHING)	INDOOR NON-FOOD
EGG WASHING TREATMENTS (HATCHING)	INDOOR NON-FOOD
FUR FARM EQUIPMENT/PREMISES	INDOOR NON-FOOD

* Use of a product on sites in this category will be considered a food use and registration must be supported by data sufficient to support establishment of a tolerance or exemption from the requirement of a tolerance under the Federal Food, Drug and Cosmetic Act. The Agency will consider label modifications which clarify practices such that use of the product is unlikely to result in pesticide residues in food. Uses will be considered nonfood if food is covered or removed during application and the treated surfaces are rinsed with potable water prior to any contact with food. Registrants are advised to contact the Agency if they are uncertain as to whether a proposed application is a food use.

II. Food handling/storage establishments premises and equipment

a. Food area premises and equipment - indirect food contact *

AIRTIGHT STORAGE (FLAT)-EMPTY	INDOOR FOOD
AIRTIGHT STORAGE (SMALL)-EMPTY	INDOOR FOOD
AIRTIGHT STORAGE-EMPTY	INDOOR FOOD
COMMERCIAL SHIPPING CONTAINERS-FEED/FOOD-EMPTY	INDOOR FOOD
COMMERCIAL TRANSPORTATION FACILITIES-FEED/FOOD-EMPTY	INDOOR FOOD
DAIRIES/CHEESE PROCESSING PLANT EQUIPMENT (FOOD CONTACT)	INDOOR FOOD

DAIRIES/CHEESE PROCESSING PLANT PREMISES (NONFOOD CONTACT)	INDOOR FOOD
DISHWASHING WATER	INDOOR FOOD
EATING ESTABLISHMENTS (FOOD CONTACT)	INDOOR FOOD
EATING ESTABLISHMENTS EQUIPMENT/UTENSILS (FOOD CONTACT)	INDOOR FOOD
EATING ESTABLISHMENTS FOOD HANDLING AREAS (FOOD CONTACT)	INDOOR FOOD
EATING ESTABLISHMENTS FOOD SERVING AREAS (FOOD CONTACT)	INDOOR FOOD
EGG HANDLING EQUIPMENT (COMMERCIAL)	INDOOR FOOD
EGG HANDLING ROOMS (COMMERCIAL)	INDOOR FOOD
EGG PACKING PLANTS (COMMERCIAL)	INDOOR FOOD
EMPTY CONTAINERS TO BE USED FOR PROCESSED FEED/FOOD	INDOOR FOOD
FEED MILLS/FEED PROCESSING PLANTS	INDOOR FOOD
FEED/FOOD STORAGE AREAS-EMPTY	INDOOR FOOD
FEED/FOOD TREATMENT-STORAGE/PROCESSING/	INDOOR FOOD
FISH/SEAFOOD PROCESSING PLANT EQUIPMENT (FOOD CONTACT)	INDOOR FOOD
FISH/SEAFOOD PROCESSING PLANT PREMISES (NONFOOD CONTACT)	INDOOR FOOD
FOOD CATERING FACILITIES PREMISES	INDOOR FOOD
FOOD DISPENSING EQUIPMENT/VENDING MACHINES	INDOOR FOOD
FOOD MARKETING/STORAGE/DISTRIBUTION EQUIPMENT / UTENSILS (FOOD CONTACT)	INDOOR FOOD
FOOD PROCESSING PLANT EQUIPMENT (FOOD CONTACT)	INDOOR FOOD
FOOD PROCESSING PLANT NON-FOOD HANDLING AREAS	INDOOR FOOD

FOOD PROCESSING PLANT PREMISES (NONFOOD CONTACT)	INDOOR FOOD
FOOD PROCESSING WATER SYSTEMS	INDOOR FOOD
FOOD STORES/MARKETS/SUPERMARKETS PREMISES	INDOOR FOOD
FOOD/GROCERY/MARKETING/STORAGE/DISTRIBUTION FACILITY	INDOOR FOOD
HANDLING EQUIPMENT	INDOOR FOOD
GRAIN/CEREAL/FLOUR BINS-EMPTY	INDOOR FOOD
GRAIN/CEREAL/FLOUR ELEVATORS-EMPTY	INDOOR FOOD
GRAIN/CEREAL/FLOUR STORAGE AREAS-EMPTY	INDOOR FOOD
MEAT PROCESSING PLANT EQUIPMENT (FOOD CONTACT)	INDOOR FOOD
MEAT PROCESSING PLANT PREMISES (NONFOOD CONTACT)	INDOOR FOOD
MEAT/FISH MARKETS PREMISES	INDOOR FOOD
POULTRY PROCESSING PLANT EQUIPMENT (FOOD CONTACT)	INDOOR FOOD
POULTRY PROCESSING PLANT PREMISES (NONFOOD CONTACT)	INDOOR FOOD
PROCESSING/HANDLING EQUIPMENT (FOOD CONTACT SURFACES	INDOOR FOOD

b. Direct food contact

EGG WASHING TREATMENTS (COMMERCIAL)	INDOOR FOOD
FRUIT AND VEGETABLE RINSES	INDOOR FOOD

c. Areas without potential for food contact

EATING ESTABLISHMENTS (NONFOOD CONTACT)	INDOOR NON-FOOD
EATING ESTABLISHMENTS FOOD HANDLING AREAS (NONFOOD CONTACT)	INDOOR NON-FOOD

EATING ESTABLISHMENTS FOOD SERVING AREAS (NONFOOD CONTACT)	INDOOR NON-FOOD
EATING ESTABLISHMENTS NON-FOOD AREAS (NONFOOD CONTACT)	INDOOR NON-FOOD
HYDROSTATIC STERILIZER WATER SYSTEMS	INDOOR NON-FOOD
TOBACCO PROCESSING PLANT PREMISES/EQUIPMENT	INDOOR NON-FOOD
PASTEURIZER/WARMER/CANNERY/RETORT WATER SYSTEMS	INDOOR NON-FOOD
PROCESSING/HANDLING EQUIPMENT (NONFOOD CONTACT)	INDOOR NON-FOOD

* Use of a product on sites in this category will be considered a food use and registration must be supported by data sufficient to support establishment of a tolerance or exemption from the requirement of a tolerance under the Federal Food, Drug and Cosmetic Act. The Agency will consider label modifications which clarify practices such that use of the product is unlikely to result in pesticide residues in food. Uses will be considered nonfood if food is covered or removed during application and the treated surfaces are rinsed with potable water prior to any contact with food. Registrants are advised to contact the Agency if they are uncertain as to whether a proposed application is a food use.

III. Commercial, institutional and industrial premises and equipment

a. Indoor

AIRTIGHT STORAGE (FLAT)-EMPTY	INDOOR NON-FOOD
AIRTIGHT STORAGE (SMALL)-EMPTY	INDOOR NON-FOOD
AIRTIGHT STORAGE-EMPTY	INDOOR NON-FOOD
CARPETS (COMMERCIAL SANITIZER)	INDOOR NON-FOOD
COMMERCIAL/INSTITUTIONAL/INDUSTRIAL FLOORS	INDOOR NON-FOOD
COMMERCIAL/INSTITUTIONAL/INDUSTRIAL PREMISES/EQUIPMENT (INDOOR)	INDOOR NON-FOOD
COMMERCIAL STORAGE/WAREHOUSES PREMISES (INDOOR)	INDOOR NON-FOOD
COMMERCIAL TRANSPORTATION FACILITIES-	INDOOR

NONFEED/NONFOOD	NON-FOOD
DIAPERS (COMMERCIAL LAUNDRY)	INDOOR NON-FOOD
DUST MOPS/CLOTHS/TOOL COVERS/DUSTERS (LAUNDRY/DRYCLEAN)	INDOOR NON-FOOD
LAUNDRY (COMMERCIAL)	INDOOR NON-FOOD
LAUNDRY (DRYCLEANING)	INDOOR NON-FOOD
LAUNDRY EQUIPMENT	INDOOR NON-FOOD
MACHINERY (NON-FOOD)	INDOOR NON-FOOD
NONFEED/NONFOOD COMMODITIES (TEMPORARY STORAGE)	INDOOR NON-FOOD
NONFEED/NONFOOD CONTAINERS-EMPTY/FULL	INDOOR NON-FOOD
NONFEED/NONFOOD STORAGE AREAS-EMPTY/FULL	INDOOR NON-FOOD
NONFEED/NONFOOD TREATMENTS-STORAGE/PROCESSING/HANDLING EQUIPMENT	INDOOR NON-FOOD
REFUSE/SOLID WASTE TRANSPORTATION FACILITIES/HANDLING EQUIPMENT	INDOOR NON-FOOD

b. Outdoor

COMMERCIAL/INSTITUTIONAL/INDUSTRIAL PREMISES/EQUIPMENT (OUTDOOR)	TERRESTRIAL NON-FOOD

IV. Residential and public access premises

a. Indirect food contact *

HOUSEHOLD/DOMESTIC DWELLINGS	INDOOR FOOD, INDOOR RESIDENTIAL
HOUSEHOLD/DOMESTIC DWELLINGS INDOOR FOOD HANDLING AREAS	INDOOR FOOD

b. Nonfood indoor

AMPHIBIANS (PET)	INDOOR

	RESIDENTIAL
ANIMALS (LABORATORY/RESEARCH)	INDOOR NON-FOOD
BIRDS (PET)	INDOOR RESIDENTIAL
CATS (ADULTS/KITTENS) (PET)	INDOOR RESIDENTIAL
CATS (LABORATORY/RESEARCH)	INDOOR NON-FOOD
DOGS (SHOW/MILITARY/SPECIAL)	INDOOR NON-FOOD
DOGS/CANINES (ADULTS/PUPPIES) (PET)	INDOOR RESIDENTIAL
DONKEYS	INDOOR NON-FOOD
FERRETS (PET)	INDOOR RESIDENTIAL
FISH (PET)	INDOOR RESIDENTIAL
FOX	INDOOR NON-FOOD
GOATS (WOOL/ANGORA ANIMAL)	INDOOR NON-FOOD
GREENHOUSE-EMPTY	INDOOR NON-FOOD
HORSES (SHOW/RACE/SPECIAL/PONIES)	INDOOR NON-FOOD
MINK	INDOOR NON-FOOD
MONKEYS (PET)	INDOOR RESIDENTIAL
MULES (WORK)	INDOOR NON-FOOD
NUTRIA	INDOOR NON-FOOD
RABBITS (FUR ANIMAL)	INDOOR NON-FOOD
RABBITS (PET)	INDOOR RESIDENTIAL
REPTILES (PET)	INDOOR RESIDENTIAL

RODENTS (GUINEA PIGS/HAMSTERS/GERBILS/MICE/RATS) (PET)	INDOOR RESIDENTIAL
RODENTS, WILD (CAPTURED FOR SALE)	INDOOR NON-FOOD
SHEEP (WOOL ANIMAL)	INDOOR NON-FOOD
SHEEP, DESERT BIGHORN	INDOOR NON-FOOD
AIR TREATMENTS (COMMERCIAL/HOUSEHOLD)	INDOOR RESIDENTIAL
BATHROOM PREMISES/HARD SURFACES	INDOOR RESIDENTIAL
CARPETS (HOUSEHOLD SANITIZER)	INDOOR RESIDENTIAL
DIAPER PAILS (EMPTY)	INDOOR RESIDENTIAL
DIAPERS (HOUSEHOLD/COIN-OPERATED LAUNDRY)	INDOOR RESIDENTIAL
DIAPERS (PRESOAK)	INDOOR RESIDENTIAL
DOMESTIC/COMMERCIAL NONPOTABLE WATER (WATERBED WATER)	AQUATIC NON-FOOD RESIDENTIAL,
FILTERS (AIR/AIR CONDITIONER/FURNACE)	INDOOR RESIDENTIAL
HOUSEHOLD TRASH COMPACTOR/FOOD DISPOSAL	INDOOR RESIDENTIAL
HOUSEHOLD/DOMESTIC DWELLINGS CONTENTS	INDOOR RESIDENTIAL
HOUSEHOLD/DOMESTIC DWELLINGS INDOOR NONFOOD HANDLING AREAS	INDOOR RESIDENTIAL
HOUSEHOLD/DOMESTIC DWELLINGS INDOOR PREMISES	INDOOR RESIDENTIAL
HUMAN BEDDING/MATTRESSES	INDOOR RESIDENTIAL
HUMAN CAMPING EQUIPMENT	INDOOR RESIDENTIAL
HUMAN DENTURES/TOOTHBRUSHES/MOUTHPIECES	INDOOR RESIDENTIAL
HUMAN FACE GEAR	INDOOR RESIDENTIAL

HUMAN FOOTWEAR	INDOOR RESIDENTIAL
HUMAN GROOMING INSTRUMENTS (BRUSHES,COMBS)	INDOOR RESIDENTIAL
HUMAN HEADGEAR	INDOOR RESIDENTIAL
HUMAN WIGS	INDOOR RESIDENTIAL
HUMIDIFIER WATER	INDOOR RESIDENTIAL
LAUNDRY (HOUSEHOLD/COIN-OPERATED)	INDOOR RESIDENTIAL
PORTABLE/CHEMICAL TOILETS/LATRINE BUCKETS	INDOOR RESIDENTIAL
REFUSE/SOLID WASTE CONTAINERS (GARBAGE CANS)	INDOOR RESIDENTIAL
REFUSE/SOLID WASTE SITES (INDOOR)	INDOOR RESIDENTIAL
REFUSE/SOLID WASTE TRANSPORTATION FACILITIES/HANDLING EQUIPMENT	INDOOR RESIDENTIAL
RESIDENTIAL FLOORS (ANTIMICROBIALS ONLY)	INDOOR RESIDENTIAL
TOILET BOWLS (INTERIOR SURFACES)	INDOOR RESIDENTIAL
TOILET TANKS/WATER CLOSETS WATER	INDOOR RESIDENTIAL
URINALS (INTERIOR SURFACES)	INDOOR RESIDENTIAL
VEHICULAR HOLDING TANKS	INDOOR RESIDENTIAL

c. Nonfood indoor/outdoor

ANIMAL KENNELS/SLEEPING QUARTERS (COMMERCIAL)	INDOOR NON-FOOD, TERRESTRIAL NON-FOOD
HOUSEHOLD/DOMESTIC DWELLINGS OUTDOOR PREMISES	OUTDOOR RESIDENTIAL
PET LIVING/SLEEPING QUARTERS	INDOOR RESIDENTIAL, OUTDOOR RESIDENTIAL

V. Medical premises and equipment

AIR TREATMENTS (HOSPITAL)	INDOOR MEDICAL
BARBER/BEAUTY SHOP EQUIPMENT (BARBER CHAIR/CABINETS)	INDOOR MEDICAL
BARBER/BEAUTY SHOP INSTRUMENTS (SHAVERS/SCISSORS)	INDOOR MEDICAL
BIOLOGICAL SPECIMENS (ORGANS/TISSUES/MILK SAMPLES)	INDOOR MEDICAL
CADAVERS AND CASKETS	INDOOR MEDICAL
CARPETS (HOSPITAL SANITIZER)	INDOOR MEDICAL
CUSPIDORS/SPITTOONS	INDOOR MEDICAL
DIAPERS (HOSPITAL LAUNDRY)	INDOOR MEDICAL
HOSPITAL CONDUCTIVE FLOORS	INDOOR MEDICAL
HOSPITAL CRITICAL ITEMS (SURGICAL INSTRUMENTS/PACEMAKERS)	INDOOR MEDICAL
HOSPITAL JANITORIAL EQUIPMENT	INDOOR MEDICAL
HOSPITAL NONCRITICAL ITEMS (BEDPANS/FURNITURE)	INDOOR MEDICAL
HOSPITAL SEMICRITICAL ITEMS (CATHETERS/INHALATION EQUIPMENT	INDOOR MEDICAL
HOSPITAL/MEDICAL INSTITUTIONS NON-CONDUCTIVE FLOORS	INDOOR MEDICAL
HOSPITALS/MEDICAL INSTITUTIONS CRITICAL PREMISES (BURN WARDS, OPERATING ROOM AREA	INDOOR MEDICAL
HOSPITALS/MEDICAL INSTITUTIONS NONCRITICAL PREMISES	INDOOR MEDICAL
HOSPITALS/MEDICAL INSTITUTIONS PATIENT PREMISES	INDOOR MEDICAL
HOSPITALS/MEDICAL INSTITUTIONS PREMISES (HUMAN/VETERINARY)	INDOOR MEDICAL
HOUSEHOLD SICKROOMS PREMISES/CONTENTS/UTENSILS	INDOOR MEDICAL
HUMAN WASTE (TYPHOID STOOLS/FECES/URINE)	INDOOR

	MEDICAL
LAUNDRY (HOSPITAL)	INDOOR MEDICAL
MORGUES/MORTUARIES/AUTOPSY/EMBALMING EQUIPMENT	INDOOR MEDICAL
MORGUES/MORTUARIES/AUTOPSY/EMBALMING INSTRUMENTS	INDOOR MEDICAL
MORGUES/MORTUARIES/AUTOPSY/EMBALMING ROOM PREMISES	INDOOR MEDICAL
REVERSE OSMOSIS WATER SYSTEM	INDOOR MEDICAL
UPHOLSTERY (HOSPITAL/COMMERCIAL)	INDOOR MEDICAL, INDOOR NON-FOOD
VOMITUS	INDOOR MEDICAL

VI. Human drinking water systems *

PUBLIC WATER SYSTEMS	INDOOR FOOD
INDIVIDUAL WATER SYSTEMS	INDOOR FOOD
EMERGENCY WATER SYSTEMS	INDOOR FOOD
WATER PURIFIER UNITS	INDOOR FOOD

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VII. Materials preservatives

a. Indoor Food

ADHESIVES, INDUSTRIAL (INDIRECT FOOD CONTACT SURFACES)	INDOOR FOOD
COATINGS, INDUSTRIAL	INDOOR

	FOOD
PAINTS (FINGER)	INDOOR FOOD
PAPERMAKING (FOOD CONTACT)	INDOOR FOOD
PLASTIC-MAKING *	INDOOR FOOD

b. Indoor Nonfood

ADHESIVES, INDUSTRIAL (NONFOOD CONTACT)	INDOOR NON-FOOD
CAULKS	INDOOR NON-FOOD
DIAPERS, DISPOSABLE	INDOOR NON-FOOD
FEATHERS/FELT/FELT PRODUCTS/FURS	INDOOR NON-FOOD
FUELS/OIL STORAGE TANK BOTTOM WATER	INDOOR NON-FOOD
FUELS/OIL (CRUDE)	INDOOR NON-FOOD
HIDES/LEATHER/LEATHER PRODUCTS (SURFACES)	INDOOR NON-FOOD
JANITORIAL PRODUCTS (IN-CONTAINER)	INDOOR NON-FOOD
METALWORKING CUTTING FLUIDS	INDOOR NON-FOOD
PAINTS (IN-CAN)	INDOOR NON-FOOD
PAPER (STORED)	INDOOR NON-FOOD
PAPERMAKING (NONFOOD CONTACT)	INDOOR NON-FOOD
PLASTIC/PVC/VINYL PRODUCTS	INDOOR NON-FOOD
RUBBER PRODUCTS	INDOOR NON-FOOD
SIZES(ING)	INDOOR NON-FOOD
SLURRIES	INDOOR NON-FOOD
SPECIALTY PRODUCTS	INDOOR NON-FOOD
TEXTILES/CORDAGE PRODUCTS	INDOOR NON-FOOD
TEXTILE-/TEXTILE FIBERS-MAKING	INDOOR NON-FOOD

b. Indoor/Outdoor Nonfood

COATINGS, INDUSTRIAL	AQUATIC NON-FOOD INDUSTRIAL, INDOOR NON-FOOD, INDOOR RESIDENTIAL, OUTDOOR RESIDENTIAL,

	TERRESTRIAL NON-FOOD
DISPERSIONS/EMULSIONS/SOLUTIONS/SUSPENSIONS	INDOOR NON-FOOD, TERRESTRIAL NON-FOOD CROP
PAINTS (APPLIED FILM)	AQUATIC NON-FOOD RESIDENTIAL, INDOOR NON-FOOD, TERRESTRIAL NON-FOOD CROP

* Use of a product on sites in this category will be considered a food use and registration must be supported by data sufficient to support establishment of a tolerance or exemption from the requirement of a tolerance under the Federal Food, Drug and Cosmetic Act. The Agency will consider label modifications which clarify practices such that use of the product is unlikely to result in pesticide residues in food. Uses will be considered nonfood if food is covered or removed during application and the treated surfaces are rinsed with potable water prior to any contact with food. Registrants are advised to contact the Agency if they are uncertain as to whether a proposed application is a food use.

VIII. Industrial processes and water systems

a. Indoor Nonfood

PASTEURIZER/CAN WARMER/CANNERY/RETORT WATER SYSTEMS	INDOOR NON-FOOD
HYDROSTATIC STERILIZER WATER SYSTEMS	INDOOR NON-FOOD
IMMERSION ULTRASONIC TANK WATER	INDOOR NON-FOOD
LEATHER PROCESSING WATER/LIQUORS	INDOOR NON-FOOD
PHOTO PROCESSING WASH WATER	INDOOR NON-FOOD
RECIRCULATING ELECTRODEPOSITION SYSTEMS	INDOOR NON-FOOD
REVERSE OSMOSIS WATER SYSTEM	INDOOR NON-FOOD

b. Aquatic/Outdoor exposure

AIR CONDITIONER/REFRIGERATION CONDENSATE WATER SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL
AIR WASHER WATER SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL
COAL SLURRY SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL
COMMERCIAL/INDUSTRIAL COOLING WATER [RECIRCULATING]	AQUATIC NON-FOOD INDUSTRIAL, INDOOR NON-FOOD
COMMERCIAL/INDUSTRIAL COOLING WATER [ONCE-THROUGH]	AQUATIC NON-FOOD INDUSTRIAL
DRAINAGE SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL
EVAPORATIVE CONDENSER WATER SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL
INFLUENT WATER FILTRATION SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL, INDOOR NON-FOOD
TEXTILE MILL WATER SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL
INDUSTRIAL SCRUBBING SYSTEM	AQUATIC NON-FOOD INDUSTRIAL
INDUSTRIAL WASTEWATER TREATMENT SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL, INDOOR NON-FOOD
LABORATORY EQUIPMENT WATER BATHS	AQUATIC NON-FOOD INDUSTRIAL
PULP/PAPER MILL WATER SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL
GAS/OIL DRILLING MUDS/PACKER FLUIDS [OFFSHORE]	AQUATIC NON-FOOD INDUSTRIAL
GAS/OIL DRILLING MUDS/PACKER FLUIDS [TERRESTRIAL]	TERRESTRIAL NON-FOOD
GAS/OIL PIPELINES MAINTENANCE	AQUATIC NON-FOOD INDUSTRIAL, TERRESTRIAL NON-FOOD
SEWAGE SYSTEMS	AQUATIC NON-FOOD INDUSTRIAL

c. Environmentally contained

GAS/OIL RECOVERY INJECTION WATER SYSTEMS	INDOOR NON-FOOD
GAS/OIL FRACTURING FLUID SYSTEMS	INDOOR NON-FOOD

IX. Antifouling coatings

BOATS/SHIPS HULL/BOTTOM	ANTIFOULANT
CRAB/LOBSTER POTS	ANTIFOULANT
FRESHWATER STRUCTURES/EQUIPMENT	ANTIFOULANT
MARINE STRUCTURES/EQUIPMENT	ANTIFOULANT
WOOD PROTECTION TREATMENT TO WOOD	ANTIFOULANT

X. Wood preservatives

a. Heavy duty

SEASONED WOOD PRESSURE/THERMAL TREATMENT	WOOD PRESERVATIVES
SEASONED WOOD NONPRESSURE TREATMENT (JOINERY)	WOOD PRESERVATIVES
SEASONED WOOD NONPRESSURE TREATMENT(REMEDIAL)	WOOD PRESERVATIVES
UNSEASONED FOREST PRODUCTS TREATMENT (SAPSTAIN)	WOOD PRESERVATIVES

b. Ready to Use

SEASONED WOOD NONPRESSURE TREATMENT (READY-TO-USE)	WOOD PRESERVATIVES

XI. Swimming Pools

SWIMMING POOL WATER SYSTEMS	AQUATIC NON-FOOD RESIDENTIAL

XII. Aquatic areas

AGRICULTURAL DRAINAGE SYSTEMS	AQUATIC FOOD
COMMERCIAL FISHERY WATER SYSTEMS	AQUATIC FOOD
INTERMITTENTLY FLOODED AREAS/WATER	AQUATIC FOOD, AQUATIC NON-FOOD OUTDOOR

IRRIGATION SYSTEMS	AQUATIC FOOD
LAKES/PONDS/RESERVOIRS (WITH HUMAN OR WILDLIFE USE)	AQUATIC FOOD
ORNAMENTAL PONDS/AQUARIA	AQUATIC NONFOOD
STREAMS/RIVERS/CHANNELED WATER	AQUATIC FOOD, AQUATIC NON-FOOD OUTDOOR
LAKES/PONDS/RESERVOIRS (WITHOUT HUMAN OR WILDLIFE USE)	AQUATIC NON-FOOD INDUSTRIAL

Appendix C. Glossary of Terms

AMERICAN CHEMISTRY COUNCIL
ANTIMICROBIAL EXPOSURE ASSESSMENT TASK FORCE II

GLOSSARY of TERMS
(derived in part from 40CFR Part 158W)

May 2007

PART I. ANTIMICROBIAL APPLICATION METHODS

PART II. EPA ANTIMICROBIAL USE SITE GROUPS

PART III. GENERAL TERMS

I. ANTIMICROBIAL APPLICATION METHODS

AEROSOL SPRAY – A suspension of fine solid or liquid particles in gas that is dispensed from a pressurized container. The suspension is relatively stable, that is, the particles will remain suspended for a period of time barring an external influence. Standard-setting organizations, ISO, ACGIH, and BMRC, have established inspirable (able to enter the respiratory system) and reparable (able to enter the alveolar area of the lung) levels for aerosols. Generally, particles under 8 to 10 microns are considered respirable. One micron particles are considered 95 percent inspirable, 10 micron particles are 70 percent inspirable, and 100 micron particles are considered to be 20 percent inspirable. For example, disinfectant aerosol sprays contain less than 1% droplets 10 microns or smaller. Median size typically is 100 microns (mass median diameter or mmd), normally distributed. However, government risk assessors usually assume that all measured air levels are not only inspirable but also respirable. Thus, the only time when it would be critical to distinguish particle size would be if a particular chemical had an inhalation toxicology study that showed damage to the alveolar region of the lung.

AIRLESS SPRAY – A spray application that occurs by directly creating pressure to drive a liquid out of a nozzle for transfer through the air to a final target surface. Typical pressures for paints/coatings are in the range of 5,000 psi with orifice diameters of approximately 0.018 inches. Airless spray particles must be large enough to reach the target surface and small enough to achieve uniform deposition.

BRUSH – Application of a liquid material to a surface area, such as a wall, by repeatedly inserting a brush (e.g., a paint brush) into a container for loading and then brushing it back and forth across the surface to be covered or treated.

FOGGING – An application that requires a device that generates very small liquid particulate for transfer through the air, so it can penetrate into areas difficult to physically reach. These devices require some type of mechanical pump to generate the needed

pressure to drive the biocide through the nozzles. A "dry fog" has droplets ranging in size from 10-15 microns in volume. A "wet fog" or "mist" has droplets ranging in size from 30-60 microns in volume. A "fine spray" has droplets larger than 60 microns in volume.

IMMERSION/DIP/ SOAK - Interchangeable terms. Differences in applicator exposure potential are attributable primarily to scale, but also may be associated with use patterns employing this application method and common industry practices.

Wood treatment. The American Wood Preservers' Association (AWPA) 2001 Standards define dip as "application of a liquid preservative to a wood by immersing the wood in the liquid for a short period of time," typically 3 to 20 minutes. Soaking involves leaving the lumber in the solution for a longer period of time (for example, 12-48 hours) in an attempt to get the chemical to go below the surface. Typically, these operations are large scale, highly automated processes where stacks of wood are mechanically lowered into baths. The stacks are inserted, removed and stacked in an automated manner with very little human exposure.

Sanitizer/Disinfectant. Items requiring disinfection or sanitization may be immersed in an antimicrobial solution. Examples include flatware, glassware, barber and hair salon articles, etc. The length of time immersed has no impact on the amount of absorption by non-porous articles. For example, a non-porous material soaked in an antimicrobial chemical does not retain the chemical or have any residual antimicrobial activity. A good example would be dishes sanitized in sodium hypochlorite by soaking. The dishes are sanitized but retain no parent chemical or antimicrobial activity once dry.

MOP – Application of a liquid material to a large surface area, such as a floor. This can be performed by repeatedly inserting an implement made of absorbent material (e.g., string mop head) fastened to a handle into a bucket and wiping it back and forth across the surface to be treated. Alternatively, "ready-to-use" mop technologies can be used, for example, pre-impregnated absorbent materials attached to a "mop head" with a handle, or spray delivery systems integrated with the mop head and handle. The ready-to-use systems do not require dipping into a bucket. All of these mop technologies transfer the antimicrobial product from the liquid formulation to the surface.

PLACE SOLID – Application of a solid biocide material into a container or final application that is accomplished in a single action. The form of the solid may be water-soluble packets, water-permeable containers, tablets, single dose delivery containers, or other solid permeable or soluble delivery forms. The application occurs in a single step without a continuous flow from one container to another.

POUR LIQUID – A biocide in a liquid form is poured from a container, either manually or with some equipment, into another container or mixing apparatus without the use of devices that create a vacuum or pressure (i.e. pumps) to facilitate or force the transfer of the liquid.

POUR SOLID – A solid biocide material (flake, pellet, powder, etc.) is transferred in a continuous flow from one container to another, either manually or with the aid of equipment.

PRESSURE TREATMENT – This is a special application method used in wood preservation using vacuum and/or external pressure to drive a biocide product deep into a product matrix. . The process involves sealing product within a pressurized container (retort) for various lengths of time, pulling a vacuum, and then introducing treating solution that is forced into the wood as air pressure is reintroduced into the retort.

PUMP - Transfer of a liquid antimicrobial from the original container to another by pumping as part of the transfer for (1) subsequent use to formulate other pesticides or for industrial use or (2) end use applications, such as recirculating water treatment, paper mill slimicide application, metalworking fluid preservation, etc. Gravity or hand pumps and automated metering pumps are typically used. This type of application is anticipated to use hoses and various connection devices to facilitate the transfer in most situations.

ROLL – Application of a liquid material to a surface area, such as a wall, by repeatedly inserting a cylindrical device covered with an absorbent material (e.g., a paint roller) into a container, and rolling the cylinder back and forth across the surface to be covered or treated.

SPRAY – A spray application occurs when a liquid is forced through an orifice under pressure for dispersal to a target object or surface. There is no accepted standard for biocide applications that distinguishes between high pressure and low pressure sprays. Pressure and orifice size are the variables that impact particle size, which is important depending on the specific application. Following are some typical examples of spray applications.

Industrial Use. High pressure sprays are delivered by electric pumps at pressures ranging from 500 to 50,000 psi. Droplet size may be less than 10 microns.

Industrial Use. Low pressure sprays used in industrial applications may be either manual or electric at pressures ranging from 1 to 500 psi. Droplet size is usually above 10 microns.

Wood Preservation. A high pressure spray nozzle delivers a wide range of particle sizes, depending on liquid pressure and nozzle opening. For example, to generate a “fog,” typical liquid pressures are 500-1500 psi and nozzle orifices are 0.005 inch or smaller. High pressure spray delivers low volume of liquid using a higher concentration of the chemical. The equipment creates a "fog" or "mist" (low particle size) that the lumber passes through. Treated lumber is almost dry to the touch immediately after the spray process; there is no dripping. Generally high-pressure systems have a vacuum that returns overspray to a holding tank for re-use. This method of application results in low exposures via inhalation when a vacuum is used and low exposures for dermal contact because lumber is almost dry to touch with a lower opportunity for transfer than a wet surface. This method is growing in popularity.

Wood preservation. Low pressure spray delivers higher volumes of liquid and actually "floods" the surface of the wood with a solution that is lower in concentration of chemical through larger sized nozzles than a high pressure spray. This results in a board that drips as though it were dipped in a bulk dip vat.

Sanitizer/Food Processing. Low pressure sprays are commonly used for sanitizer applications. There are a number of different application devices including: (1) hand pressurized (garden type) sprayers. (2) trigger spray bottles; (3) low pressure spray or foam devices (typically connected to the water system in the plant and operate at 20 -100 psi; antimicrobial is injected into the water stream and sprayed; either hose-

end devices or dispensed through a centralized system within a facility); (4) “Cleaning in Place” or CIP (automated cleaning/sanitization procedures conducted in large food processing establishments; cleaning equipment is actually built in to the food handling equipment itself; a complete cycle of pre-cleaning, cleaning, rinsing and finally sanitizing is conducted automatically through all areas of the food processing line; typically, these operations are completely enclosed; for example, pipes are flushed with the cleaning solution; tanks are cleaned and sanitized using a dishwasher type spray arm at the top of the tank which sprays the chemical solution onto the tank walls.)

Textile Treatment. Antimicrobial formulation used in a fabric treatment in which it is essentially dispensed in a series of small streams at low pressure onto the surface of the fabric, with the excess running off. Aerosol formation is typically low.

WIPE -- Application of a liquid material to a surface area, such as a counter or wall, by use of a small hand held piece of absorbent material (e.g., a sponge or woven or non-woven fabric) pre-wetted, sprayed or dipped into a container and wiping it back and forth across the surface to be treated. Industrial uses of wipes include in-factory kiss rolls, dry-wipe lines, doctor bars, or consumer-like wipes used by building restoration and maintenance personnel.

PART II. ANTIMICROBIAL USE PATTERNS

AGRICULTURAL PREMISES AND EQUIPMENT - Includes *only* application of disinfectants, sanitizers, fungicides, etc. to reduce or eliminate infectious or other undesired microorganisms on inanimate surfaces in farm and livestock premises. (e.g., pens, parlors, stalls, barns, etc.), and on equipment, (e.g., forks, shovels, halters, feeders, troughs, milking equipment, etc.)

ANTIFOULANT COATINGS - Antifoulant paints for underwater structures and underwater equipment including ship and boat bottoms and hulls, crab and lobster pots, and structures and equipment used on fish farms.

AQUATIC AREAS - Application of antimicrobials to control slime-forming bacteria, fungi and algae in lakes, ponds, streams, drainage ditches and other bodies of water.

COMMERCIAL, INSTITUTIONAL AND INDUSTRIAL PREMISES AND EQUIPMENT – Includes *only* application of disinfectants, sanitizers, fungicides, etc. to reduce or eliminate infectious or other undesired microorganisms, on inanimate surfaces, in commercial (e.g., hotels, motels, theaters, office buildings, airports, etc.), industrial (factories, mills, plants, etc.), and institutional (schools, camps, public offices, prisons, etc.) premises. Equipment includes ceilings, doors, doorknobs, fixtures, floors, woodwork, walls, and windows.

FOOD HANDLING/STORAGE PREMISES AND EQUIPMENT – Includes *only* application of disinfectants, sanitizers, fungicides, etc. to reduce or eliminate infectious or other undesired microorganisms, on inanimate surfaces, as part of good housekeeping or good manufacturing practice programs, in food/feed processing plants (e.g., meat, poultry, diary, seafood, beverage, etc.); eating establishments and food storage and transportation facilities (e.g., stores, markets, vending machines, trucks, shipping containers, etc.)

HUMAN DRINKING WATER SYSTEMS - Includes application of disinfectants to public water systems, including water supplies and components (e.g., pipes, casings, reservoir surfaces, filter sands, etc.); individual water systems (homes, farms, institutions, camps, industrial facilities, etc.); emergency water systems and water purifier systems (e.g., campers, travelers, military, etc.).

INDUSTRIAL WATER SYSTEMS - Application to commercial and industrial systems (e.g., cooling towers, evaporative condensers, air washers, heat exchangers), pulp and paper mill systems, gas/oil recovery systems, drainage, wastewater and sewage systems, and specialized uses (e.g., immersion ultrasonic tank water, laboratory equipment water baths, photo processing water, electro-deposition systems, etc.)

MATERIAL PRESERVATIVES - Bacteriostats, microbiostats, and fungistats added to industrial process intermediate materials (e.g., dispersions, slurries, emulsions, solutions, etc.) and resulting products (e.g., paints, coatings, adhesives, textiles, paper, etc.) to control growth of slime-forming microorganisms (e.g., papermaking) and prevent deterioration or spoilage of material during storage and/or in-use life.

EPA makes no distinction for purposes of exposure assessment between preserved materials (in-can) and exempt treated articles, that is, articles that make a claim of

protection for the articles themselves. EPA regards all exposures associated with the application of a pesticide to be applicator exposures. As a result, EPA regards the application of a preserved material, whether or not it makes a pesticidal claim, as secondary application for which it requires exposure data. For example, painter studies are required, but EPA does not care whether the paint used in the study make pesticidal claims, because it considers use of all paints that contain antimicrobials, even if only for in-can preservation, to be secondary pesticide application. As a result, all applications of paints and coatings, other than those specific to antifoulants and wood preservatives, are included in this category. (However, for purposes of exposure monitoring, there may be some possibility of combining replicates from these three use patterns.) Similarly, machine operators in contact with metalworking fluids are considered to be secondary applicators.

When exposure to the preserved article occurs following application of the pesticide, as is the case with most preserved articles, EPA may be interested in obtaining post-application exposure data.

MEDICAL PREMISES AND EQUIPMENT – Includes only application of disinfectants, sanitizers, fungicides, etc. to reduce or eliminate infectious or other undesired microorganisms, on inanimate surfaces in medical environments. Premises include hospitals, clinics, dental and medical offices, veterinaries, nursing homes, “sick rooms,” etc. Equipment is limited to non-critical care equipment, that is, equipment that does not contact the patient or contacts the patient’s intact skin (e.g., furniture, carts, bedpans, telephones, etc.) It is not clear from the EPA definition whether residential “sick rooms” are included within this use pattern or the preceding use pattern.

RECREATIONAL WATER - Antimicrobial treatment of “hydrologically isolated and contained manmade bodies of water,” including swimming pools, Jacuzzis and hot tubs. Exposure monitoring is limited to the applicator of the antimicrobial to the recreational water. Exposure of a bather or swimmer to the antimicrobial is considered post-application exposure and is determined by use of the EPA’s “Swim Model.”

RESIDENTIAL AND PUBLIC ACCESS PREMISES – Includes *only* application of disinfectants, sanitizers, fungicides, etc. to reduce or eliminate infectious or other undesired microorganisms, on inanimate surfaces in private residences and public access areas. (There is no clear distinction between EPA’s use of the terms institutional premises and public access premises.)

SWIMMING POOLS -- see Recreational Water

WOOD PRESERVATIVES - Preservative treatments for all types of wood, applied by pressure or vacuum treatment, remedial applications (i.e., application to utility poles, support timbers, etc. while in-service); non-pressure treatments (e.g., joinery and millwork), anti-sapstain treatments and ready-to-use coatings.

PART III. GENERAL TERMS

Adequacy of BHED™ Data - Each handler scenario within BHED™ will contain sufficient monitoring units (MUs; also referred to as monitoring events, i.e., MEs) to achieve a pre-determined level of accuracy for statistical descriptors (e.g., mean, geometric mean, and 95th percentile) of the distribution of exposure. Generally, the data set will be considered accurate if these measures are within 3-fold of the true value and the number of MEs collected will be chosen to achieve this level of accuracy.

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AEATF II = Agricultural Handlers Exposure Task Force, L.L.C. - A consortium of 43 companies that formed a FIFRA joint data development task force to design and develop a database of exposure measurements for agricultural subjects during mixing, loading, and/or application of pesticides. The exposure data will cover important types of mixing/loading systems, application equipment, and formulations. The results will satisfy FIFRA data requirements and be used to assess handler, and for some scenarios bystander, exposure potential and associated risk assessments for antimicrobial pesticide products marketed by AEATF II members. AEATF II was formed in November, 2004.

Biomonitoring - Measurement of a pesticide or its metabolite(s) in the body of a pesticide handler and the conversion to an equivalent absorbed dose based on knowledge of metabolism and pharmacokinetics. This generally includes measurement of chemical in blood or urine, but does not include measurement of biological effects such as cholinesterase levels. The result is an estimate of total exposure from the dermal, inhalation, and oral routes combined.

Cluster - A set of monitoring units or events (MUs or MEs) from the same scenario considered a higher-level sampling unit for the purpose of statistical design and analysis. Exposures between MEs from the same cluster (e.g., building location) tend to be more similar than those between MEs from different clusters.

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Distribution of Exposure - A statistical description of the probability that a given exposure level is attained; derived from a set of monitoring units (or monitoring events) within a given scenario and generally described by standard measures such as the arithmetic mean, geometric mean, and percentile values.

Engineering Controls - Equipment or equipment modifications which eliminate or reduce exposure to a chemical, such as enclosed cabs, ventilation, or closed transfer systems.

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

GLP (Good Laboratory Practice Standards) - Federal regulations (40 CFR 160) that prescribe good laboratory practices for conducting studies that support pesticide registrations. The standards address the scientific integrity of study conduct and data collection, including specific requirements for study management, equipment calibration, facilities maintenance, record keeping, reporting, and quality assurance.

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

IRB (Institutional Review Board) - An independent board that reviews and approves study proposals and oversees research to ensure the protection of human subjects who volunteer to participate in those studies. IRB responsibilities and authorities are defined at 40 CFR Part 26.

Monitoring Program (or Testing Program) - The testing program consists of all the MUs (or MEs) from the studies that will be conducted by AEATF II to monitor exposure to antimicrobial pesticide handlers and that will be used to develop a generic database to support pesticide registrations. The planned testing program will cover pesticide handling and bystander scenarios.

Monitoring Unit (MU) or Monitoring Event (ME) - All exposure monitoring activities pertaining to a single worker for a time period that represents a typical workday, including the exposure measurements for the worker involved. A specified number of monitoring events (MEs) will be conducted for each scenario to adequately define the distribution of exposure expected for that scenario. MEs defined in different scenarios may be collected in a single study.

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

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

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

Regulatory Agency Advisory Committee (RAAC) - comprised of representatives of the U.S. EPA, the Canadian Pest Management Regulatory Agency (PMRA), the California Department of Pesticide Regulation (CDPR), and European regulatory authorities. This committee meets on an ad hoc basis to review the program progress and provide technical input to the AEATF II

Scenario - A specific pesticide handling situation that will be represented by data with defined common properties; generally a combination of a work task(s), pesticide formulation, equipment, engineering controls, and work practices. For example, a scenario of interest is 'mopping indoor surfaces with defined application equipment and related tasks, e.g., filling a mop bucket with a defined end-use mop solution using an automated dispensing system and disposing of dirty mop solution'. Tasks that are common across more than one exposure scenario, e.g., pouring liquids into containers, may be specifically addressed in a separate study (e.g., mixing/loading or pouring of liquids, such as filling a mop bucket with end-use liquid solution using an automated dispensing system, or preparing an end-use mop solution, prior to mopping application).

Scripting, Scripted Study - Scripting is the partial control of the conditions in a particular study. A scripted study is considered to "involve intentional exposure" within the meaning of the regulatory definition at 40 CFR 26.1102(i). Subjects are asked to conduct their work activities under a set of scripted conditions very similar but not identical to those they experience in their normal work activities. Scripted or semi-scripted tasks may also refer to repetitive operations performed by workers or consumers (e.g., wiping countertops) that are not expected to vary significantly from one person (or location) to another.

Study - A convenient grouping of monitoring units or events (MEs) covered by one protocol and one final report. Typically a study will address one or more tasks associated with a specifically defined exposure scenario and will be conducted over a short period of time (1 to 2 weeks), with one surrogate chemical. Tasks that are common across more than one exposure scenario, e.g., pouring liquids into containers, may be specifically addressed in a separate study.

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Surrogate Chemical - A pesticide active ingredient which is present in test materials which are handled during collection of an monitoring unit or event (MU or ME). AEATF II develops validated analytical methods for each surrogate chemical and each exposure matrix so residues collected can be determined. AEATF II chooses surrogates which have low volatility and are commercially available in suitable formulations and packaging. Since exposure to handlers is a generic function, exposure measurements from these chemicals are suitable for estimating exposure to other pesticide active ingredients.

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Target Population (or Universe) - Each element of the target population is a potential task (or set of tasks) performed by a worker under a particular scenario in a day. Each element is defined by a set of all conditions that might have any impact at all on that worker's exposure. These conditions include the particular chemical product tested, the worker, his behavior, and all relevant environmental conditions. Each ME is assumed to be a realization of an element from the target population.

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Appendix D. AEATF II Acceptance Criteria for Existing Studies

Data Review and Study Acceptance Criteria
For Inclusion of Existing Antimicrobial Exposure Monitoring Studies In The Antimicrobial Exposure Assessment Task Force II (AEATF II) Database

November 28, 2006

I. DATA REVIEW PROCESS

All existing antimicrobial exposure monitoring studies, whether offered by a third party for sale or from the public domain, will undergo a 3-step review process to determine whether they meet the selection criteria listed in this document. In addition to the specific review process outlined below, a continued dialogue will take place with U.S. EPA to discuss each exposure scenario to be studied and the general study design elements (e.g., worker tasks, equipment, locations, replicates) proposed by AEATF II. This discussion will serve to inform the existing study review team as to the minimum study design and data collection requirements needed for an existing study to be deemed acceptable to fulfill a given data requirement. The non-acceptance of a given study, via the AEATF II study review process, does not imply that it is not suitable for use by any individual member company to fulfill a specific data requirement, only that the AEATF II has made the determination that the study will not be purchased for broader use by the AEATF II member companies.

A. Preliminary Review

1. The preliminary review will be conducted by the study submitter (or a designated representative) and provided to AEATF II along with a complete copy of the study report at the time the study is submitted to the Task Force for consideration.

2. The AEATF II will consider all studies, including any that are presently in PHED version 1.1 or version 2. The studies in PHED version 1.1 are all more than 15 years old and are not subject to data compensation requirements. However, these data were originally submitted to PHED without attribution to compound or company ownership. If any of these data fulfill acceptance criteria, they could potentially provide very beneficial information that would complement data developed by AEATF II.

3. Raw data for a study must be made available, if requested.

4. A list of potential studies and all preliminary review forms and reports should be submitted by dates requested by AEATF II.

5. The purpose of the preliminary review will be to eliminate the submission of studies that clearly do not meet the selection criteria, and to serve as a check on the availability and submission of supporting information.

6. AEATF II will provide an Excel spreadsheet to the submitter for use in summarizing the study details and data.

7. AEATF II will provide a confidentiality agreement to the submitter to protect the proprietary nature of the data and the study.

B. Intermediate Review

1. The intermediate review will be conducted by a qualified AEATF II contractor, hired and trained for this purpose.

2. The purpose of the intermediate review will be to verify the accuracy of the preliminary review and, where necessary, provide a more detailed discussion summarizing each specific area of the criteria, including whether each criterion was met and possible deficiencies in the study data.

3. The intermediate review will be evaluated and a determination made as to whether the study or any of the data could be used in the AEATF II database. Only studies that have met the design considerations will be presented to EPA, PMRA and CDPR for final review.

C. Final Review

1. A Committee consisting of representatives from the AEATF II and EPA, PMRA and CDPR will make the final review and decision on whether a study is accepted for purchase.

2. The intermediate review by the contractor of studies will be made available to the Committee and will serve as the basis for the final review.

3. Studies or portions of studies selected after final review will then be considered for purchase by the AEATF II for inclusion in the Task Force database.

4. Reports for studies that the Committee deems not acceptable for the AEATF II database will be returned to the submitter with an explanation as to why the

study did not meet the selection criteria. Reports of studies that are purchased by AEATF II will be placed in the AEATF II archives.

D. Appeals Process

Study contributors whose studies are not accepted for possible purchase may appeal that decision, but should do so within 30 days of such notification.

II. STUDY ACCEPTANCE CRITERIA: STUDY DESIGN CONSIDERATIONS

1. All monitored activities and equipment must be described in detail and representative of typical antimicrobial handling practices.

2. It should be clear that the individuals monitored 1) either are normally employed in the mixing/loading and/or application of antimicrobial products or pesticide products and handled them comparably, or, 2) if consumers (i.e., non-professionals), are applying antimicrobials products by methods they would use in the course of their normal activities. .

3. Appropriate supporting information such as the formulation type, mixing and application method, application rate, duration of the work cycle, amount of AI handled/replicate, etc. must be available.

4. The use of protective equipment (PPE) is acceptable but must be part of normal work practices.

5. The study location and environmental/weather conditions during the monitoring period should be available.

6. All elements of a given study may not have been conducted under GLP, but must have critical elements of GLP e.g., protocol, final report, and raw data available in order to be considered by the AEATF II.

III. STUDY ACCEPTANCE CRITERIA: EXPOSURE MONITORING

A. Field Aspects

1. Field recoveries should have been collected on a site-specific basis for time periods and environmental conditions representative of those during collection of field activity exposure samples.

2. Field fortification data should include at least triplicate samples at two rates and triplicate samples of controls; however, duplicate samples will be considered with justification.

3. Dermal exposure monitoring techniques should be specified and should include one of the following approaches. Note that glove washes of chemical resistant gloves are not an allowable method.

a) whole-body dosimeters inside and/or outside of typical clothing plus hand (cotton gloves can substitute for hand exposure) and head/face exposure determinations,

b) a minimum of 10 patch dosimeters attached inside or outside normal work clothing to the chest, back, both upper arms, both lower arms, both upper legs, both lower legs, plus hand (cotton gloves can substitute for hand wash) and head/face exposure determinations (exceptions for head/face and upper arms and upper or lower legs and bilateral measurements will be considered on a case by case basis). Conversion and use criteria have been developed by the NAFTA harmonization group and should be considered for adaptation of the PHED data.

c) combination of patches and clothing that are representative of the whole body, including hand and head/face exposure determinations.

4. Inhalation exposure – Inhalation data are required if the vapor pressure of the chemical under study is >10-4 mm Hg or if the chemical is used in an environment that results in significant volatilization (e.g., around steam pipes or in metal working fluids), or if the method produces inspirable aerosols. If data were collected, inhalation exposure should have been measured by sampling the person's breathing zone.

5. Exposure monitoring duration – The monitoring period should be at least half of a normal work period duration or mix/load and/or apply at least half of the daily amount normally used.

6. If the exposure monitoring duration does not meet the requirement of item number 5, then the number of non-detects/less than LOQ values should account for less than 40% for dermal exposure. This cut-off is specified because the distribution of exposures can be reasonably extrapolated from a data set with up to 40% non-detects. Data sets with ≥50% non-detects produce a degree of uncertainty deemed unacceptable for a generic database.

If the exposure monitoring duration and number of non-detects/less than LOQ values do not meet the criteria in items 5 and 6, then the LOQ should be no more than 20 ng/cm2 for average dermal exposure (across body part areas) and no more than 500 ppb for hand wash solution. The LOQ cutoffs are conservative in that if all data were at the LOQ, the resulting calculated exposure (at ½ LOQ) would yield an MOE of ≥100 for a compound with a systemic (absorbed dose) NOAEL ≥1 mg/kg.

B. Analytical Aspects - QA/QC

1. Analytical methods should have been validated for each analyte and substrate by the performing laboratory including establishment of the method's working concentration range to cover values anticipated in the field studies, determination of detector response over a reasonable standard concentration range, and determination of the accuracy and precision of the method within the analytical environment.

2. The study should include both field fortification samples and concurrent laboratory spikes.

3. The average recoveries of lab spikes should be between 70-120 percent and the precision value (coefficient of variation; CV) should be less than or equal to 20 percent.

4. Recovery of field fortification samples should be 50-120% with a C.V. $\leq$25%.

5. Exposure samples should have been analyzed in such a manner that the stability of each analyte in each substrate was assessed for the entire time period from collection to analysis.

C. Biomonitoring

Biological monitoring studies will be accepted for further review if they meet the selection criteria (excluding passive dosimetry) and there is a primate (human or monkey) dermal absorption study for the chemical monitored and pharmacokinetic data identifying the major excretory metabolite or parent compound.

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Appendix E. Designing Monitoring Events to Predict Future Exposure under Antimicrobial Handling Scenarios

Background

Future Exposure and Monitoring Events

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An antimicrobial handling scenario is a well-defined worker exposure situation, usually characterized by specific antimicrobial handling tasks and equipment. For the purposes of the AEATF II monitoring program, the basic element of a scenario is considered to be the handler-day (HD). Each handler-day corresponds to a particular worker and the scenario-related activities that he performs during a single work day.

Implicitly associated with each HD is a complex set of conditions denoted simply by **C**. The practically infinite number of components of **C** includes, but is not limited to worker behaviors, active ingredient used, amount of chemical contacted, surfaces treated, and numerous environmental factors. Some, but certainly not all, of these conditions can actually be observed and measured.

Each particular set of HD conditions, **C**, results in a particular worker exposure, E=E(**C**). In principle, although always subject to some measurement error, handler-day exposures (e.g., dermal or inhalation) can be obtained by actual monitoring.

Regulatory interest for each antimicrobial handling scenario is focused on predicting occupational exposure under a specific set of **generic future handler-day conditions**. In particular, it is desired to characterize exposures resulting from the future use of an arbitrary (and perhaps currently non-existent) antimicrobial active ingredient assuming some arbitrary, but quantifiable, amount of active ingredient contact.

A **monitoring event** (or ME) is the basic tool used by the AEATF II Monitoring Program to predict exposures under. An ME is a set of scenario-specific handler-day conditions that have been experimentally **selected** (i.e., chosen, simulated, or constructed) to represent expected future HD conditions. Each ME is monitored to yield a set of exposure measurements. Therefore each ME provides a measurement of the actual exposure resulting from the simulated or selected HD conditions. The ME will also provide a predicted future exposure if the handling conditions of the ME are similar to future HD conditions.

The Generic Active Ingredient Principle

The most obvious handler-day condition is the identity of the **active ingredient** (ai) to be used in the scenario task(s). Every experimental monitoring event must use at least one active ingredient. It might seem, therefore, that prediction of future exposure to a particular ai would require that every ME use that active ingredient. If this were true, a **generic exposure database** for arbitrary active ingredients would not be feasible.

Fortunately, exposure is not always chemical-specific. For compounds with low volatility (which include all the antimicrobials considered), a generally accepted **generic principle** is:

> ***If all other conditions are the same, the magnitude of exposure does not depend on the particular active ingredient used***

More formally, if A_1 and A_2 are any two active ingredients and if the exposure resulting from any active ingredient X under conditions **C** is denoted by E(X, **C**), then the generic principle is simply:

(1) $$E(A_1, \mathbf{C}) = E(A_2, \mathbf{C}) = E(\mathbf{C})$$

The practical importance of the generic assumption is that it permits an ME based on one **surrogate chemical** to be used to predict HD exposure to other active ingredients under the same set of handling conditions.

Normalized Exposure

For prediction purposes, it is useful to express handler-day exposure relative to the value of a **normalizing factor** (NF). If H is the value of the normalizing factor and **C** represents all other HD conditions then:

(2) $$nE(\mathbf{C}) = E(\mathbf{C})/H$$

is called **normalized exposure**. The quantity nE is also often referred to as **unit exposure** because it is viewed as exposure 'per unit' of the normalizing factor.

In the AEATF II Monitoring Program the normalizing factor is always an experimentally measurable quantity that is expected to be proportional to the potential contact the worker has with active ingredient. **Potential ai contact** (or PaiC) is defined as the amount of active ingredient that a worker is expected to come into contact with during a workday. Because it is always expected to be at least proportional to PaiC, an AEATF II normalizing factor is a **relative measure of active ingredient contact**.

It is generally assumed that under identical conditions exposure is proportional to potential ai contact. That is, if P_1 and P_2 are different amounts of PaiC, and **C** represents other HD conditions, then the **proportionality principle** states that:

(3) $$E(P_2, \mathbf{C}) / E(P_1, \mathbf{C}) = P_2 / P_1$$

Exposure may not be directly to proportional to contact in extreme situations (e.g., skin saturation). However, such a relationship is expected to hold for the levels of active ingredient contact that occur in practice. If the normalizing factor is expected to be proportional to PaiC then the proportionality principle relationship holds for the NF as well since:

(4) $$H_2 / H_1 = (k \cdot P_2)/(k \cdot P_1) = P_2 / P_1$$

Thus, under the same conditions, **C**, exposure for any value, H_2, of the normalizing factor can be obtained from an ME based on a different value of NF, H_1 say, since:

(5) $$E(H_2, \mathbf{C}) = (H_2/H_1) \cdot E(H_1, \mathbf{C}) = H_2 \cdot \{ E(H_1, \mathbf{C})/H_1 \} = H_2 \cdot nE(\mathbf{C})$$

For most antimicrobial scenarios, a reasonable normalizing factor is the **amount of active ingredient 'handled'** (AaiH) by a worker during the workday. However, for some scenarios (e.g., the pump liquid scenario) a worker might actually process (i.e., 'handle') a large amount of active ingredient, but may have the opportunity to contact only a small fraction of this amount. In such cases, there may be other measures of PaiC that are more appropriate than AaiH.

It is important to note that the term normalized (or unit) exposure is not always defined as a relative measure of ai contact. A familiar example occurs in studies of exposure to agricultural reentry workers. Here, exposure, E, is often normalized by duration of the reentry activities to give exposure per hour worked. Unless the concentration of active ingredient on treated foliage is always constant, the normalizing factor 'hours worked' is not expected to be proportional to contact with ai. However, the quantity:

(6) D = (hours worked) x (dislodgeable foliar ai residue)

is expected to be proportional to the amount of ai contacted by the reentry worker. In agricultural reentry studies, the quantity E/D is often called the **transfer coefficient** (TC) and corresponds to normalized exposure as defined by AEATF II.

Using MEs to Predict Future Exposure

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The generic and proportionality principles together imply that, under the same conditions, the normalized exposure from any ME can be used to obtain a **predicted future HD exposure** (pE) for any arbitrary chemical, X, at any arbitrary level of the normalizing factor, H_X, simply as:

(7) $$pE(H_X, \mathbf{C}) = H_X \cdot nE(\mathbf{C})$$

Although this relationship permits a single ME to predict exposure for a broader range of future handler-days, it cannot describe all future exposures. Even when H_X is specified, the number of possible 'other conditions' (i.e., different **C**s), is extremely large. (Although some of these **C**s are more likely than others to occur in the future HD population.) Because each ME is expensive, it will only be possible in practice to construct MEs having a limited set of **C**s. This set of N MEs will then be used to obtain a set of N predicted exposures using (7):

$$pE(H_X, \mathbf{C}_1) = H_X \cdot nE(\mathbf{C}_1)$$
$$pE(H_X, \mathbf{C}_2) = H_X \cdot nE(\mathbf{C}_2)$$
$$pE(H_X, \mathbf{C}_3) = H_X \cdot nE(\mathbf{C}_3)$$
$$\vdots$$
$$pE(H_X, \mathbf{C}_N) = H_X \cdot nE(\mathbf{C}_N)$$

Obviously, a set of only N predicted exposures cannot cover every possible future HD condition. Nor is it reasonable to expect that a small set of N MEs will provide experimental material to develop statistical models for exposure as a function of **C**. In fact, only some, but by no means all, of the components of each **C** can be controlled or measured when constructing MEs. The unknown components might have the biggest impact on exposure.

Nevertheless, this set of pEs will need to be sufficient to allow regulatory issues to be addressed in a practical manner. If some components of **C** that can be controlled are chosen appropriately, then a useful set of MEs can still be constructed. In this case the resulting set of pEs will be used as a predictor of future HD exposure in an aggregate sense.

The Future Exposure Distribution

An exposure **distribution** provides a natural aggregate description of future handler-day exposures for a scenario. It is the most common way to think about the set of exposures resulting from all possible future HD conditions. The future HD distribution (Figure 1) describes the likely exposure that would result if one were to randomly pick a future HD among those using ai X when the level of the normalizing factor is H_X.

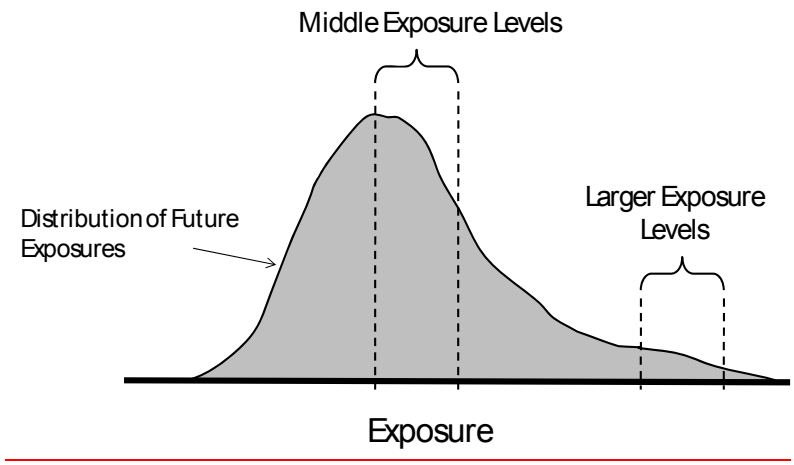

Figure 1. The distribution of future handler-day exposures

The complete exposure distribution is rarely considered. Regulatory interest is most often focused on two general aspects of this distribution:

- The **middle values** such as the arithmetic mean or the median. These exposure values tend to characterize average or 'typical' exposure levels.

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- The **larger values** of exposure possible, such as the 95th percentile of the distribution. This aspect better characterizes the extreme, one-time, worker exposures.

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Obviously the exposures can vary proportionally with the value of the normalizing factor, H. Therefore there are actually a series of predicted exposure distributions, one for each possible value of HX. Since any predicted exposure can be computed from the normalized exposure, it is simpler to focus only on the distribution of normalized exposure.

The Set of MEs as a Pseudo-Random Sample

The set of predicted exposures obtained from the constructed set of MEs should adequately characterize the middle and larger values of the future HD distribution. This might appear simple, since it is quite common practice to treat any set of values as a random sample from a distribution. Thus, one could treat the set of pEs as a simple random sample from the future exposure distribution.

This cannot be strictly the case since exposure is a function of the HD conditions, **C**, and the likelihood of the various **C**'s in a future HD population (for X and H_X)

are not known in advance. Therefore the **C**'s for the MEs cannot be randomly chosen with probability proportional to the future population frequencies.

But some random sampling interpretation might still be a convenient and reasonable model for how the set of predicted exposures from the MEs might relate to the future exposures for an arbitrary ai and H_X. Confidence in this approximation is increased by using a nested reference random sampling model rather than assuming just simple random sampling. In addition, diversity selection (using both purposive and random components) is used whenever possible. This increases the likelihood that the range of conditions in the future HD population expected to impact exposure is reflected in the 'pseudo-sample' of MEs as well.

Diversity Selection

Diversity selection is an attempt to make the set of MEs (and resulting pEs) more useful for regulatory purposes when they are treated as random sample. Often some factors that are likely to influence exposure are known or can at least be reasonably hypothesized. Diversity selection results from any procedure that improves the chance that different MEs differ with respect to such factors. It is an attempt to obtain, as much as is practical for small sample sizes, a diversity of conditions that are expected to influence exposure, either directly or indirectly. With a small set of MEs, it is more practical to construct MEs that differ that to reproduce the (unknown) frequencies of selected future HD conditions.

In the AEATF II Monitoring Program, the term **diversity selection** is preferred in lieu of the phrase **diversity sampling**. This is to emphasize the fact that the future HD conditions used for MEs are selected from either existing or from synthesized conditions (or from both). This selection of conditions can employ both **purposive and random elements**. When there are multiple diverse configurations available, random selection from among such configurations can reduce the likelihood of intentional selection bias. On the other hand, when some possible ME configurations are more diverse or more cost effective than others, it might be preferable to select these purposively.
Diversity selection attempts to create a sample that contains as many of the different conditions as possible that exist in the population. If the diversifying conditions are associated with exposure, then a diversity sample will tend to be more variable with respect to exposure than would a same-sized representative sample. In effect it will be analogous to representative sampling from a distribution that is more diverse than the actual future one (Figure 2). As a result, a diversity selection sample should tend to have more extreme exposures (both higher and lower) and fewer exposures 'in the middle'. Thus, a diversity selection sample will tend to estimate central tendencies of the exposure distribution better than it will either upper or lower percentiles. To the extent that the diversifying conditions are associated with exposure, diversity selection will tend to under-predict lower percentiles and over-predict upper percentiles. (This

effect is illustrated by envisioning a normal, or even lognormal, distribution compared with its most extreme 'diversity selection' counterpart, a uniform distribution covering a similar range.) For regulatory purposes the important aspects of the distribution of exposures are the central tendencies and the upper percentiles. In addition, overestimation of these characteristics is less of a problem than underestimation.

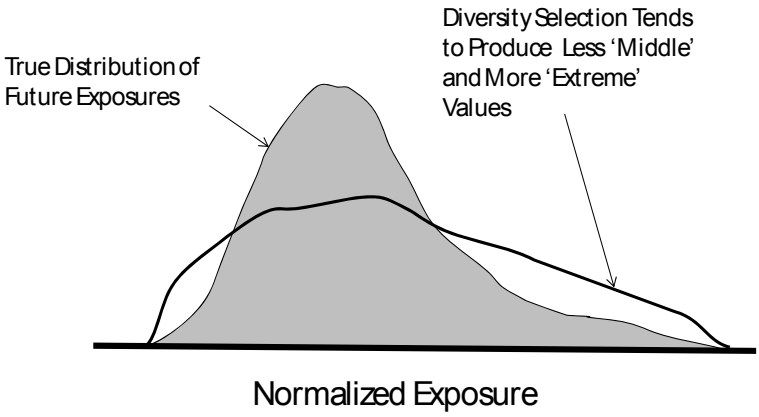

Figure 2. Diversity selection tends to make the distribution of future handler-day exposure appear more diverse than it is.

Design Objectives and Sample Size

The Two-Stage ME Selection Process

Obtaining potential workers and scenario-specific handling-day conditions needed to create monitoring events is a complicated process. Of necessity, the specific selection process used will vary from scenario to scenario. This is especially true for the two major categories of AEATF II studies: **simulated-condition** studies and **in situ** studies. Simulated-condition MEs are created synthetically whereas in situ MEs must be located from among existing handler-day conditions in facilities willing to participate.

However, as shown in Table 1, the ME construction process for both types of studies can be envisioned as occurring in **two successive stages of selection**. The first stage consists of selecting or constructing specific locations and specifying a range of dates for monitoring at each location. Each such local area and range of potential monitoring dates is termed a **monitoring site**. For in situ studies, a site might consist of a particular wood-treating facility during one particular week. In contrast, a site in a simulated-condition study might be a week-long period of monitoring activities in a particular leased office building.

Table 1
The general two-stage structure for selecting MEs in AEATF II studies

	Study Type Used for Scenario:	
	Simulated-Condition	***In Situ (Observational)***
First Stage Units (Monitoring Sites):	Synthetic environments constructed (or vacant facilities leased) expressly for the purpose of the study	Existing facilities where scenario-related tasks occur and that agree to participate in the study
Second Stage Units (Monitoring Events):	Monitoring events (ME) constructed at the sites using subjects selected from a volunteer pool	Monitoring events (ME) selected for observation from among those occurring at the site

The second stage consists of selecting one or more subjects and handling conditions within each site and constructing the MEs. For simulated-condition studies the MEs are created by assigning appropriate subjects to scenario tasks under conditions that are expected to exist in the future HD population. For in situ studies, appropriate handler-days are selected from among existing subjects and conditions that are also expected to represent future HD conditions.

In general, N_C sites are selected at the first stage and N_M monitoring events will be obtained within each site at the second stage. When N_M is greater than one, the set of MEs at the same site is termed a 'cluster'. In general, MEs in the same cluster are expected to be more similar than those in different clusters. This correlation usually means that the smallest total sample sizes (i.e. total number of MEs) are attainable when there is only a single ME per site. On the other hand, there are often substantial overhead costs per site that make multi-ME sites more efficient.

The Two-Stage Random Sampling Reference Model

In the strictest sense, sample sizes can only be determined using statistical theory alone when either

1. There is assumed random, representative sampling from a population and the goal is to estimate some characteristic of that population; or
2. There is assumed randomization of experimental units to treatments and the goal is only to compare or to contrast treatments in some manner.

Only in these two situations will statistical theory predict how increasing sample size decreases estimation error. In other experimental situations, sample size must be determined using one of the two 'random' situations above as a **reference model**. The random reference model is defined so that it reflects the actual situation (e.g., a mixture of random and non-random selection) as closely as is practical. The sample size that is appropriate for the reference model is then used for the actual study design. In a real sense, then, the reference random sampling model is used to establish **benchmark sample sizes** that can satisfy **benchmark objectives**. Although rarely stated explicitly, the use of reference sampling models and benchmark objectives are quite common.

Because all AEATF II scenario studies have a two-stage selection structure, they all assume the same reference sampling model. For each scenario, two-stage random nested (or cluster) sampling is the reference model used for the combination of purposive and random two-stage diversity selection that actually occurs. This reference model assumes that:

1. Exposure, normalized by the potential active ingredient contact factor, is lognormally distributed with geometric standard deviation GSD. Equivalently, the logarithm of normalized exposure is normally distributed with standard deviation Log(GSD).
2. There are N_C clusters (i.e. sites) and N_M MEs per cluster. The total number of MEs in this scenario is, therefore, $N=N_C \times N_M$.
3. The within cluster (i.e., within-site) correlation of log normalized exposure is equal to ICC.

The reference sampling model incorporates a two-stage selection structure and the potential for within-cluster correlation, but ignores any effects of diversity selection. Thus, for determining sample sizes, normalized exposures, nE, are assumed to follow the nested variance component model

$$\text{(8)} \qquad \text{Log}\left(E_{ij} / H_{ij}\right) = \text{Log}\, nE_{ij} = \text{Log}\, GM_{nE} + Q_i + W_{ij}$$

where

E_{ij} = the exposure obtained for ME j in cluster i
H_{ij} = the value of the normalizing factor for worker for ME j in cluster i

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nE_{ij} = the exposure for ME j in cluster i normalized by NF
GM_{nE} = the population geometric mean for normalized exposure
Q_i = a random effect of cluster i
W_{ij} = a random effect of ME j within cluster i

The random effects Q_i and W_{ij} are normally distributed with means 0 and variances V_Q and V_w, respectively.

The population variance of log nE is then equal to $V = V_Q + V_w$ and the square root of V is the true population standard deviation, SD. The quantity GSD_{nE} = antilog (SD) is the true population geometric standard deviation of normalized exposure. The **intra-cluster correlation** (i.e., the intraclass correlation due to clusters) is defined as

(9) $$ICC = V_Q / V = 1 - V_w / V$$

The ICC is irrelevant to the future distribution of normalized exposure, per se. However, this intra-cluster correlation is a necessary part of the reference sampling model because the MEs are obtained in clusters (i.e. there are multiple MEs per site).

Relative Accuracy and Fold Relative Accuracy

The benchmark objective of the AEATF II monitoring program will be to achieve adequate relative accuracy of selected parameter estimates if the reference sampling model described above were used. This benchmark target can be stated more precisely as:

If there are N_C clusters and N_M MEs per cluster and the underlying lognormal two-stage reference sampling model were actually true, then selected parameter estimates will be within K-fold of the true values at least 95% of the time.

If θ denotes the distributional parameter of interest and T is the estimate of that parameter obtained from monitoring data, then the relative accuracy of T is defined simply as:

(10) $$RA(T|\theta) = T/\theta$$

Satisfying the benchmark objective above requires that there be at least a 95% chance that T/θ is between 1/K and K. More formally this is stated as:

(11) $$\text{Prob}\{1/K \le RA(T|\theta) \le K\} \ge 0.95$$

It is more convenient, however, to consider relative accuracy expressed as a 'fold relative difference'. This is because statements such as "T is within K-fold of θ" are more intuitive than the formulation given in (11). The 'fold relative accuracy', *fRA*, is defined as:

(12) $fRA(T|\theta) = \text{Max}\{ RA(T|\theta), 1/RA(T|\theta) \} = \text{Max} (T/\theta, \theta/T)$

Then, statement (11) is equivalent to

(13) $\text{Prob} \{ fRA(T|\theta) \leq K \} \geq 0.95$

and simply says that the estimate, T, will be within K-fold of the true parameter, θ, at least 95% of the time. The 95th percentile of *fRA*, fRA_{95}, is the specific fold-accuracy value that satisfies (13). Consequently, the benchmark adequacy goal reduces to requiring that:

(14) $fRA_{95} \leq K$

If we denote the 2.5th and 97.5th percentiles of the sampling distribution of T by $T_{2.5}$ and $T_{97.5}$, respectively, then the 95th percentile of fold relative accuracy can also be calculated from

(15) $fRA_{95} = \text{Max} (T_{97.5}/\theta, \theta/T_{2.5})$

Benchmark Objective for Antimicrobial Scenarios

The default benchmark objective for all antimicrobial scenarios in the AEATF II Monitoring Program is that a sample from the hypothetical reference sampling distribution above be of adequate size to describe selected measures of the (normalized) exposure distribution with a pre-determined level of accuracy. EPA provides guidance to AEATF II on the minimum degree of accuracy needed for regulatory use in particular scenarios. The current consensus is that estimates of the geometric mean, the arithmetic mean, and the 95th percentile generally should be accurate to within approximately 3-fold of their true value.

It should always be kept in mind, however, that this objective is specified in terms of the reference random sampling distribution. This reference sampling model does have the same two-stage nesting structure as the actual sampling approach. The lognormal distribution assumption is also reasonable, robust, and consistent with existing data. However, the reference distribution assumes simple random sampling at each stage. It does not, and cannot, incorporate the combination of purposive and random diversity sampling actually used.

As noted above, the consequence of diversity sampling is expected to be a tendency for the sampling variation of normalized exposure to be overestimated. The sample should tend to over-represent extremes and under-represent the more common values. Such diversity-oriented data collected for this scenario, but analyzed with respect to the two-stage reference distribution, is expected to have minimal bias for central tendency. In contrast, upper percentiles of exposure are expected to be, on the average, too large. There is no way to determine the actual magnitude of such overestimation. For regulatory purposes, however, overestimation of upper percentiles is of minimal concern: for practical exposure assessments, overestimation of exposures is a conservative practice utilized by regulatory agencies. A tendency to both consider and even overestimate upper percentiles is consistent with this practice.

Parameter Estimates Used for Benchmark Objectives

As defined above, relative accuracy applies to the particular quantity, T, that is used to estimate the reference distribution parameter θ. Thus, it is important to consider which types of estimates of the geometric mean, arithmetic mean, and 95th percentile are used to evaluate fRA_{95}. The relative accuracies could differ depending on the particular estimates used.

There are often multiple choices for the parameter estimates. The estimators can be broadly grouped into either empirical or parametric. Empirical estimates are the commonly-used statistics available in spreadsheet programs. They do not (explicitly) assume any distribution. However, they can sometimes require simple random sampling for greatest efficiency. Parametric estimates incorporate the fact that the reference distribution is lognormal and could also account for cluster sampling being used.

The most straightforward parameter is the geometric mean (GM_{nE}). In the balanced case, the simple empirical estimate of GM_{nE} can be calculated by averaging the log-transformed normalized exposures and then taking the antilog of this value. In this case, the empirical and parametric estimates of GM_{nE} are identical. If the number of MEs per cluster varies, however, one could consider geometric means with different degrees of weighting by cluster size. The arithmetic mean can also be calculated empirically by summing up the normalized exposures and dividing by the total number of MEs. Again, when the cluster sizes differ, other types of weighted empirical arithmetic means exist. In the unbalanced case, neither the weighted nor the unweighted estimates of GM_{nE} or AM_{nE} are universally best. Consequently, for the purposes of sample size determination, the simple (and most common) versions of the empirical geometric and arithmetic means seem preferable. Empirical percentiles could, theoretically be calculated in the conventional manner. However, when there is cluster sampling and the number of MEs are not large, empirical estimates of the

extreme upper (or lower) percentiles are not especially efficient. The parametric percentiles (see below) are preferred in this case.

Parametric estimates are those closely aligned with the sampling model used. In this case one uses the fit to the variance component model described in (8) above to get estimates for the geometric mean (GM_{nE}) and the total geometric standard deviation (GSD_{nE}). To estimate the arithmetic mean (AM_{nE}) and 95th percentile (nE_{95}) one could then use the lognormal relationships:

$$AM_{nE} = GM_{nE} \times \text{Exp}\{ \tfrac{1}{2} (\log_e GSD_{nE})^2 \} \quad (16)$$

$$nE_{95} = GM_{nE} \times \text{Exp}\{ Z_{95} \log_e GSD_{nE} \}$$

where Z_{95} is the 95th percentile of the standard normal distribution. For simplicity, these will be labeled the 'parametric cluster sampling estimates'.

It can be argued that few if any users of the AEATF II monitoring data will choose to (or be able to) fit variance component models to the data. They will probably ignore the sampling model and use more conventional estimates. In this case empirical estimates of GM_{nE} and AM_{nE} defined above would probably be used.

Potential data users might also be less inclined to use empirical percentiles, especially with smaller sample sizes. The lognormal percentile estimate of nE_{95} in (16) above would then still be used but perhaps with the mixed model GSD_{nE} estimate replaced with the more conventional GSD_{nE} (i.e., the back-transformed simple standard deviation of log exposures.) For convenience, estimates that assume lognormality but not cluster sampling will be labeled 'simple random sampling parametric percentiles'.

Any or all of the above estimators could be evaluated. However, for the purposes of determining sample sizes, it is recommended that focus be on the following estimators:

- GM_{nE} – simple empirical estimate
- AM_{nE} – simple empirical estimate
- nE_{95} – parametric cluster sampling estimate

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The Determination of Sample Size

As stated above, the benchmark adequacy goal reduces to requiring that the 95% percentile of fold relative accuracy, fRA_{95}, be less than or equal to K. Under the reference two-stage random sampling model described above, the only quantities needed to determine relative accuracy of population parameter estimates are reasonable values for GSD_{nE} and ICC. Such values could be based on existing exposure data for scenario-specific tasks, surrogate exposure

data from similar tasks, and/or reasonable assumptions based on subject-matter expertise.

Given these values, fRA_{95}, can be computed for any combination of the N_C and N_M. Calculation of the 95% percentile of fold relative accuracy is complex and is usually best accomplished using Monte Carlo simulation methods. When the number of MEs per cluster, N_m, is the same for all clusters, the geometric mean, fRA_{95} can be calculated directly from the GSD_{nE} and ICC as:

$$fRA_{95} = \exp\left\{1.96 \ln GSD_{nE} \sqrt{\frac{ICC}{N_c} + \frac{1 - ICC}{N}}\right\} \quad (17)$$

where N is the total number of MEs (i.e., $N=N_C \times N_m$). For parameters other than the geometric mean, a straightforward simulation approach can be used to determine fRA_{95}. This procedure is:

1. Simulate a set of normalized exposure data for N_C clusters and N_m monitoring units per cluster using the reference sampling model defined in (8) above.
2. From each set of simulated data, calculate T, the estimate of θ
3. Repeat steps 1 and 2 above M times to get M values of the estimate T
4. From these M T-values calculate $T_{2.5}$ and $T_{97.5}$, the 2.5th and 97.5th percentiles of T, respectively.
5. Calculate the 95th percentile of fold relative accuracy, fRA_{95}, using formula (15) above.

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The number of simulations, M, should be some large number such as 1,000 or 10,000. This process can be continued until a combination of N_C and N_M are found that satisfy to benchmark objective.

General Guidelines for Diversity Selection of Monitoring Events

Although diversity selection is simple in theory, practical implementation is often complex and usually scenario specific. This section presents diversity selection procedures and recommendations that apply generally to all scenarios. Scenario-specific design documents and study protocols will provide details of ME selection and construction.

As described previously, the objective of diversity selection is to obtain a diverse set of handler-day conditions from among those conditions possible when an arbitrary ai is used in future scenario-related tasks. These selected HD conditions are then used to construct monitoring events. Diversity selection is

done independently at each stage of 'sampling'. Thus, a diverse set of sites is selected followed by a diverse set of ME conditions within each site.

Diversity should always be with respect to characteristics (i.e. particular components of **C**) that are expected to impact exposure. Whenever possible, the characteristics used should be **meta-factors**. Meta-factors are characteristics that indirectly influence a number of other characteristics. For example, a worker is a meta-factor because substituting one worker for another alters a number of factors (e.g., behavior, physical appearance, stamina) that might affect exposure. Other common meta-factors are geographic location and time-of-year. Not every characteristic that may impact exposure can be, or even should be, considered in diversity selection. The number of possible combinations of factors that may impact exposure will always greatly exceed the number of planned MEs. Consequently, only a few characteristics, preferably meta-factors, can be used effectively in diversity selection.

Diversity Selection Approaches

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There are a number of ways to achieve diversity among ME handler-day conditions. The most straightforward approach is to purposively select MEs that appear to be sufficiently different with respect to the characteristics of interest. Documentation for such direct purposive selection should include the characteristics considered and how much these characteristics differ among the ME. Although flexible, and likely to achieve a set of MEs with a great amount of diversity, this approach is subjective and, therefore, difficult to reproduce.

More formal approaches are also possible. A general, albeit quite sophisticated, approach is to define **diversity scores** for each possible configuration of the characteristics of interest. A total configuration score might be defined as a function of the dissimilarity between possible pairs of units. Then, one simply selects (or synthetically constructs) those configurations that result in the greatest diversity score. If multiple configurations have the highest score, a random selection among these is possible. While achieving diversity in an objective and reproducible manner, this approach is quite complex and difficult to implement.

A formal approach that is both common and simple to implement is **stratified diversity selection**. In this approach available selectable units (e.g., sites, MEs) are partitioned into strata based on characteristics likely to impact exposure. Each possible selection unit must belong to one and only one stratum. The number of strata must be at least as large as the number of units that will be selected. For example, if there are three units to be selected, then there should be at least three strata. Diversity could be achieved by selecting (purposively or randomly) no more than one unit from each stratum. If there are more strata than units to be selected, then a subset of the strata should be selected first.

This could be either purposively (to increase diversity) or randomly (to reduce intentional selection bias).

Stratified diversity selection is similar to the method of stratification used in population sampling. Unlike the case with stratified sampling, however, diversity is increased by selecting only a single unit from each stratum. There is no attempt to sample or to weight results in proportion to stratum size. In fact stratum size in the future HD population is usually unknown.

Diversity Selection of First-Stage Units

At the first stage of ME selection, sites are the 'selectable' units. As defined previously, site is considered a particular experimental location and timeframe for monitoring. Diversity selection of sites means obtaining sites that are different from each other, on the average, with respect to some characteristic(s) expected to impact exposure. Thus, there should be little surprise if exposure, on the average, differs between sites. If sites are constructed environments, then they can be built to be different from each other with respect to important characteristic(s). If there are a number of possible sites available and a set is to be selected (randomly or purposively), then stratified diversity selection of sites, based on the important characteristic(s), is a feasible approach

Diversity Selection of Second-Stage Units

Ultimately the second stage selection units are the final MEs. The MEs should be diversified independently within each selected site. In most cases within-site diversity selection of MEs focuses only on two characteristics: subject and normalizing factor.

Handling-day exposures for the same individual are expected to be correlated. That is, many components of **C** relating to same worker will be identical, even on different days. In contrast, different individuals are less correlated. Worker behaviors are expected to have great impact on exposure. Consequently, diversity is increased by simply requiring that each ME be constructed using a different individual.

MEs should also be diverse with respect to the normalization factor that is deemed appropriate for the scenario. One feasible approach is to partition the possible levels of NF into strata and construct one ME from each NF stratum.

In some cases (e.g. simulated-condition studies) there is a pool of available workers that can be assigned to any NF stratum. If all possible configurations of assignment are equivalent, then workers could be randomly allocated to strata. If some allocations are non-equivalent (e.g. more cost effective or there are scheduling issues) then a purposive assignment of individuals to NF levels might be preferable.

In other cases (e.g. In Situ/observational studies) worker availability depends on the particular NF level chosen. Some individuals may only work with higher NF levels and some with only lower NF, say. Selection of workers could still be random, although random choice might be restricted to within each NF stratum. However, when such associations between subject and NF levels exist, purposive allocation might result in a more cost effective and practical configuration.

Rationale for Using the Normalizing Factor in Diversity Selection

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It might at first appear pointless to select MEs with differing levels of the normalizing factor when diversity of normalized exposures is desired. If the NF is approximately proportional to the amount of potential ai contact, then normalized exposure should be independent of the levels of NF. Consequently, it should make no difference whether all MEs are at the same level or at different levels of the NF.

This would be true if the value of the normalizing factor had no impact on the other ME conditions selected. However, this might not be true. Because amount of active ingredient contact is so important to exposure, it is likely that the NF is also a meta-factor. That is, it is not unreasonable to expect that different values of the NF will be naturally associated with specific sets of handler-day conditions, **C**. Suppose, for example, that the normalizing factor for wiping application exposure was correlated with duration of task. It is conceivable that some worker behaviors (e.g. fatigue) and diversity of surfaces wiped might be different for shorter duration MEs than for longer duration MEs. By insuring that the levels of NF are varied, the set of MEs indirectly captures diversity in those components of **C** that are naturally associated with the normalizing factor.

Appendix F: Evaluation of Existing PHED Applicator Exposure Data for Hand-Held Aerosol Spray

The Pesticide Handlers Exposure Database (PHED, version 1.1) contains two studies involving the monitoring of dermal and inhalation exposure during the use of a pressurized aerosol container. The current HED PHED Surrogate Guide uses the data only from Study 521 for aerosols (Scenario 10). The two studies were accessed in PHED by subsetting the applicator file for method of application equal to aerosol can. The two studies were identified as Study 456 and 521 and both involved the application of an insecticide. A general review of these studies is provided in the "PHED SCENARIO DISCUSSION" section of this report. This is followed by the "ACCEPTANCE CRITERIA EVALUATION" section of this report, wherein the following information and "data acceptance criteria" were evaluated:

1. Meta information: Scenario (e.g., hand held aerosols) study(ies) code(s), total number of replicates or monitoring events, range of AaiH, dermal and inhalation sampling durations, average limits of quantitation (LOQ's) for dermal and inhalation exposure, percentage of samples with undetectable residues body area.
2. Results of selected AEATF II/AHETF data acceptance criteria applied to the scenario-specific study data set(s):

    a. Identification of the number of monitoring events classified in PHED as A and B grade; A and B grade data indicate compliance with the criteria: the average recoveries of lab spikes should be between 70-120 percent and the precision value (coefficient of variation; CV) should be less than or equal to 20 percent AND recovery of field fortification samples should be 50-120% with a C.V. +/-25%;
    b. The number monitoring events where non-detects/less than LOQ values account for less than 40% of dermal exposure; and
    c. The number of monitoring events with a minimum of 10 dermal patch dosimeters attached inside or outside normal work clothing to the chest, back, both upper arms, both lower arms, both upper legs, both lower legs, plus hand (cotton gloves can substitute for hand wash) and head/face exposure determinations.

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PHED SCENARIO DISCUSSION

Method of Application

PHED Study 456 involved the application of one 15-ounce aerosol can of insecticide per house in each of 15 houses in Kansas City, Missouri. Three study volunteers treated five houses each. The aerosol cans contained 1% of the active ingredient under study, equivalent to 4.33 grams a.i. per can. Applicators held the aerosol can in one hand and sprayed the contents of the container into cracks and crevices, along baseboards, under sinks, behind appliances, and in other areas were insects would be expected to hide.

PHED Study 521 involved the application of one 16-ounce aerosol can of insecticide per house in each of 15 houses in Vero Beach, Florida. Five study volunteers treated three houses each. The aerosol cans contained 1% active ingredient, equivalent to 4.54 grams a.i. per can. Applicators held the aerosol can in one hand and sprayed the contents into cracks and crevices, along baseboards, under sinks, behind appliances, and in other areas where insects were expected to hide.

Exposure Monitoring Methodology

Both Study 456 and Study 521 used gauze patches for dermal exposure monitoring. Volunteers wore a single layer of clothing that included a long-sleeved shirt, long pants, and shoes. The dermal gauze patches were in holders with an open diameter of 5.6 cm, and were placed under the single layer of clothing on the participant's upper arms, forearms, chest, back, thighs, and lower legs. These dosimeters provide dermal exposure estimates under a single layer of clothing.

A second set of dermal dosimeters were placed outside the clothing, but so as not to occlude the inner dosimeters. The outer dermal dosimeters were also placed on the upper arms, forearms, chest, back, thighs, and lower legs. This set-up provides dermal dosimetry data needed to estimate actual dermal exposure for a variety of clothing possibilities ranging from long-sleeved shirt and long pants to short pants and a short-sleeved shirt. Head exposure was monitored by the placement of a gauze dosimeter on a ball cap just above the bill of the hat.

Hand exposure was monitored using hand-rinses. Applicator's hands were rinsed at the completion of application in each house. Each hand was rinsed separately using 200 mL of ethanol and each hand was rinsed twice in a total of 400 mL of ethanol. The total rinsate from the four rinses (two for each hand) were combined for analysis. Volunteers in Study 456 wore chemical-resistant gloves during all 15 replications; the results of this study represent hand exposure under protective gloves. Volunteers in Study 521 wore no gloves, and

the results represent exposure to unprotected hands. Taken together, both studies support a comparison of protected and unprotected hand exposure during aerosol can use.

Inhalation exposure was monitored using personal air samplers with the sampling cassette placed on the collar near the participant's breathing zone. Air was drawn through the sampling cassettes at a flow rate of 1 liter per minute. The air pumps were sampled before and after each monitoring period.

PHED Data Quality Grades

Data in PHED are graded for quality based on analytical quality assurance. The data are assigned to one of five grades, A through E, based on the recovery of the active ingredient from fortified field samples, fortified laboratory samples, and storage stability samples. Grade A and B data meet the minimum analytical quality assurance requirements as described in EPA's Subdivision U of the Pesticide Assessment Guidelines. Grade A and B data have laboratory recoveries of 80% to 110% with a coefficient of variation of 25% or less. The field recoveries are between 50% and 120%. Grade C data have laboratory recoveries of 70% to 120% with a coefficient of variation of 33% or less. Grade C data must also have either field recoveries of 30% to 120%, or the data must have storage stability recoveries of 50% to 120%. Grade D data have laboratory recoveries of 60% to 120% with a coefficient of variation of 33% or less. Field recovery or storage stability data are not required for a grade D classification. Grade E data do not meet any of these standards. To support the registration of a pesticide, the data subset should contain a minimum of 15 replications for each body area except the feet. The data should also meet the minimum analytical quality assurance requirements of grades A or B. The Health Effects Division uses the number of replicates in a scenario and the data quality grades to rate the PHED data for a given scenario as high confidence, medium confidence, or low confidence data.

Study 521 contains 15 replications of hand, dermal, and inhalation data that were graded A. The hand data in Study 456 were graded A, but the dermal and inhalation data were graded C. The HED PHED Surrogate Guide lists aerosol application as Scenario 10. Because of the grading, Scenario 10 lists only the 15 replicates from Study 521 and gives them a high confidence rating.

Study 456 Dermal Exposure

The dermal exposures from Study 456 are presented below. The dermal exposure is presented both as the "no clothing" scenario and as long-sleeved shirt and long pants to permit analysis of multiple clothing scenarios. The exposure data are presented in micrograms and were not normalized by the amount of a.i. handled. As previously noted, all replicates in Study 456 involved handling 4.33 grams of active ingredient.

<< Specifications >>
Subset Specifications for STUDY456.APPL

With Study Code Equal to 456
Subset originated from AEROSAL.APPL
With Application Method Equal to 4
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES
SCENARIO: No clothing (total deposition)

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	288.6	435.5867	90.9793	209.1935	15
NECK.FRONT	Lognormal	14.25	30.07	126.9042	11.7512	15
NECK.BACK	Lognormal	13.86	20.5847	80.8261	13.0283	15
UPPER ARMS	Lognormal	776.97	1129.177	125.0676	508.4372	15
CHEST	Lognormal	337.25	711.6567	126.9042	278.1117	15
BACK	Lognormal	447.3	664.3233	80.826	420.4601	15
FOREARMS	Lognormal	362.395	714.9083	137.7725	276.778	15
THIGHS	Lognormal	255.94	328.0107	97.1166	210.1775	15
LOWER LEGS	Lognormal	86.87	137.564	90.5475	97.689	15
FEET			0			
HANDS			0			
TOTAL DERM:	**2025.6265**	2583.435	4171.8814		2025.6265	

95% C.I. on Mean: Dermal: [-29183.6113, 37527.3741]

Number of Records: 15
Data File: APPLICATOR Subset Name: STUDY456.APPL

The dermal exposure to all body areas had a lognormal distribution. The total geometric mean dermal exposure was 2.03 mg/replicate. Note that this dermal exposure represents exposure outside the clothing and because of the use of protective gloves, there are no data for the hands.

The dermal exposure under a single layer of clothing and protective gloves is presented below.

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES
SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	288.6	435.5867	90.9793	209.1935	15
NECK.FRONT	Lognormal	14.25	30.07	126.9042	11.7512	15
NECK.BACK	Lognormal	13.86	20.5847	80.8261	13.0283	15
UPPER ARMS	Other	43.65	43.65	0	43.6502	15
CHEST	Other	53.25	53.25	0	53.2503	15
BACK	Other	53.25	53.25	0	53.2503	15
FOREARMS	Other	18.15	18.3113	3.4121	18.3022	15
THIGHS	Other	57.3	57.3	0	57.3003	15
LOWER LEGS	Other	35.7	37.128	9.5542	36.9913	15
FEET				0		
HANDS	Other	5	15.7067	152.4528	9.0385	15
TOTAL DERM:	**500.273**	583.01	764.8374		505.7561	

95% C.I. on Mean: Dermal: [-5623.8395, 7153.5143]
Number of Records: 15
Data File: APPLICATOR Subset Name: STUDY456.APPL

The dermal exposure to the head and neck are the same as in the “no clothing” scenario because they are based on the same outer dosimeters. The dermal exposure to the upper arms, chest, back, and thighs is based on residue levels below the limit of quantification and therefore are based on half of the LOQ as per PHED and HED guidelines. It can be determined that all 15 observations for these body areas were below the LOQ because the coefficient of variation is 0. The forearms had only one study participant with detectable residues and then only to the right forearm dosimeter. The lower legs had one replication with detectable residues to both dosimeters and two additional replicates with detectable residues to the left lower leg dosimeter. The dermal dosimeter LOQ in Study 456 was 0.03 µg/cm^2. The hand wash LOQ was 10 µg per sample. The total dermal exposure for an individual wearing long pants, a long-sleeved shirt, and protective gloves is 0.50 mg based on the PHED “best fit” guideline.

Study 521 Dermal Exposure

The potential dermal exposure under the “no clothing scenario is presented below.

<< Specifications >>
Subset Specifications for STUDY521.APPL

With Study Code Equal to 521
Subset originated from AEROSAL.APPL
With Application Method Equal to 4
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES
SCENARIO: No clothing (total deposition)

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	419.9	697.6927	124.9606	410.258	15
NECK.FRONT	Lognormal	21	71.499	217.76	25.1292	15
NECK.BACK	Lognormal	21.34	26.1235	80.9252	19.9517	15
UPPER ARMS	Lognormal	1063.896	1320.4028	69.3397	999.3333	15
CHEST	Lognormal	497	1692.143	217.7599	594.7233	15
BACK	Lognormal	688.7	843.0777	80.9252	643.8954	15
FOREARMS	Lognormal	752.62	800.2295	82.2052	488.1726	15
THIGHS	Lognormal	223.47	483.612	124.2601	299.811	15
LOWER LEGS	Lognormal	169.456	627.3363	177.4108	248.3608	15
FEET			0			
HANDS	Lognormal	1100	1210.2667	51.0748	1056.7992	15
TOTAL DERM:		**4786.4345**	4957.382	7772.3832	4786.4345	

95% C.I. on Mean: Dermal: [-60276.6132, 75821.3796]

Number of Records: 15
Data File: APPLICATOR Subset Name: STUDY521.APPL

The total potential exposure under the “no clothing scenario” is 4.79 mg/replicate. All body areas had a lognormal distribution. Because hand exposure is included in the Study 521 data the hand exposure must be subtracted from the total potential exposure to permit a direct comparison with Study 456. The geometric mean hand exposure was 1.057 mg and the dermal exposure excluding the hands is 3.73 mg/replicate. The total potential dermal exposure in Study 456 was 2.03 mg/replicate.

The actual dermal exposure to an individual wearing long pants and a long sleeved shirt is presented below.

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES
SCENARIO: Long pants, long sleeves, no gloves

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	419.9	697.6927	124.9606	410.258	15
NECK.FRONT	Lognormal	21	71.499	217.76	25.1292	15
NECK.BACK	Lognormal	21.34	26.1235	80.9252	19.9517	15
UPPER ARMS	Other	59.073	59.073	0	59.075	15
CHEST	Other	72.065	72.065	0	72.0675	15
BACK	Other	72.065	72.065	0	72.0675	15
FOREARMS	Other	24.563	27.3783	39.8253	26.2578	15
THIGHS	Other	77.546	77.546	0	77.5487	15
LOWER LEGS	Other	48.314	48.314	0	48.3157	15
FEET				0		
HANDS	Lognormal	1100	1210.2667	51.0748	1056.7992	15
TOTAL DERM:		**1865.7641**	1915.866	2362.0232	1867.4703	

95% C.I. on Mean: Dermal: [-14926.1143, 19650.1607]
Number of Records: 15
Data File: APPLICATOR Subset Name: STUDY521.APPL

The exposure pattern under a single layer of clothing in Study 521 is similar to that reported in Study 456. All covered body areas except the forearms had residue levels on all dosimeters that were below the study’s LOQ. Among the forearm dosimeters there was one replicate with quantifiable residues on the left forearm dosimeter. The limit of quantification in Study 521 was 0.0406 µg/cm^2 for the dermal dosimeters and 100 µg/replicate for the hand rinses. The dermal exposure under a single layer of clothing from Study 521 can be compared to exposure in Study 456 by subtracting the 1.058 mg hand exposure from the total dermal exposure of 1.866 mg. The total dermal exposure excluding the hands in Study 521 is 0.809 mg/replicate compared to the total dermal exposure excluding the hands of 0.495 mg/replicate.

By combining the dermal exposure data from Studies 456 and 521 it is possible to estimate the reduction in exposure attributable to the use of protective gloves. Although EPA does not routinely consider the use of protective gloves for homeowner uses of aerosols, the use of protective gloves may possibly be considered for occupational uses of aerosol containers.

Combined Dermal Exposure Estimate

The combined dermal exposure data based on Studies 456 and 521 are presented below. The first scenario represents exposure when wearing a long-sleeved shirt, long pants, and no gloves. The second scenario represents exposure when wearing a long-sleeved shirt, long pants, and protective gloves. The difference between the two estimates provides insight into the protection provided by chemical-resistant gloves.

<< Specifications >>
Subset Specifications for AEROSAL.APPL
With Application Method Equal to 4
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES
SCENARIO: **Long pants, long sleeves, no gloves**

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	353.6	566.6397	119.763	292.9561	30
NECK.FRONT	Lognormal	20.1	50.7845	223.2098	17.1842	30
NECK.BACK	Lognormal	18.095	23.3541	80.9408	16.1226	30
UPPER ARMS	Other	51.3615	51.3615	15.2708	50.7803	30
CHEST	Other	62.6575	62.6575	15.2708	61.9485	30
BACK	Other	62.6575	62.6575	15.2708	61.9485	30
FOREARMS	Other	22.5665	22.8448	38.8679	21.922	30
THIGHS	Other	67.423	67.423	15.2709	66.66	30
LOWER LEGS	Other	48.314	42.721	14.5118	42.276	30
FEET				0		
HANDS	Lognormal	1100	1210.2667	51.0748	1056.7992	15
TOTAL DERM:	**1698.0421**	1806.775	2160.7103		1688.5974	

95% C.I. on Mean: Dermal: [-10432.2269, 14753.6475]
Number of Records: 30
Data File: APPLICATOR Subset Name: AEROSAL.APPL

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES
SCENARIO: **Long pants, long sleeves, gloves**

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	353.6	566.6397	119.763	292.9561	30
NECK.FRONT	Lognormal	20.1	50.7845	223.2098	17.1842	30
NECK.BACK	Lognormal	18.095	23.3541	80.9408	16.1226	30
UPPER ARMS	Other	51.3615	51.3615	15.2708	50.7803	30
CHEST	Other	62.6575	62.6575	15.2708	61.9485	30
BACK	Other	62.6575	62.6575	15.2708	61.9485	30
FOREARMS	Other	22.5665	22.8448	38.8679	21.922	30
THIGHS	Other	67.423	67.423	15.2709	66.66	30
LOWER LEGS	Other	48.314	42.721	14.5118	42.276	30
FEET				0		
HANDS	Other	5	15.7067	152.4528	9.0385	15
TOTAL DERM:	**646.2429**	711.775	966.1503		640.8367	

95% C.I. on Mean: Dermal: [-6835.8234, 8768.124]

Number of Records: 30
Data File: APPLICATOR Subset Name: AEROSAL.APPL

Based on the PHED analysis the use of protective gloves reduces the dermal exposure from 1.7 mg/aerosol can to 0.65 mg/aerosol can, where an aerosol can is 15 to 16 ounces.

Inhalation Exposure

PHED was used to estimate the inhalation exposure potential for Studies 456 and 521 separately and combined. PHED requires the user to select a breathing volume. Past analysis by OPP's Health Effects Division HED assumed a breathing volume of 29 liters/minute. For this analysis a breathing volume of approximately 17 liters/minute was used (U.S. EPA Exposure Factors Handbook; http://www.epa.gov/ncea/efh/).

The inhalation exposure from Study 456 is as follows:

<< Specifications >>
Subset Specifications for STUDY456.APPL
With Study Code Equal to 456
Subset originated from AEROSAL.APPL
With Application Method Equal to 4
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR INHALATION EXPOSURES

	DISTRIB. TYPE	NANOGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Lognormal	27523.8095	26580.3734	49.7805	**22356.8193**	15

95% C.I. on Geo. Mean: [5704.4462, 87620.6649]
Number of Records: 15
Data File: APPLICATOR Subset Name: STUDY456.APPL

The inhalation exposure in Study 456 was 22 µg/replicate or aerosol can. The inhalation exposure is 1.3% of the dermal exposure when gloves are not worn.

The inhalation exposure from Study 521 is as follows:

<< Specifications >>
Subset Specifications for STUDY521.APPL

With Study Code Equal to 521
Subset originated from AEROSAL.APPL
With Application Method Equal to 4
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR INHALATION EXPOSURES

	DISTRIB. TYPE	NANOGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Other	7456.1404	10594.0506	61.6887	**9345.3422**	15

95% C.I. on Geo. Mean: [3720.0299, 23477.0745]
Number of Records: 15
Data File: APPLICATOR Subset Name: STUDY521.APPL

The inhalation exposure in Study 521 was 9.3 µg/replicate. The inhalation exposure is similar to the exposure monitored in Study 456 and represents 0.5% of the dermal exposure when gloves are not worn.

The combined inhalation exposure from both studies is presented below.

<< Specifications >>
Subset Specifications for AEROSAL.APPL
With Application Method Equal to 4
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR INHALATION EXPOSURES

	DISTRIB. TYPE	NANOGRAMS Median	Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Other	13379.6296	18587.212	70.4015	**14454.4846**	30

95% C.I. on Geo. Mean: [3433.5175, 60850.7529]
Number of Records: 30
Data File: APPLICATOR Subset Name: AEROSAL.APPL

The inhalation exposure is 14 µg/aerosol can when the container is 15 to 16 ounces.

Conclusions

PHED contains two studies that monitored dermal and inhalation exposure during the application of the entire contents of one container per replicate. EPA's PHED Surrogate Guide (Scenario 10) uses the data only from Study 521.

Study 456 provides data for hands protected by gloves while Study 521 presents data for unprotected hands. This permits an estimate of exposure reduction when gloves are worn (for scenarios where protective glove use is reasonable.)

A significant limitation of these existing data is that the use conditions for both studies, including the number of cans applied per replicate and the AaiH, were very similar. This prevents evaluating any potential relationship between exposure and either the number of cans used or the AaiH. PHED study 521 provides MUs that meet key AEATF II acceptance criteria, but additional monitoring events should be considered to provide a wider range of amount of formulation sprayed (AaiH) under conditions relevant to antimicrobial aerosol product use.

Attachment 1. Individual Replicate Dosimeter Residue Levels

<< AEROSAL.APPL >>

Record I.D.	Total AI Applied (lb)	Total US Gal Sprayed
0456*B*4	.0094	.1200
0456*B*5	.0094	.1200
0456*C*1	.0094	.1200
0456*C*2	.0094	.1200
0456*C*3	.0094	.1200
0456*C*4	.0094	.1200
0456*C*5	.0094	.1200
0521*B*02	.0100	.1250
0521*D*02	.0100	.1250
0456*A*01	.0094	.1200
0456*A*02	.0094	.1200
0521*A*02	.0100	.1250
0521*C*01	.0100	.1250
0521*A*03	.0100	.1250
0521*C*02	.0100	.1250
0521*C*03	.0100	.1250
0521*E*01	.0100	.1250
0521*E*02	.0100	.1250
0521*E*03	.0100	.1250
0521*A*01	.0100	.1250
0456*A*3	.0094	.1200
0456*A*4	.0094	.1200
0456*A*5	.0094	.1200
0456*B*1	.0094	.1200
0456*B*2	.0094	.1200
0456*B*3	.0094	.1200
0521*B*01	.0100	.1250
0521*D*01	.0100	.1250
0521*D*03	.0100	.1250
0521*B*03	.0100	.1250

<< AEROSAL.APPL >>

Record I.D.	Air Smpl Time (min)	Air Quan. Limit (ug)	Air Volume (l)	Air Amount (ug)
0456*B*4	28.0	.1000	30.8	3.0300
0456*B*5	18.0	.1000	19.4	1.3900
0456*C*1	15.0	.1000	16.2	.8900
0456*C*2	21.0	.1000	22.6	1.2500
0456*C*3	19.0	.1000	19.7	1.3700
0456*C*4	26.0	.1000	27.0	.5800
0456*C*5	13.0	.1000	13.5	.7800
0521*B*02	28.0	1.0000	33.0	ND
0521*D*02	19.0	1.0000	22.4	ND
0456*A*01	30.0	.1000	31.5	1.7000
0456*A*02	28.0	.1000	29.4	.2200
0521*A*02	33.0	1.0000	38.9	ND
0521*C*01	32.0	1.0000	34.9	ND
0521*A*03	31.0	1.0000	35.3	ND
0521*C*02	27.0	1.0000	31.9	1.6143
0521*C*03	32.0	1.0000	36.5	ND
0521*E*01	31.0	1.0000	33.8	1.3600
0521*E*02	32.0	1.0000	37.8	ND

0521*E*03	36.0	1.0000	41.0	ND
0521*A*01	28.0	1.0000	30.5	ND
0456*A*3	33.0	.1000	34.6	2.6700
0456*A*4	30.0	.1000	32.7	2.0300
0456*A*5	25.0	.1000	27.2	2.6000
0456*B*1	23.0	.1000	25.0	2.6200
0456*B*2	30.0	.1000	32.7	2.2500
0456*B*3	31.0	.1000	34.1	1.8900
0521*B*01	27.0	1.0000	29.4	ND
0521*D*01	26.0	1.0000	28.3	1.6000
0521*D*03	22.0	1.0000	25.1	ND
0521*B*03	18.0	1.0000	20.5	ND

<< AEROSAL.APPL >> (H)P

Record I.D.	Outside Both Hands (ug)	Inside Both Hands (ug)	Dermal Smpl Time (hrs)	Avg Hand Quan. Limit (ug/sq cm)
0456*B*4		ND	.470	10.0000
0456*B*5		ND	.310	10.0000
0456*C*1		ND	.250	10.0000
0456*C*2		21.6000	.350	10.0000
0456*C*3		97.6000	.320	10.0000
0456*C*4		ND	.430	10.0000
0456*C*5		ND	.220	10.0000
0521*B*02	430.0000		.470	100.0000
0521*D*02	981.0000		.320	100.0000
0456*A*01		ND	.500	10.0000
0456*A*02		ND	.470	10.0000
0521*A*02	1240.0000		.550	100.0000
0521*C*01	1750.0000		.530	100.0000
0521*A*03	1070.0000		.520	100.0000
0521*C*02	645.0000		.450	100.0000
0521*C*03	2690.0000		.530	100.0000
0521*E*01	1530.0000		.520	100.0000
0521*E*02	299.0000		.530	100.0000
0521*E*03	1060.0000		.600	100.0000
0521*A*01	1100.0000		.470	100.0000
0456*A*3		22.4000	.550	10.0000
0456*A*4		24.8000	.500	10.0000
0456*A*5		ND	.420	10.0000
0456*B*1		19.2000	.380	10.0000
0456*B*2		ND	.500	10.0000
0456*B*3		ND	.520	10.0000
0521*B*01	1150.0000		.450	100.0000
0521*D*01	2010.0000		.430	100.0000
0521*D*03	1440.0000		.370	100.0000
0521*B*03	759.0000		.300	100.0000

Note: Avg. Hand Quantification is µg/sample.
The 100 µg LOQ for study 521 was erroneously entered into PHED as 100 µg. The correct value is 10 µg.

<< AEROSAL.APPL >> (H)Page 1 (V

Record I.D.	Uppr Arm In Rght (ug/sq cm)	Uppr Arm In Left (ug/sq cm)	Uppr Arm Out Rght (ug/sq cm)	Uppr Arm Out Left (ug/sq cm)	Avg Dermal Quan. Limit (ug/sq cm)
0456*B*4	ND	ND	.2880	.2050	.0300
0456*B*5	ND	ND	.3250	.2090	.0300
0456*C*1	ND	ND	.0340	.0140	.0300
0456*C*2	ND	ND	.0180	.0280	.0300

0456*C*3	ND	ND	ND	ND	.0300
0456*C*4	ND	ND	.0650	.1610	.0300
0456*C*5	ND	ND	.0170	.0320	.0300
0521*B*02	ND	ND	.1770	ND	.0406
0521*D*02	ND	ND	.9990	.4340	.0406
0456*A*01	ND	ND	1.1970	.1930	.0300
0456*A*02	ND	ND	.7630	.0730	.0300
0521*A*02	ND	ND	.5030	.9990	.0406
0521*C*01	ND	ND	.1400	.3760	.0406
0521*A*03	ND	ND	.1360	.0830	.0406
0521*C*02	ND	ND	.4300	.7920	.0406
0521*C*03	ND	ND	.7430	.9660	.0406
0521*E*01	ND	ND	.4710	.1790	.0406
0521*E*02	ND	ND	.7880	.3670	.0406
0521*E*03	ND	ND	.1560	.3000	.0406
0521*A*01	ND	ND	.9700	.0620	.0406
0456*A*3	ND	ND	.1970	.8200	.0300
0456*A*4	ND	ND	.9730	.3980	.0300
0456*A*5	ND	ND	.0780	.1390	.0300
0456*B*1	ND	ND	.7500	.2530	.0300
0456*B*2	ND	ND	1.3070	2.5330	.0300
0456*B*3	ND	ND	.2180	.3230	.0300
0521*B*01	ND	ND	.7110	ND	.0406
0521*D*01	ND	ND	.7630	1.4940	.0406
0521*D*03	ND	ND	.1830	.1830	.0406
0521*B*03	ND	ND	.1020	.0650	.0406

<< AEROSAL.APPL >>

Record I.D.	Forearm In Rght (ug/sq cm)	Forearm In Left (ug/sq cm)	Forearm Out Rght (ug/sq cm)	Forearm Out Left (ug/sq cm)
0456*B*4	ND	ND	.1860	1.0100
0456*B*5	ND	ND	.1830	1.3750
0456*C*1	ND	ND	.0180	.0240
0456*C*2	.0190	ND	.0330	.0500
0456*C*3	ND	ND	ND	ND
0456*C*4	ND	ND	.0750	.0370
0456*C*5	ND	ND	.0460	.0800
0521*B*02	ND	ND	ND	ND
0521*D*02	ND	ND	ND	1.3400
0456*A*01	ND	ND	2.8240	.5200
0456*A*02	ND	ND	.4640	.1350
0521*A*02	ND	ND	.3290	.6740
0521*C*01	ND	ND	.2740	.9700
0521*A*03	ND	ND	1.2630	.1420
0521*C*02	ND	ND	.5810	1.5790
0521*C*03	ND	ND	1.4290	.3690
0521*E*01	ND	ND	.4300	1.2300
0521*E*02	ND	ND	.8930	.2900
0521*E*03	ND	ND	.0510	.1920
0521*A*01	ND	ND	4.1410	.2540
0456*A*3	ND	ND	.3060	.7240
0456*A*4	ND	ND	.0960	.2350
0456*A*5	ND	ND	.0370	.5380
0456*B*1	ND	ND	1.3150	.7400
0456*B*2	ND	ND	.6510	5.3930
0456*B*3	ND	ND	.2000	.4000
0521*B*01	ND	ND	.4590	.4140
0521*D*01	ND	.0900	.9180	1.1000
0521*D*03	ND	ND	.1730	.2090
0521*B*03	ND	ND	.0550	ND

<< AEROSAL.APPL >>

Record I.D.	Chest In Left (ug/sq cm)	Chest Out Rght (ug/sq cm)	Back In Rght (ug/sq cm)	Back Out Left (ug/sq cm)
0456*B*4	ND	.4940	ND	.1650
0456*B*5	ND	.2270	ND	.4470
0456*C*1	ND	.0130	ND	.0200
0456*C*2	ND	ND	ND	.0230
0456*C*3	ND	.0190	ND	.1210
0456*C*4	ND	ND	ND	.0270
0456*C*5	ND	ND	ND	.0280
0521*B*02	ND	ND	ND	ND
0521*D*02	ND	.1310	ND	.0910
0456*A*01	ND	.1310	ND	.1260
0456*A*02	ND	.2610	ND	.0900
0521*A*02	ND	.0850	ND	.2960
0521*C*01	ND	.1370	ND	.2510
0521*A*03	ND	ND	ND	.1440
0521*C*02	ND	.4790	ND	.8440
0521*C*03	ND	.3900	ND	.3480
0521*E*01	ND	.4990	ND	.1640
0521*E*02	ND	.3170	ND	.3170
0521*E*03	ND	.1120	ND	.3090
0521*A*01	ND	4.1820	ND	.1940
0456*A*3	ND	.3880	ND	.3190
0456*A*4	ND	.0340	ND	.3690
0456*A*5	ND	.0190	ND	.0930
0456*B*1	ND	.3710	ND	.4000
0456*B*2	ND	.9100	ND	.3300
0456*B*3	ND	.0950	ND	.2490
0521*B*01	ND	.2610	ND	.1170
0521*D*01	ND	.3560	ND	.1970
0521*D*03	ND	.1400	ND	.1260
0521*B*03	ND	ND	ND	.1440

<< AEROSAL.APPL >>

Record I.D.	Thigh In Rght (ug/sq cm)	Thigh In Left (ug/sq cm)	Thigh Out Rght (ug/sq cm)	Thigh Out Left (ug/sq cm)
0456*B*4	ND	ND	.1570	.1650
0456*B*5	ND	ND	.1250	.0780
0456*C*1	ND	ND	ND	ND
0456*C*2	ND	ND	.0150	.0140
0456*C*3	ND	ND	.0240	.0270
0456*C*4	ND	ND	ND	.0210
0456*C*5	ND	ND	ND	ND
0521*B*02	ND	ND	ND	ND
0521*D*02	ND	ND	.0820	ND
0456*A*01	ND	ND	.3070	.1510
0456*A*02	ND	ND	.1560	.0520
0521*A*02	ND	ND	.0850	.0970
0521*C*01	ND	ND	.1430	.1470
0521*A*03	ND	ND	.0450	.0610
0521*C*02	ND	ND	.2410	.3380
0521*C*03	ND	ND	.1300	1.1040
0521*E*01	ND	ND	.1060	.0630
0521*E*02	ND	ND	.0590	.0530
0521*E*03	ND	ND	.0730	.0530

0521*A*01	ND	ND	.0500	.0670
0456*A*3	ND	ND	.1600	.4260
0456*A*4	ND	ND	.0670	.0800
0456*A*5	ND	ND	.0310	.0440
0456*B*1	ND	ND	.1240	.0490
0456*B*2	ND	ND	.0730	.0610
0456*B*3	ND	ND	.0490	.0450
0521*B*01	ND	ND	.0650	ND
0521*D*01	ND	ND	.1190	.3890
0521*D*03	ND	ND	ND	.0860
0521*B*03	ND	ND	ND	ND

<< AEROSAL.APPL >>

Record I.D.	Shin In Rght (ug/sq cm)	Shin In Left (ug/sq cm)	Shin Out Rght (ug/sq cm)	Shin Out Left (ug/sq cm)
0456*B*4	.0170	.0240	.1270	.1270
0456*B*5	ND	ND	.0590	.0400
0456*C*1	ND	ND	.0130	.0140
0456*C*2	ND	ND	.0260	.0440
0456*C*3	ND	ND	.0290	.0380
0456*C*4	ND	ND	ND	.0170
0456*C*5	ND	ND	ND	ND
0521*B*02	ND	ND	.1220	ND
0521*D*02	ND	ND	.0490	ND
0456*A*01	ND	ND	.2060	.0380
0456*A*02	ND	ND	.0800	.0310
0521*A*02	ND	ND	.1220	ND
0521*C*01	ND	ND	1.8640	.0500
0521*A*03	ND	ND	.1120	.2550
0521*C*02	ND	ND	.5360	.2680
0521*C*03	ND	ND	2.8060	.6210
0521*E*01	ND	ND	.0860	.0500
0521*E*02	ND	ND	.0590	.0450
0521*E*03	ND	ND	.0430	ND
0521*A*01	ND	ND	ND	.0690
0456*A*3	ND	.0190	.0110	.1500
0456*A*4	ND	ND	ND	.0200
0456*A*5	ND	ND	.0220	ND
0456*B*1	ND	.0180	.0810	.0250
0456*B*2	ND	ND	.0750	.3130
0456*B*3	ND	ND	.0330	.0400
0521*B*01	ND	ND	ND	.1120
0521*D*01	ND	ND	.1860	.1100
0521*D*03	ND	ND	ND	.1600
0521*B*03	ND	ND	ND	ND

ACCEPTANCE CRITERIA EVALUATION:

PHED SCENARIO 10: AEROSOL APPLICATION (APPL)

Study Code 456: Handheld Aerosols

Task: Evaluate handheld aerosols (specifically study code 456) from the applicator file of the Pesticide Handlers Exposure Database. The following criteria are reviewed to determine if the study code is complete enough for future use.

1. Are the dermal grades (covered/uncovered) for all study codes listed as “A” or “B”? No
2. Are the airborne grades for all study codes listed as “A” or “B”? No
3. Are the hand grades for all study codes listed as “A” or “B”? No
4. Is the percentage of non-detect values for all body part depositions less than 40% when determining whole body exposures? Total Deposition: Yes
   Single Layer Clothing: No
5. Are the 10 selected body parts (head, neck (front and back), both upper arms, both forearms, chest, back, upper legs, lower legs, and hands) available to determine whole body exposures?

<u>Total Deposition/No Normalization</u>
Traditional - No
Substitution method - Yes

<u>Total Deposition/Normalized by lb ai handled</u>
Traditional - No
Substitution method - Yes

Single layer clothing (non protective), long sleeve/long pants/no glove/no head protection/
<u>No normalization</u>

Traditional - No
Substitution method – Yes

Single layer clothing (non protective), long sleeve/long pants/no glove/no head protection/
Normalized by lb ai handled

Traditional - No
Substitution method – Yes

Summary:

Number of Replicates:	15
Range of lbs AI Handled:	9.40E-03 lbs ai - 9.40E-03 lbs ai
Range of inhalation sampling durations:	13 minutes – 33 minutes
Range of dermal sampling durations:	0.22 hrs – 0.55 hrs
Average Dermal LOQ:	3.02 ug/cm^2
Average Inhalation LOQ:	10.0 ug
Inhalation Rate/Minute:	16 L/minute
Non-Detect Handling:	Half LOQ Values
Hand Protection:	No
Head Protection:	No

Section 1: Clothing Layer: Total Deposition

Table 1.1 is a listing of Non-Detect Counts of total deposition. For each column, the number of non-detect values and the number of replicates with a value is listed.

Head	Neck (front/ back)	Upper Arms Right Left	Chest Right Left	Back Right Left	Forearms Right Left	Thighs Right Left	Lower Legs shin right shin left calf right calf left ankle right ankle left	Feet	Hands
4/15=27%	0/0=NA% 0/0=NA%	1/15=7% 1/15=7%	3/15=20% 0/0=NA%	0/0=NA% 0/15 = 0%	1/15 =7% 1/15 =7%	3/15=20% 2/15=13%	3/15 =20% 2/15=13% 0/0=NA% 0/0=NA% 0/0=NA% 0/0=NA%	0/0=NA%	0/0=NA%

Table 1.1. Non-Detect Counts of body part values (total deposition)

Percentage Non-Detects: 21/165 = 13%

1a. No Normalization – Total Deposition

Table 1.2 is a listing of all replicates with a study code of 456. The exposure values are results of no normalization and total deposition. No replicates had a whole body exposure using the traditional exposure evaluation method. The Substitution Body Method resulted in all 15 replicates having a whole body exposure value.

Replicate	Sample Time (hrs)	Whole Body Exposure (Traditional Method) (ug)	Whole Body Exposure (Substitution Body Method) (ug)	Inhalation Exposure (ug)	Average Dermal Quantification Limit (ug/cm^2)	Average Hand Quantification Limit (ug/cm^2)	Airborne Grade	Dermal Grade Uncovered	Dermal Grade Covered	Hand Grade
456-A-3	0.55	-	7.58e+03	4.07E+04	3.0e-02	10	C	C		A
456-A-4	0.50	-	4.57e+03	2.98E+04	3.0e-02	10	C	C		A
456-A-5	0.42	-	1.76e+03	3.82E+04	3.0e-02	10	C	C		A
456-A-1	0.50	-	8.45e+03	2.59E+04	3.0e-02	10	C	C		A
456-A-2	0.47	-	4.53e+03	3.35E+04	3.0e-02	10	C	C		A
456-B-1	0.38	-	7.09e+03	3.85E+04	3.0e-02	10	C	C		A
456-B-2	0.50	-	1.81e+03	3.30E+04	3.0e-02	10	C	C		A
456-B-3	0.52	-	3.20e+03	2.75E+04	3.0e-02	10	C	C		A
456-B-4	0.47	-	5.61e+03	4.41E+0	3.0e-02	10	C	C		A

456-B-5	0.31	-	5.90e+03	2.06E+04	3.0e-02	10	C	C	A
456-C-1	0.25	-	343	1.32E+04	3.0e-02	10	C	C	A
456-C-2	0.35	-	449	1.85E+04	3.0e-02	10	C	C	A
456-C-3	0.32	-	1.05e+03	2.11E+04	3.0e-02	10	C	C	A
456-C-4	0.43	-	723	8.92E+04	3.0e-02	10	C	C	A
456-C-5	0.22	-	470	1.20E+04	3.0e-02	10	C	C	A

Table 1.2. Exposure values using no normalization and total deposition.

Table 1.3 displays the body parts and their corresponding geometric mean exposure values in ug using the Body Part Substitution Method.

Head	Neck (front)	Neck (back)	Upper Arms	Chest	Back	Forearms	Thighs	Lower Legs	Feet	Hands
209	11.8	13.0	508	278	420	277	210	97.7	NA	188

Table 1.3. Body parts and corresponding geometric mean exposure values (ug)

Figure 1.1 shows a log-log graph of whole body exposures vs. total lbs AI handled. This graph is a result of substitution body part method, no normalization and total deposition. No data exists for the traditional body part method.

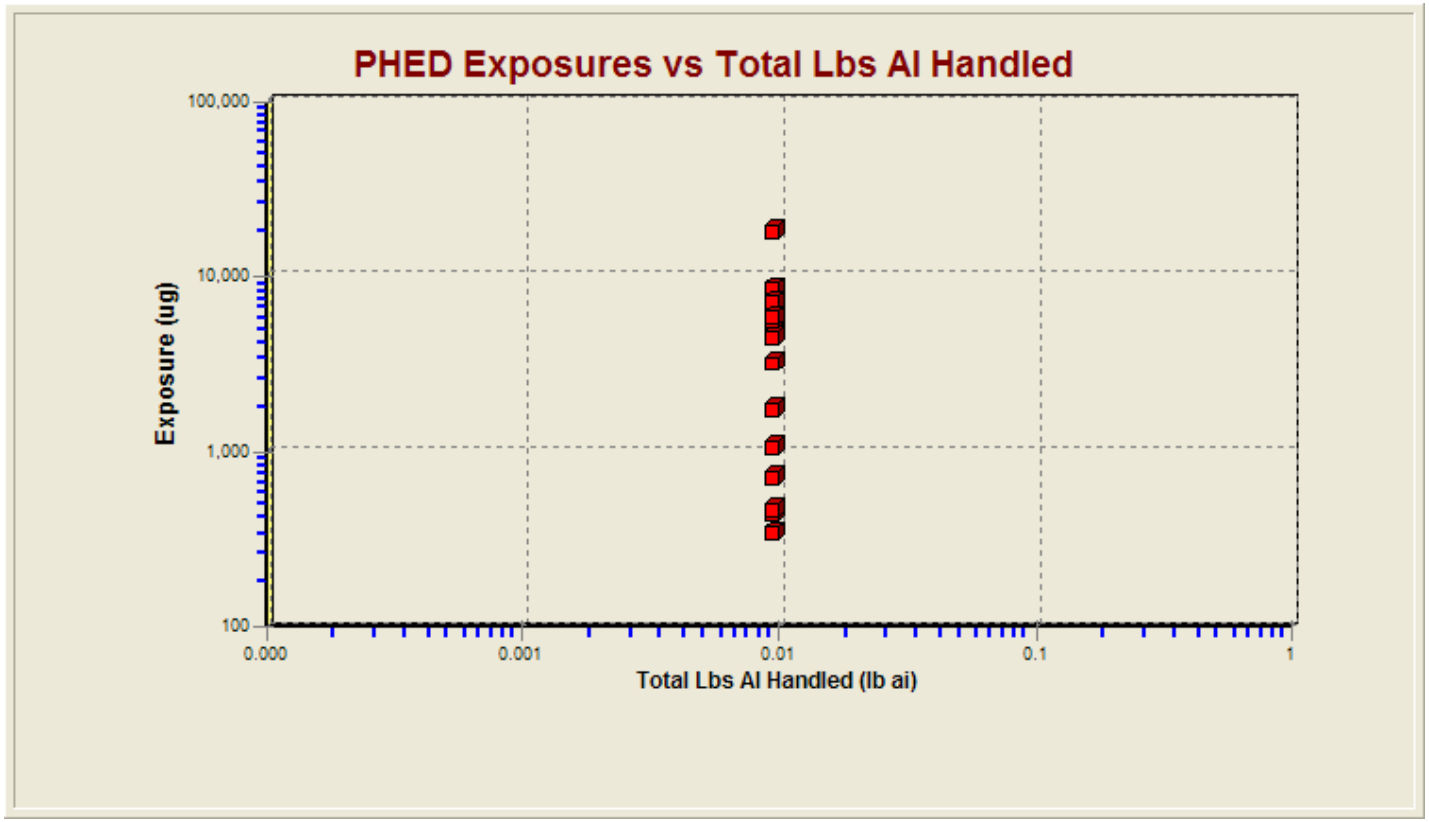

Figure 1.1 Whole Body Exposure vs. Total Lbs AI Handled (not normalized, total deposition)

1b. Normalized by Lb AI Handled – Total Deposition.

Table 1.4 is a listing of all replicates with a study code of 456. These values are based on normalization by Lbs AI Handled and total deposition. No replicates had a whole body exposure using the traditional exposure evaluation method. The Substitution Body Method resulted in all 15 replicates having a whole body exposure value.

Replicate	Sample Time (hrs)	Whole Body Exposure (Traditional Method) (ug)	Whole Body Exposure (Substitution Body Method) (ug)	Inhalation Exposure (ug)	Average Dermal Quantification Limit (ug/cm2)	Average Hand Quantification Limit (ug/cm2)	Airborne Grade	Dermal Grade Uncovered	Dermal Grade Covered	Hand Grade
456-A-3	0.55	-	8.06e+05	7.87E+06	3.0e-02	10	C	C		A
456-A-4	0.50	-	4.86e+05	6.34E+06	3.0e-02	10	C	C		A
456-A-5	0.42	-	1.88e+05	9.74E+06	3.0e-02	10	C	C		A
456-A-1	0.50	-	8.99e+05	5.51E+06	3.0e-02	10	C	C		A
456-A-2	0.47	-	4.82e+05	7.64E+06	3.0e-02	10	C	C		A
456-B-1	0.38	-	7.54e+05	1.07E+07	3.0e-02	10	C	C		A
456-B-2	0.50	-	1.93e+06	7.03E+06	3.0e-02	10	C	C		A
456-B-3	0.52	-	3.40e+05	5.66E+06	3.0e-02	10	C	C		A
456-B-4	0.47	-	5.97e+05	1.00E+07	3.0e-02	10	C	C		A
456-B-5	0.31	-	6.27e+05	7.30E+06	3.0e-02	10	C	C		A
456-C-1	0.25	-	3.65e+04	5.61E+06	3.0e-02	10	C	C		A
456-C-2	0.35	-	4.78e+04	5.63E+06	3.0e-02	10	C	C		A
456-C-3	0.32	-	1.12e+04	7.08E+06	3.0e-02	10	C	C		A
456-C-4	0.43	-	7.69e+04	2.19E+06	3.0e-02	10	C	C		A
456-C-5	0.22	-	5.00e+04	5.89E+06	3.0e-02	10	C	C		A

Table 1.4. Exposure values normalized by lbs AI handled and total deposition.

Table 1.5 displays the body parts and their corresponding geometric mean exposure values in ug using the Body Part Substitution Method.

Head	Neck front	Neck back	Upper Arms	Chest	Back	Forearms	Thighs	Lower Legs	Feet	Hands
5.58E04	3.13E03	3.47E03	1.36E05	7.41E04	1.12E05	7.38E04	5.60E04	2.60E04	NA	5.00E04

Table 1.5. Body parts and corresponding geometric mean exposure values (ug)

Figure 1.2 shows a log-log graph of whole body exposures vs. total lbs AI handled. This graph is a result of substitution body part method, normalized by lb ai handled and total deposition. No data exists for the traditional body part method.

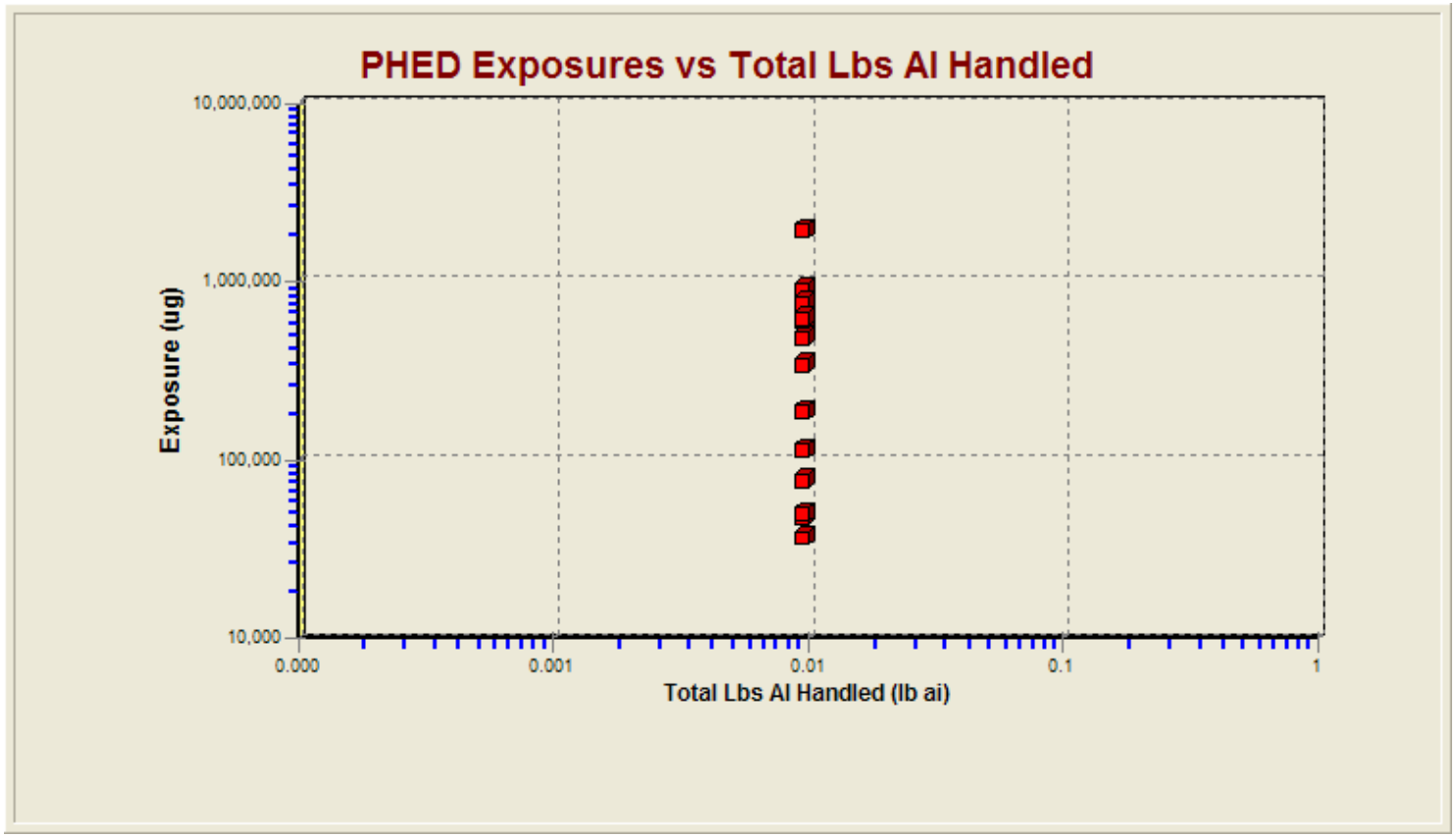

Figure 1.2 Whole Body Exposure vs. Total Lbs AI Handled (normalized, total deposition)

Section 2. Clothing Layer: Long Sleeves, Long Pants, No gloves.

Table 2.1 is a listing of Non-Detect Counts with a clothing layer of long sleeves, long pants and no gloves. For each column, the number of non-detect values and the number of replicates with a value is listed.

Head	Neck (front/ back)	Upper Arms Right Left	Chest Right Left	Back Right Left	Forearms Right Left	Thighs Right Left	Lower Legs shin right shin left calf right calf left ankle right ankle left	Feet	Hands
4/15=27%	15/15=100% 15/15=100%	15/15=100 % 15/15=100 %	0/0=NA% 15/15=100 %	15/15=100 % 0/0 = NA	14/15 =93% 15/15=100 %	15/15=100 % 15/15=100 %	14/15 =93% 12/15=80% 0/0=NA% 0/0=NA% 0/0=NA% 0/0=NA%	0/0=NA%	0/0=NA%

Table 2.1. Non-Detect Counts of body part values (permeable layer clothing – long sleeves, long pants, no gloves)

Percentage Non-Detects: 179/195 = 92%

2a. No Normalization – Permeable Clothing

Table 2.2 is a listing of all replicates with a study code of 456. The exposure values are results of no normalization with permeable clothing - long pants, long sleeves and no gloves. No replicates had a whole body exposure using the traditional exposure evaluation method. The Substitution Body Method resulted in all 15 replicates having a whole body exposure value.

Replicate	Sample Time (hrs)	Whole Body Exposure (Traditional Method) (ug)	Whole Body Exposure (Substitution Body Method) (ug)	Inhalation Exposure (ug)	Average Dermal Quantification Limit (ug/cm^2)	Average Hand Quantification Limit (ug/cm^2)	Airborne Grade	Dermal Grade Uncovered	Dermal Grade Covered	Hand Grade
456-A-3	0.55	-	1.51e+03	4.07E+04	3.0e-02	10	C	C		A
456-A-4	0.50	-	761	2.98E+04	3.0e-02	10	C	C		A
456-A-5	0.42	-	552	3.82E+04	3.0e-02	10	C	C		A
456-A-1	0.50	-	1.23e+03	2.59E+04	3.0e-02	10	C	C		A
456-A-2	0.47	-	1.20e+03	3.35E+04	3.0e-02	10	C	C		A
456-B-1	0.38	-	630	3.85E+04	3.0e-02	10	C	C		A
456-B-2	0.50	-	1.55e+03	3.30E+04	3.0e-02	10	C	C		A
456-B-3	0.52	-	590	2.75E+04	3.0e-02	10	C	C		A
456-B-4	0.47	-	713	4.41E+04	3.0e-02	10	C	C		A
456-B-5	0.31	-	913	2.06E+04	3.0e-02	10	C	C		A
456-C-1	0.25	-	297	1.32E+04	3.0e-02	10	C	C		A
456-C-2	0.35	-	302	1.85E+04	3.0e-02	10	C	C		A
456-C-3	0.32	-	578	2.11E+04	3.0e-02	10	C	C		A
456-C-4	0.43	-	298	8.92E+04	3.0e-02	10	C	C		A
456-C-5	0.22	-	298	1.20E+04	3.0e-02	10	C	C		A

Table 2.2. Exposure values using no normalization with permeable clothing – long sleeves, long pants, no gloves.

Table 2.3 displays the body parts and their corresponding geometric mean exposure values in ug using the Body Part Substitution Method.

Head	Neck front	Neck back	Upper Arms	Chest	Back	Forearms	Thighs	Lower Legs	Feet	Hands
209	11.8	13.0	43.7	53.2	53.2	18.3	57.3	37.0	NA	12.4

Table 2.3. Body parts and corresponding geometric mean exposure values (ug)

Figure 2.1 shows a log-log graph of whole body exposures vs. total lbs AI handled. This graph is a result of substitution body part method, no normalization with permeable layer clothing consisting of long sleeves, long pants and no gloves. No data exists for the traditional body part method.

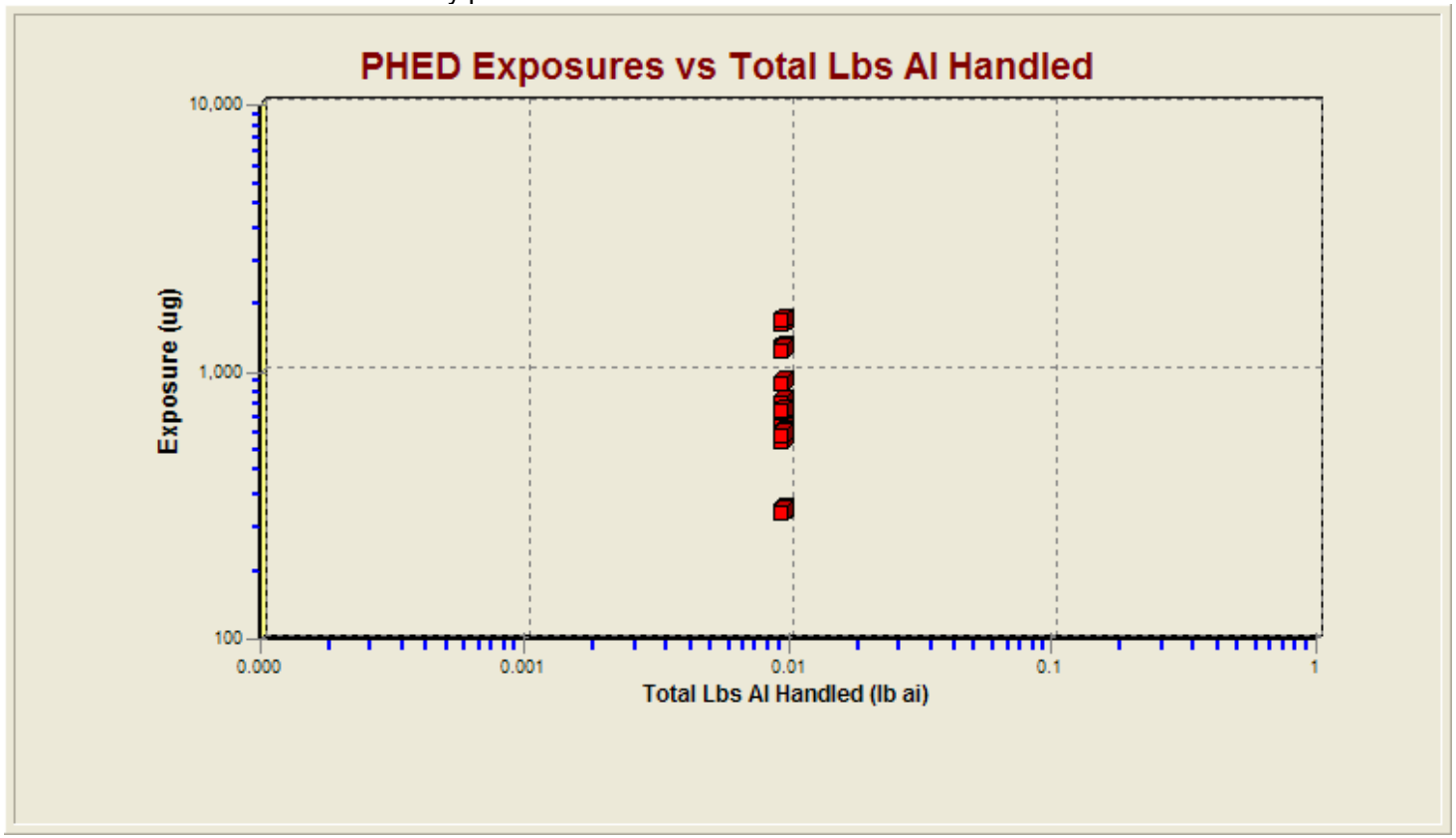

Figure 2.1 Whole Body Exposure vs. Total Lbs AI Handled (not normalized, permeable single layer clothing – long sleeves, long pants, no gloves)

2b. Normalized by Lb AI Handled – Permeable Clothing.

Table 2.4 is a listing of all replicates with a study code of 456. These values are based on normalization by Lbs AI Handled with permeable single layer clothing (long sleeves, long pants, no gloves). No replicates had a whole body exposure using the traditional exposure evaluation method. The Substitution Body Method resulted in all 15 replicates having a whole body exposure value.

Replicate	Sample Time (hrs)	Whole Body Exposure (Traditional Method) (ug)	Whole Body Exposure (Substitution Body Method) (ug)	Inhalation Exposure (ug)	Average Dermal Quantification Limit (ug/cm2)	Average Hand Quantification Limit (ug/cm2)	Airborne Grade	Dermal Grade Uncovered	Dermal Grade Covered	Hand Grade
456-A-3	0.55	-	1.61e+05	7.87E+06	3.0e-02	10	C	C		A
456-A-4	0.50	-	8.10e+04	6.34E+06	3.0e-02	10	C	C		A
456-A-5	0.42	-	5.87e+04	9.74E+06	3.0e-02	10	C	C		A
456-A-1	0.50	-	1.31e+04	5.51E+06	3.0e-02	10	C	C		A
456-A-2	0.47	-	1.28e+04	7.64E+06	3.0e-02	10	C	C		A
456-B-1	0.38	-	6.71e+04	1.07E+07	3.0e-02	10	C	C		A
456-B-2	0.50	-	1.65e+05	7.03E+06	3.0e-02	10	C	C		A
456-B-3	0.52	-	6.27e+04	5.66E+06	3.0e-02	10	C	C		A
456-B-4	0.47	-	7.59e+04	1.00E+07	3.0e-02	10	C	C		A
456-B-5	0.31	-	9.72e+04	7.30E+06	3.0e-02	10	C	C		A
456-C-1	0.25	-	3.16e+04	5.61E+06	3.0e-02	10	C	C		A
456-C-2	0.35	-	3.21e+04	5.63E+06	3.0e-02	10	C	C		A
456-C-3	0.32	-	6.15e+04	7.08E+06	3.0e-02	10	C	C		A
456-C-4	0.43	-	3.17e+04	2.19E+06	3.0e-02	10	C	C		A
456-C-5	0.22	-	3.17e+04	5.89E+06	3.0e-02	10	C	C		A

Table 2.4. Exposure values normalized by lbs AI handled with permeable clothing – long sleeves, long pants, no gloves.

Table 2.5 displays the body parts and their corresponding geometric mean exposure values in ug using the Body Part Substitution Method.

Head	Neck front	Neck back	Upper Arms	Chest	Back	Forearms	Thighs	Lower Legs	Feet	Hands
5.58E04	3.13E03	3.47E03	1.16E04	1.42E04	1.42E04	4.88E03	1.53E04	9.86E03	NA	3.31E03

Table 2.5. Body parts and corresponding geometric mean exposure values (ug)

Figure 2.2 shows a log-log graph of whole body exposures vs. total lbs AI handled. This graph is a result of substitution body part method, normalized by lb ai handled with permeable layer clothing – long sleeves, long pants, no gloves. No data exists for the traditional body part method.

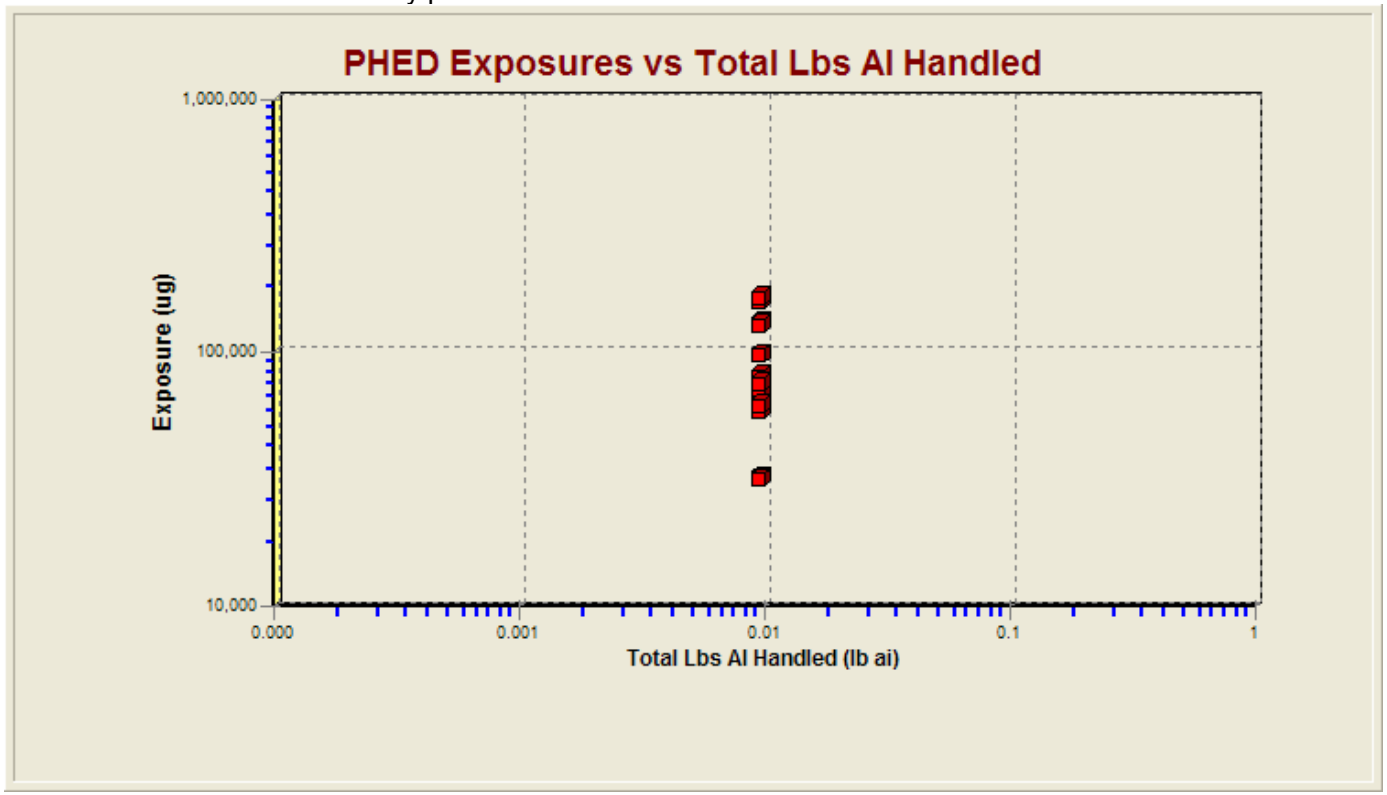

Figure 2.2 Whole Body Exposure vs. Total Lbs AI Handled (normalized, permeable single layer clothing – long sleeves, long shirt, no gloves)

Attachment A: Body Part Substitutions.

Table A.1 shows a listing of the 10 body parts inspected and the list of possible body part substitutions if no deposition was recorded. There are 2 methods described. The traditional body part method is used in the DOS version of PHED while the body part substitution method is an alternative used for a possible web based version of PHED:

Body Part	Traditional PHED Substitution	Body Part Substitution Method
Head	Back, Chest Shoulders	Neck (front and back)
Neck (front)	Chest	Shoulders, Upper Arms, Head
Neck (back)	Back	Shoulders, Upper Arms, Head
Upper Arms	None	Back, Chest; If no results, Forearms
Forearms	None	Chest, Upper Arms, Back If no results: Shoulders
Chest	None	Shoulder, Upper arm, Neck (front) If no results: Head
Back	None	Shoulders, Upper Arms, Neck (back) If no results: Head
Thighs	None	Shin, Calf
Lower Legs	None	Hip, Thigh
Hands	None	Forearms

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Study Code 521: Handheld Aerosols

Task: Evaluate handheld aerosols (specifically study code 521) from the applicator file of the Pesticide Handlers Exposure Database. The following criteria are reviewed to determine if the study code is complete enough for future use.

1. Are the dermal grades (covered/uncovered) for all study codes listed as “A” or “B”? Yes
2. Are the airborne grades for all study codes listed as “A” or “B”? Yes
3. Are the hand grades for all study codes listed as “A” or “B”? Yes
4. Is the percentage of non-detect values for all body part depositions less than 40% when determining whole body exposures? Total Deposition: Yes
   Single Layer Clothing: No
5. Are the 10 selected body parts (head, neck (front and back), both upper arms, both forearms, chest, back, upper legs, lower legs, and hands) available to determine whole body exposures?

<u>Total Deposition/No Normalization</u>
Traditional - Yes
Substitution method - Yes

<u>Total Deposition/Normalized by lb ai handled</u>
Traditional - Yes
Substitution method - Yes

Single layer clothing (non protective), long sleeve/long pants/no glove/no head protection/
<u>No normalization</u>

Traditional - Yes
Substitution method – Yes

Single layer clothing (non protective), long sleeve/long pants/no glove/no head protection/
Normalized by lb ai handled

Traditional - Yes
Substitution method – Yes

Summary:

Number of Replicates:	15
Range of lbs AI Handled:	0.01 lbs ai - 0.01 lbs ai
Range of inhalation sampling durations:	18 minutes – 36 minutes
Range of dermal sampling durations:	0.30 hrs – 0.60 hrs
Average Dermal LOQ:	4.06e-02 ug/cm^2
Average Inhalation LOQ:	1.00 ug
Average Hand LOQ:	100 ug/ cm^2
Inhalation Rate/Minute:	16 L/minute
Non-Detect Handling:	Half LOQ Values
Hand Protection:	No

Section 1: Clothing Layer: Total Deposition

Table 1.1 is a listing of Non-Detect Counts of total deposition. For each column, the number of non-detect values and the number of replicates with a value is listed.

Head	Neck (front/ back)	Upper Arms Right Left	Chest Right Left	Back Right Left	Forearms Right Left	Thighs Right Left	Lower Legs shin right shin left calf right calf left ankle right ankle left	Feet	Hands Right Left Both
1/15=7%	15/15=100 % 15/15=100 %	0/15=0% 2/15=13%	3/15=20% 0/0=NA%	0/0=NA% 0/15 = 0%	2/15 =13% 2/15 =13%	3/15=20% 4/15=27%	4/15 =27% 5/15=33% 0/0=NA% 0/0=NA% 0/0=NA% 0/0=NA%	0/0=NA%	0/0=NA% 0/0=NA% 0/15=0%

Table 1.1. Non-Detect Counts of body part values (total deposition)

Percentage Non-Detects: 56/210 = 27%

1a. No Normalization – Total Deposition

Table 1.2 is a listing of all replicates with a study code of 521. The exposure values are results of no normalization and total deposition. No replicates had a whole body exposure using the traditional exposure evaluation method. The Substitution Body Method resulted in all 15 replicates having a whole body exposure value.

Replicate	Sample Time (hrs)	Whole Body Exposure (Traditional Method) (ug)	Whole Body Exposure (Substitution Body Method) (ug)	Inhalation Exposure (ug)	Average Dermal Quantification Limit (ug/cm^2)	Average Hand Quantification Limit (ug/cm^2)	Airborne Grade	Dermal Grade Uncovered	Dermal Grade Covered	Hand Grade
521-A-1	0.47	2.18E+04	N/A	7.34E+03	4.06E-02	100	A	A		A
521-A-2	0.55	6.57E+03	N/A	6.78E+03	4.06E-02	100	A	A		A
521-A-3	0.52	3.65E+03	N/A	7.02E+03	4.06E-02	100	A	A		A
521-B-1	0.45	4.88E+03	N/A	7.34E+03	4.06E-02	100	A	A		A
521-B-2	0.47	4.59E+03	N/A	6.78E+03	4.06E-02	100	A	A		A
521-B-3	0.30	1.99E+03	N/A	7.02E+03	4.06E-02	100	A	A		A
521-C-1	0.53	8.15E+03	N/A	7.34E+03	4.06E-02	100	A	A		A
521-C-2	0.45	1.14E+04	N/A	2.19E+04	4.06E-02	100	A	A		A
521-C-3	0.53	1.72E+04	N/A	7.02E+0	4.06E-02	100	A	A		A

521-D-1	0.43	1.02E+04	N/A	2.35E+03	4.06E-02	100	A	A	A
521-D-2	0.32	5.21E+03	N/A	6.78E+03	4.06E-02	100	A	A	A
521-D-3	0.37	3.84E+03	N/A	7.02E+03	4.06E-02	100	A	A	A
521-E-1	0.52	6.83E+03	N/A	2.00E+04	4.06E-02	100	A	A	A
521-E-2	0.53	6.17E+03	N/A	6.78E+03	4.06E-02	100	A	A	A
521-E-3	0.60	4.10E+03	N/A	7.02E+03	4.06E-02	100	A	A	A

Table 1.2. Exposure values using no normalization and total deposition.

Table 1.3 displays the body parts and their corresponding geometric mean exposure values in ug.

Head	Neck front	Neck back	Upper Arms	Chest	Back	Forearms	Thighs	Lower Legs	Feet	Hands
410	25.1	20.0	999	595	644	488	300	248	NA	1.06E+03

Table 1.3. Body parts and corresponding geometric mean exposure values (ug)

Figure 1.1 shows a log-log graph of whole body exposures vs. total lbs AI handled. This graph is a result of no normalization and total deposition.

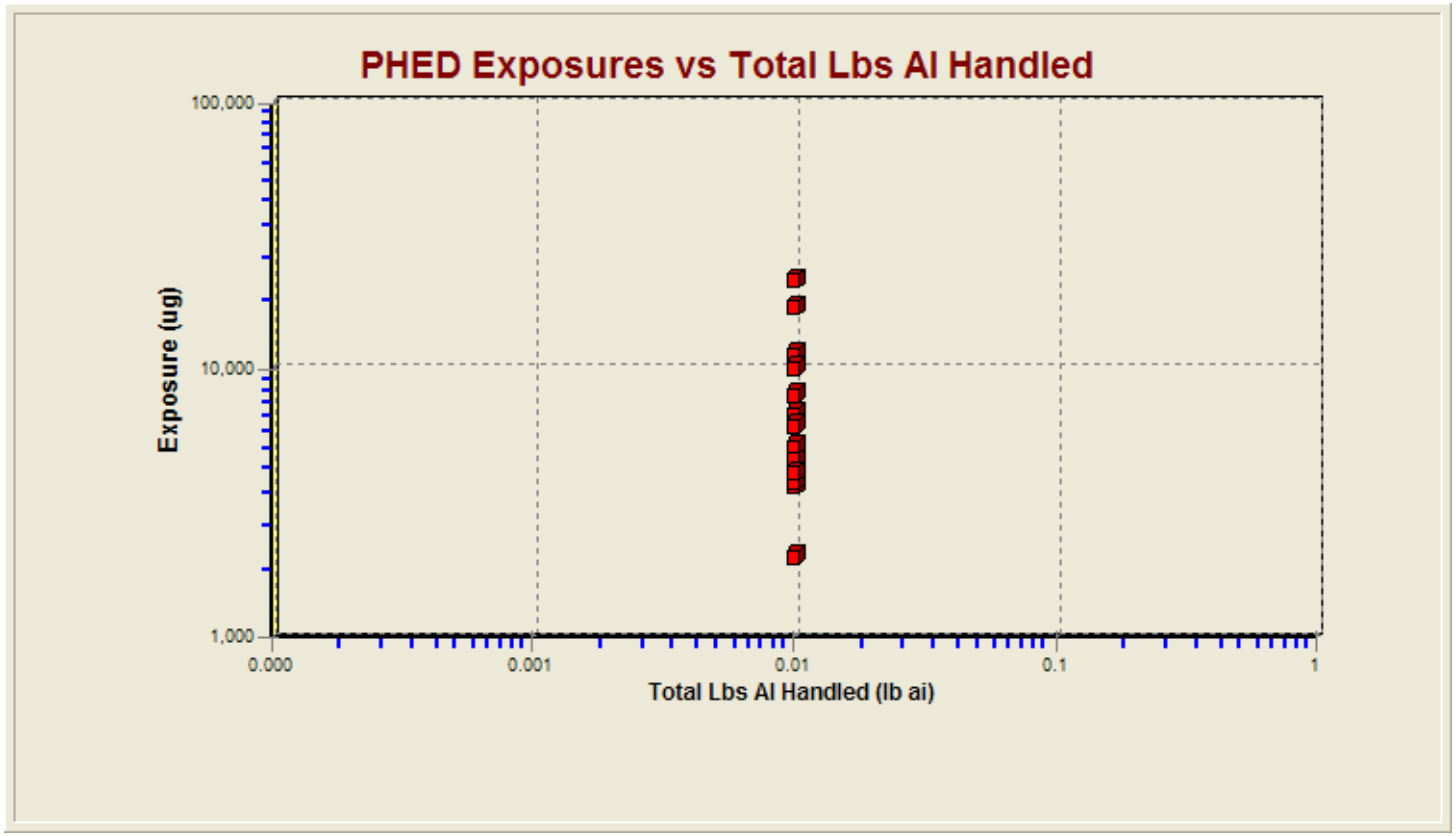

Figure 1.1 Whole Body Exposure vs. Total Lbs AI Handled (not normalized, total deposition)

1b. Normalized by Lb AI Handled – Total Deposition.

Table 1.4 is a listing of all replicates with a study code of 521. These values are based on normalization by Lbs AI Handled and total deposition.

Replicate	Sample Time (hrs)	Whole Body Exposure (Traditional Method) (ug)	Whole Body Exposure (Substitution Body Method) (ug)	Inhalation Exposure (ug)	Average Dermal Quantification Limit (ug/cm2)	Average Hand Quantification Limit (ug/cm2)	Airborne Grade	Dermal Grade Uncovered	Dermal Grade Covered	Hand Grade
521-A-1	0.47	2.18E+06	N/A	7.34E+05	4.06E-02	100	A	A		A
521-A-2	0.55	6.57E+05	N/A	6.78E+05	4.06E-02	100	A	A		A
521-A-3	0.52	3.65E+05	N/A	7.02E+05	4.06E-02	100	A	A		A
521-B-1	0.45	4.88E+05	N/A	7.34E+05	4.06E-02	100	A	A		A
521-B-2	0.47	4.59E+05	N/A	6.78E+05	4.06E-02	100	A	A		A
521-B-3	0.30	1.99E+05	N/A	7.02E+05	4.06E-02	100	A	A		A
521-C-1	0.53	8.15E+05	N/A	7.34E+05	4.06E-02	100	A	A		A
521-C-2	0.45	1.14E+06	N/A	2.19E+06	4.06E-02	100	A	A		A
521-C-3	0.53	1.72E+06	N/A	7.02E+05	4.06E-02	100	A	A		A
521-D-1	0.43	1.02E+06	N/A	2.35E+06	4.06E-02	100	A	A		A
521-D-2	0.32	5.21E+05	N/A	6.78E+05	4.06E-02	100	A	A		A
521-D-3	0.37	3.84E+05	N/A	7.02E+05	4.06E-02	100	A	A		A
521-E-1	0.52	6.83E+05	N/A	2.00E+06	4.06E-02	100	A	A		A
521-E-2	0.53	6.17E+05	N/A	6.78E+05	4.06E-02	100	A	A		A
521-E-3	0.60	4.10E+05	N/A	7.02E+05	4.06E-02	100	A	A		A

Table 1.4. Exposure values normalized by lbs AI handled and total deposition.

Table 1.5 displays the body parts and their corresponding geometric mean exposure values in ug.

Head	Neck front	Neck back	Upper Arms	Chest	Back	Forearms	Thighs	Lower Legs	Feet	Hands
4.10E+04	2.51E+03	2.00E+03	9.99E+04	5.95E+04	6.44E+04	4.88E+04	3.00E+04	2.48E+04	NA	1.06E+05

Table 1.5. Body parts and corresponding geometric mean exposure values (ug)

Figure 1.2 shows a log-log graph of whole body exposures vs. total lbs AI handled.

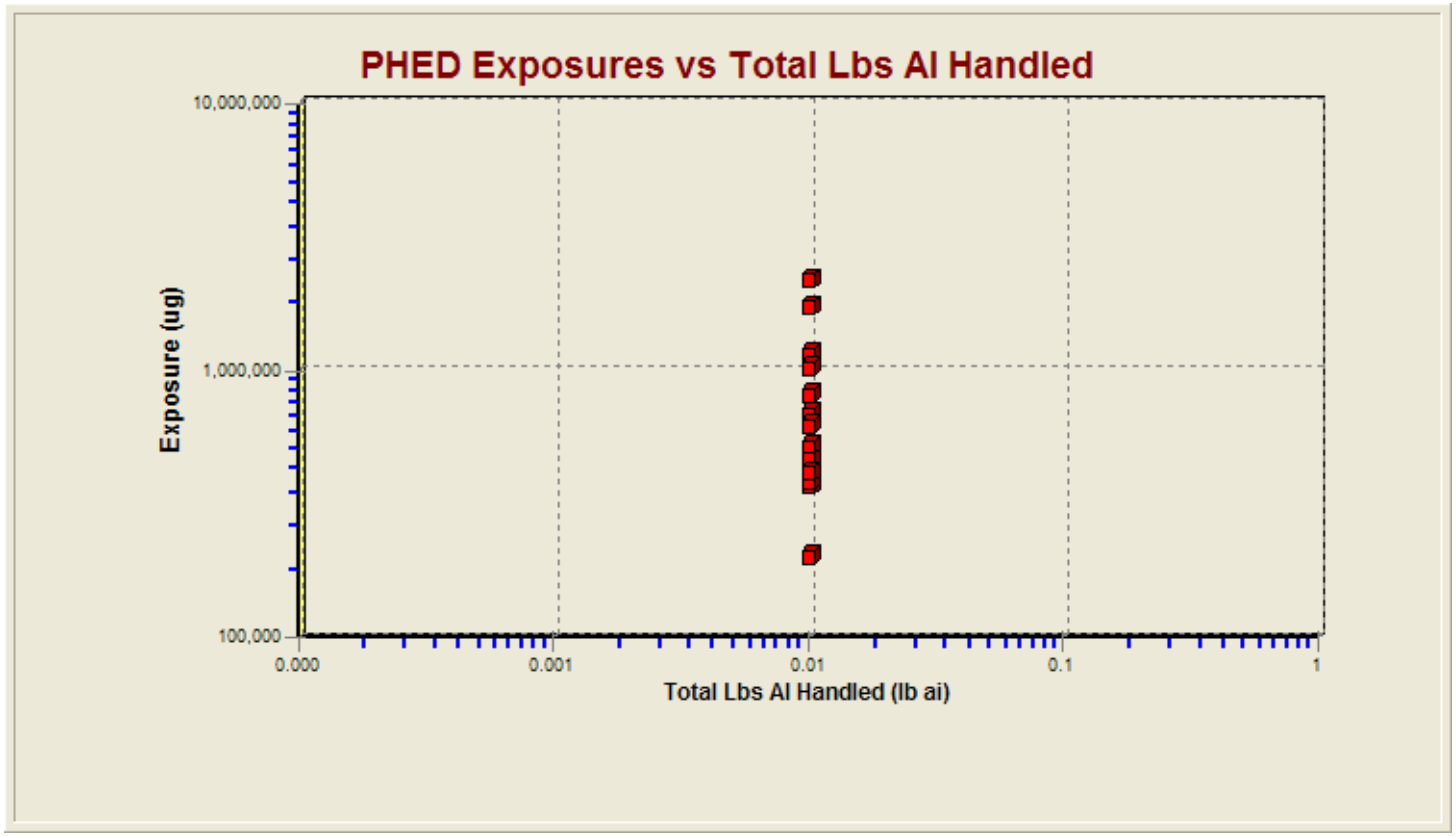

Figure 1.2 Whole Body Exposure vs. Total Lbs AI Handled (normalized, total deposition)

Section 2. Clothing Layer: Long Sleeves, Long Pants, No gloves.

Table 2.1 is a listing of Non-Detect Counts with a clothing layer of long sleeves, long pants and no gloves. For each column, the number of non-detect values and the number of replicates with a value is listed.

Head	Neck (front/ back)	Upper Arms Right Left	Chest Right Left	Back Right Left	Forearms Right Left	Thighs Right Left	Lower Legs shin right shin left calf right calf left ankle right ankle left	Feet	Hands Right Left Both
1/15=7%	15/15=100% 15/15=100%	15/15=100 % 15/15=100 %	0/0=NA% 15/15=100 %	15/15=100 % 0/0 = NA	15/15 =100% 14/15=93%	15/15=100 % 15/15=100 %	15/15 =100% 15/15=100 % 0/0=NA% 0/0=NA% 0/0=NA% 0/0=NA%	0/0=NA%	0/0=NA% 0/0=NA% 0/15=0%

Table 2.1. Non-Detect Counts of body part values (permeable layer clothing – long sleeves, long pants, no gloves)

Percentage Non-Detects: 180/210 = 86%

2a. No Normalization – Permeable Clothing

Table 2.2 is a listing of all replicates with a study code of 521. The exposure values are results of no normalization with permeable clothing - long pants, long sleeves and no gloves.

Replicate	Sample Time (hrs)	Whole Body Exposure (Traditional Method) (ug)	Whole Body Exposure (Substitution Body Method) (ug)	Inhalation Exposure (ug)	Average Dermal Quantification Limit (ug/cm2)	Average Hand Quantification Limit (ug/cm2)	Airborne Grade	Dermal Grade Uncovered	Dermal Grade Covered	Hand Grade
521-A-1	0.47	2.13E+03	N/A	7.34E+03	4.06E-02	100	A	A		A
521-A-2	0.55	2.26E+03	N/A	6.78E+03	4.06E-02	100	A	A		A
521-A-3	0.52	1.61E+03	N/A	7.02E+03	4.06E-02	100	A	A		A
521-B-1	0.45	1.98E+03	N/A	7.34E+03	4.06E-02	100	A	A		A
521-B-2	0.47	4.24E+03	N/A	6.78E+03	4.06E-02	100	A	A		A
521-B-3	0.30	1.35E+03	N/A	7.02E+03	4.06E-02	100	A	A		A
521-C-1	0.53	2.79E+03	N/A	7.34E+03	4.06E-02	100	A	A		A
521-C-2	0.45	1.91E+03	N/A	2.19E+04	4.06E-02	100	A	A		A
521-C-3	0.53	4.95E+03	N/A	7.02E+03	4.06E-02	100	A	A		A
521-D-1	0.43	2.78E+03	N/A	2.35E+04	4.06E-02	100	A	A		A
521-D-2	0.32	1.59E+03	N/A	6.78E+03	4.06E-02	100	A	A		A
521-D-3	0.37	2.07E+03	N/A	7.02E+03	4.06E-02	100	A	A		A
521-E-1	0.52	2.40E+03	N/A	2.00E+04	4.06E-02	100	A	A		A
521-E-2	0.53	1.54E+03	N/A	6.78E+03	4.06E-02	100	A	A		A
521-E-3	0.60	1.84E+03	N/A	7.02E+03	4.06E-02	100	A	A		A

Table 2.2. Exposure values using no normalization with permeable clothing – long sleeves, long pants, no gloves.

Table 2.3 displays the body parts and their corresponding geometric mean exposure values in ug.

Head	Neck front	Neck back	Upper Arms	Chest	Back	Forearms	Thighs	Lower Legs	Feet	Hands
410	25.1	20.0	59.1	72.1	72.1	26.3	77.5	48.3		1.09E+03

Table 2.3. Body parts and corresponding geometric mean exposure values (ug)

Figure 2.1 shows a log-log graph of whole body exposures vs. total lbs AI handled. This graph is a result of the traditional body part method, no normalization with permeable layer clothing consisting of long sleeves, long pants and no gloves.

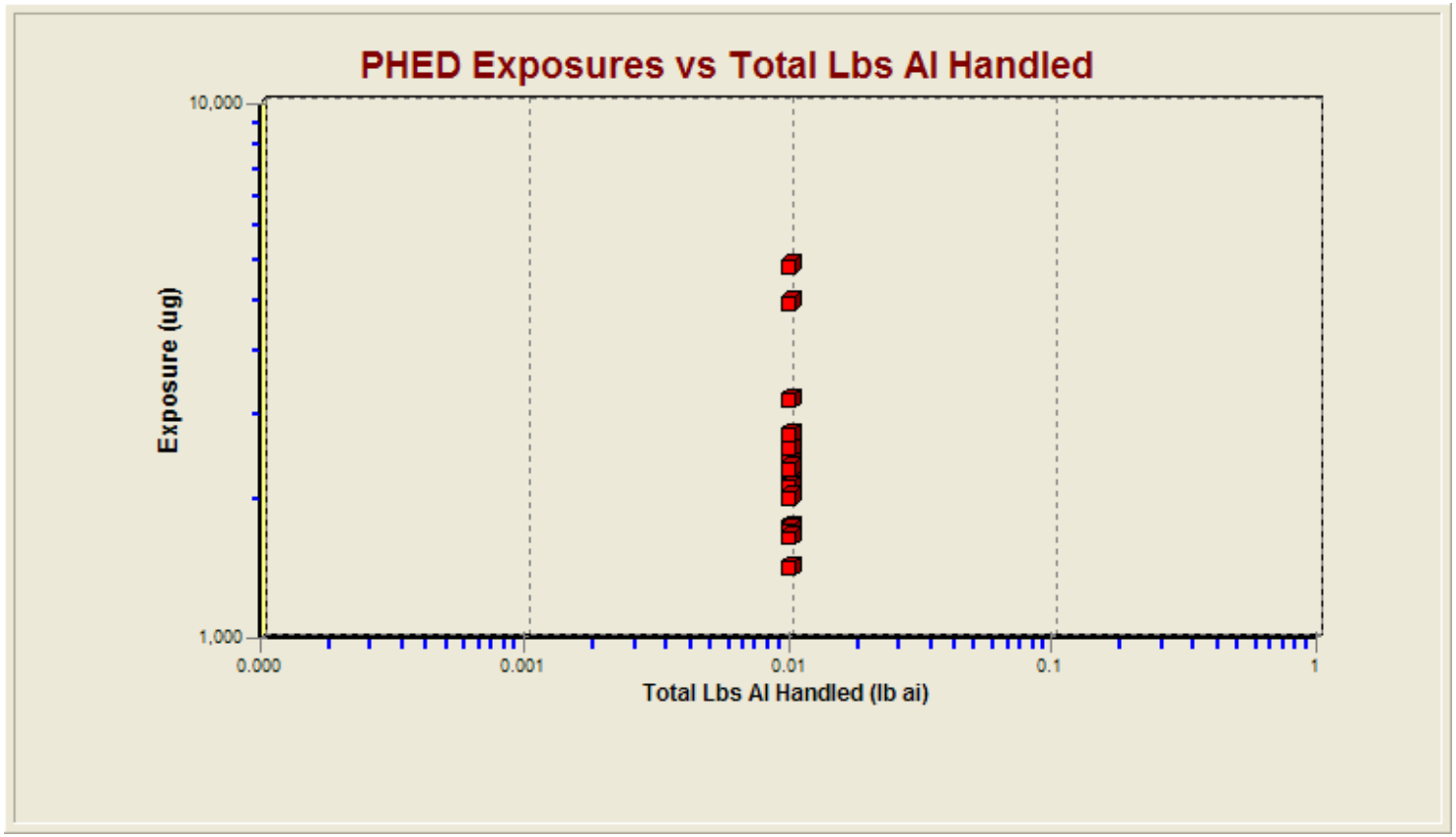

Figure 2.1 Whole Body Exposure vs. Total Lbs AI Handled (not normalized, permeable single layer clothing – long sleeves, long pants, no gloves)

2b. Normalized by Lb AI Handled – Permeable Clothing.

Table 2.4 is a listing of all replicates with a study code of 521. These values are based on normalization by Lbs AI Handled with permeable single layer clothing (long sleeves, long pants, no gloves).

Replicate	Sample Time (hrs)	Whole Body Exposure (Traditional Method) (ug)	Whole Body Exposure (Substitution Body Method) (ug)	Inhalation Exposure (ug)	Average Dermal Quantification Limit (ug/cm2)	Average Hand Quantification Limit (ug/cm2)	Airborne Grade	Dermal Grade Uncovered	Dermal Grade Covered	Hand Grade
521-A-1	0.47	2.13E+05	N/A	7.34E+05	4.06E-02	100	A	A		A
521-A-2	0.55	2.26E+05	N/A	6.78E+05	4.06E-02	100	A	A		A
521-A-3	0.52	1.61E+05	N/A	7.02E+05	4.06E-02	100	A	A		A
521-B-1	0.45	1.98E+05	N/A	7.34E+05	4.06E-02	100	A	A		A
521-B-2	0.47	4.24E+05	N/A	6.78E+05	4.06E-02	100	A	A		A
521-B-3	0.30	1.35E+05	N/A	7.02E+05	4.06E-02	100	A	A		A
521-C-1	0.53	2.79E+05	N/A	7.34E+05	4.06E-02	100	A	A		A
521-C-2	0.45	1.91E+05	N/A	2.19E+06	4.06E-02	100	A	A		A
521-C-3	0.53	4.95E+05	N/A	7.02E+05	4.06E-02	100	A	A		A
521-D-1	0.43	2.78E+05	N/A	2.35E+06	4.06E-02	100	A	A		A
521-D-2	0.32	1.59E+05	N/A	6.78E+05	4.06E-02	100	A	A		A
521-D-3	0.37	2.07E+05	N/A	7.02E+05	4.06E-02	100	A	A		A
521-E-1	0.52	2.40E+05	N/A	2.00E+05	4.06E-02	100	A	A		A
521-E-2	0.53	1.54E+05	N/A	6.78E+05	4.06E-02	100	A	A		A
521-E-3	0.60	1.84E+05	N/A	7.02E+05	4.06E-02	100	A	A		A

Table 2.4. Exposure values normalized by lbs AI handled with permeable clothing – long sleeves, long pants, no gloves.

Table 2.5 displays the body parts and their corresponding geometric mean exposure values in ug.

Head	Neck front	Neck back	Upper Arms	Chest	Back	Forearms	Thighs	Lower Legs	Feet	Hands
4.10E+04	2.51E+03	2.00E+03	5.91E+03	7.21E+03	7.21E+03	2.63E+03	7.75E+03	4.83E+03	NA	1.06E+05

Table 2.5. Body parts and corresponding geometric mean exposure values (ug)

Figure 2.2 shows a log-log graph of whole body exposures vs. total lbs AI handled. This graph is a result of the traditional method, normalized by lb ai handled with permeable layer clothing – long sleeves, long pants, no gloves.

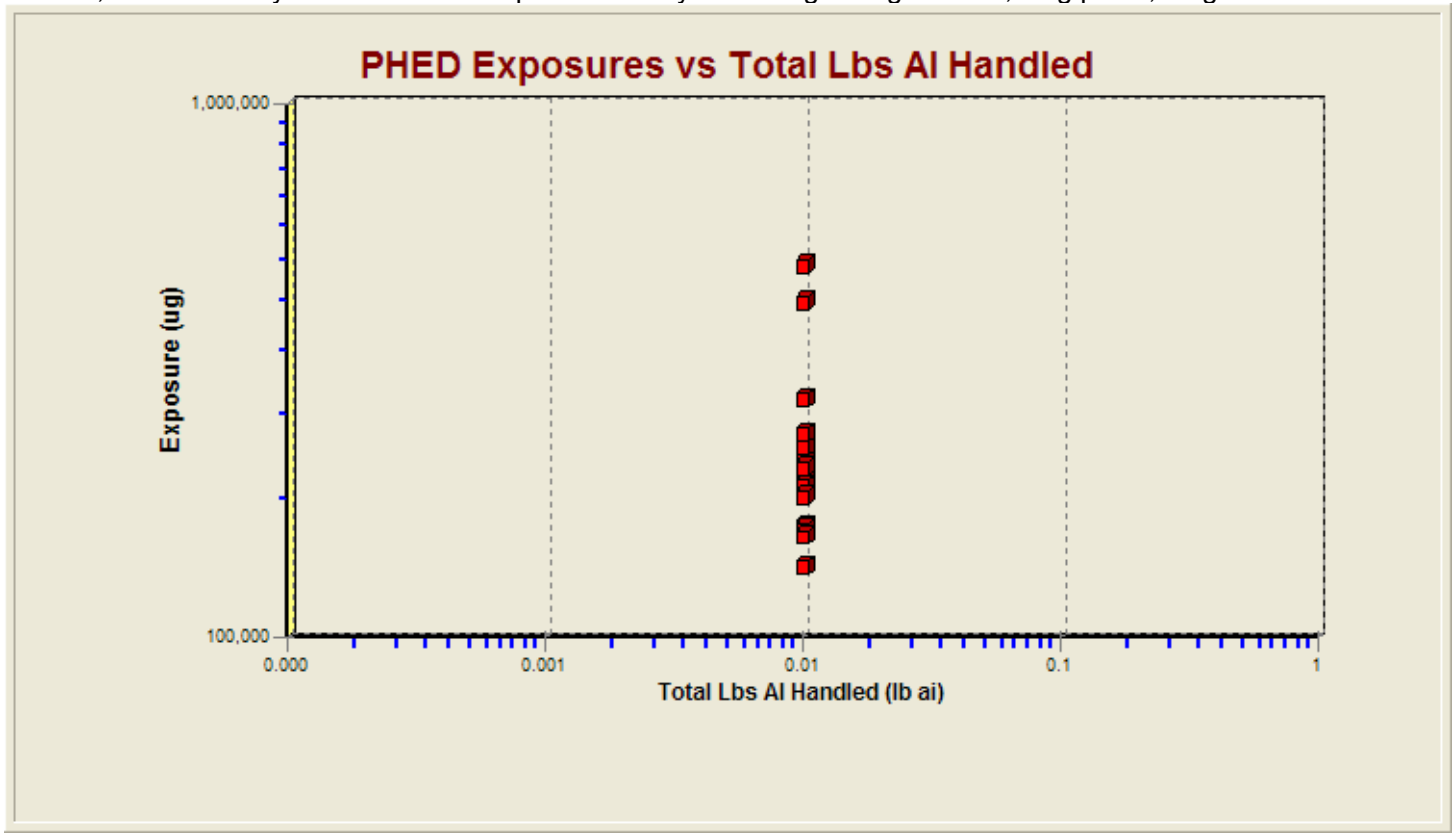

Figure 2.2 Whole Body Exposure vs. Total Lbs AI Handled (normalized, permeable single layer clothing – long sleeves, long shirt, no gloves)

Attachment A: Body Part Substitutions.

Table A.1 shows a listing of the 10 body parts inspected and the list of possible body part substitutions if no deposition was recorded. There are 2 methods described. The traditional body part method is used in the DOS version of PHED while the body part substitution method is an alternative used for a possible web based version of PHED:

Body Part	Traditional PHED Substitution	Body Part Substitution Method
Head	Back, Chest Shoulders	Neck (front and back)
Neck (front)	Chest	Shoulders, Upper Arms, Head
Neck (back)	Back	Shoulders, Upper Arms, Head
Upper Arms	None	Back, Chest; If no results, Forearms
Forearms	None	Chest, Upper Arms, Back If no results: Shoulders
Chest	None	Shoulder, Upper arm, Neck (front) If no results: Head
Back	None	Shoulders, Upper Arms, Neck (back) If no results: Head
Thighs	None	Shin, Calf
Lower Legs	None	Hip, Thigh
Hands	None	Forearms

Appendix G: List of Current AEATF II Standard Operating Procedures (SOPs)

Chapter 1 – Administration

AEATF II-1A.0	Organizational Structure
AEATF II-1B.0	Personnel Responsibilities
AEATF II-1C.0	Study Director Selection
AEATF II-1D.0	Inspection of AEATF II Facilities/Data

Chapter 2 – Protocols

AEATF II-2A.0	Study Authorization and Approval
AEATF II-2B.0	Study Number Assignment
AEATF II-2C.0	Protocols

Chapter 3 – Standard Operating Procedures

AEATF II-3A.0	SOP Preparation, Approval, Maintenance, and Distribution
AEATF II-3B.0	Use of AEATF II and Contractor SOPs

Chapter 4 – Study Reports

AEATF II-4A.0	Study Report Preparation
AEATF II-4B.0	Final Report Issue

Chapter 5 – Quality Assurance Unit

AEATF II-5A.0	QA Personnel Administration
AEATF II-5B.0	AEATF II QAU Responsibilities
AEATF II-5C.0	QAU Records
AEATF II-5D.0	QA Master Schedule
AEATF II-5E.0	Protocol and Amendment Review
AEATF II-5F.0	Inspection/Audit Types and Frequency
AEATF II-5G.0	Study Inspections
AEATF II-5H.0	Data Audits
AEATF II-5I.0	Facility Inspections
AEATF II-5J.0	Report Audits
AEATF II-5K.0	Inspection Report Distribution

Chapter 6 – Archives

AEATF II-6A.0 Storage of Raw Data
AEATF II-6B.0 Access to Archived Data
AEATF II-6C.0 Specimen and Wet Sample Storage

Chapter 7 – Test, Control and Reference Substance

AEATF II-7A.0 Test, Reference, and Control Substance Receipt and Shipment
AEATF II-7B.0 Test, Control and Reference Substance Labeling
AEATF II-7C.0 Disposal of Test, Control, and Reference Substances
AEATF II-7D.0 Test, Control, and Reference Substance Chain of Custody
AEATF II-7E.0 Test and Reference Substance Analyses

Chapter 8 – Matrix Samples

AEATF II-8A.1 Whole Body Sampling – Inner Dosimeters
AEATF II-8B.1 Hand Wash Samples
AEATF II-8C.1 Dermal Face/Neck Wipe Samples
AEATF II-8D.0 Collection of Air Samples Using OVS Tubes
AEATF II-8E.0 Fortification of Matrix Samples
AEATF II-8F.0 Sample Identification
AEATF II-8G.1 Whole Body Sampling – Outer Dosimeters

Chapter 9 – Documentation

AEATF II-9A.0 Body Surface Areas
AEATF II-9B.1 Field Fortification Adjustment Factors
AEATF II-9C.0 Numerical Formatting and Handling
AEATF II-9D.0 Analytical Method Number Assignment
AEATF II-9E.0 Raw Data Collection
AEATF II-9F.0 Data Corrections
AEATF II-9G.0 Raw Data Handling
AEATF II-9H.0 Preparation of True Copies

Chapter 10 – Field Study Procedures

AEATF II-10A.0 Rotameter Calibration
AEATF II-10B.0 Packing, Handling, and Shipping of Samples
AEATF II-10C.0 Worker and Study Observations
AEATF II-10D.0 Application Equipment Operation Verification
AEATF II-10E.0 Worker Sample Collection Sequence
AEATF II-10F.0 GPI Electronic Digital Flow Meter
AEATF II-10G.0 Personal Air Sampling Pump Calibration

Chapter 11 - Human Subject Management

AEATF II-11A.0 - Pregnancy Testing
AEATF II-11B.0 - Heat Stress
AEATF II-11C.0 - Emergency Procedures
AEATF II-11D.0 - Reportable Findings

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The primary purpose of the AEATF II monitoring program is to develop a new generation of more accurate and useful information and data on worker and consumer exposures to antimicrobials. A secondary purpose is to incorporate these data into a generic database (BHED™). These data will consist of dermal and inhalation exposure estimates derived from monitoring subjects who handle pesticides under a variety of circumstances, using various pesticides and equipment types. AEATF II refers to each unique handling situation as a 'scenario' and anticipates the database will contain sufficient data to support exposure assessments for 14 distinct scenarios (see attached "AEATF II Scoping Document" provided as Appendix A; Appendix B provides a detailed description of each use site identified in the Scoping Document; Appendix C provides a glossary of terms).

In general, each scenario is defined as a set of related tasks, pesticide formulations, equipment, engineering controls, and worker and/or consumer practices. For example, two scenarios of interest are "mopping application" and "wiping application."

A single scenario, such as "mopping", may be defined as a specific task, i.e., the mop-based application of a label-specified end-use formulation containing an antimicrobial chemical. It is common in institutional settings today that automated dispensing systems provide the applicator with ready-to-use mop solutions, and the applicator does not mix and load the end-use mop solution in a bucket. Therefore, the applicator's exposure during a single workday in these conditions would arise only from the task of application and intermittent disposing or emptying the dirty mop bucket solution. The distribution of daily exposures under the "mopping" scenario would then adequately describe the handler's daily exposure to the antimicrobial. In other circumstances, however, a mop applicator could also be manually mixing and loading the mop solution, i.e., preparing the end-use dilution by adding a concentrate to water in a bucket. In these cases, the daily exposure for an antimicrobial handler would arise from two discrete tasks, i.e., mopping (including dirty mop solution disposal) and mixing/loading of mop solution. To provide data for regulatory agencies to address the addition of this discrete task (mixing and loading), the AEATF II will conduct separate studies of mop application (which would include discrete measurement of exposures associated with mopping and dirty mop bucket solution emptying) and of mixing and loading via open pouring of liquids.

At times, user's of the BHED™ data may need to consider the distribution of a combined exposure from multiple tasks represented by separate scenarios. The arithmetic mean of a combined single-day exposure is simply the sum of the arithmetic means for each separate task. However, other aspects of the combined distribution depend on how exposures for the same individual from different tasks are correlated. If the exposures are perfectly correlated (i.e. the correlation is 1) then any percentile of the combined distribution is the sum of the percentiles for each task separately. If the same-person-different-task exposures

are independent, however, then the combined percentiles are less extreme than the sum of the separate percentiles. This 'shrinkage' of the combined distribution is rather minimal and is practically non-detectable if one task's mean exposure is much larger than any of the other tasks mean values. Thus, unless a separate estimate of the between-task correlation is available, a practical recommendation for most BHED users would be to simply assume that the tasks are maximally correlated and add all percentiles. This approach would likely be acceptable in the context of regulatory-decision making when relying upon BHED, given the overestimation (more conservative) bias associated with summed upper-percentiles. More importantly, the development of normalized exposure data for discrete tasks provides the flexibility to construct or assemble and assess multi-task exposures and thus, greater utility for a generic exposure database.

In some instances, there may exist a discrete task that falls outside all the scenarios for which monitoring is planned. This is most often because the task is rare or would be expected to give non-detectable exposure levels. When reasonable, users of BHED™ might choose to use another scenario as a surrogate for the missing task. For example, in the case of mop application, in some cases, a person may pour a concentrated formulation containing an antimicrobial into a mop bucket containing water to create a label-specified end-use dilution. The exposures (dermal and inhalation) that may occur during this liquid pouring task can be addressed with the separate "open liquid pouring" study data. The "open liquid pouring" data could be used directly as a conservative surrogate for pouring a concentrate into a mop bucket. In this example, it is important to adjust the surrogate exposure distribution for the amount of active ingredient handled in the specific mop bucket pouring situation being assessed.

In summary, the study scenarios planned by the Task Force fall into two general categories: (1) simulated-condition studies based on discrete or segmented tasks (mixing, loading and application methods) that can used to estimate exposures occurring in a variety of use scenarios; (2) *in situ* (e.g., on-site, observational) studies for complex and/or multi-task scenarios.

Within each scenario, a number of monitoring events (MEs), also referred to as monitoring units (MUs), will be conducted. Each MU will consist of measuring dermal and inhalation exposure potential for a single subject for a time period that represents a typical workday. Some scripting of tasks performed by subjects may be used to provide task-specific diversity for parameters that are either known or assumed to be exposure-related (e.g., range of amount of product handled or duration of task). Subjects will perform each task as they would during a normal workday. Collectively, all of the subject-specific MUs to be included in BHED™ are referred to as the AEATF II monitoring (or testing) program. BHED™ will be used to support North American registrations for existing and new pesticide products as required by FIFRA in the United States and the Pest Control Products Act (PCPA) in Canada.

The AEATF II monitoring program is designed to address the scientific question: "What is the expected distribution of daily worker exposures to pesticides during each pesticide handling scenario?" This information is needed by EPA (and other regulatory agencies) to assess exposure of workers and consumers who handle pesticides. Consequently, the overall goal of the AEATF II monitoring program is to obtain individual exposure data for each scenario sufficient to adequately approximate the distribution of single-day exposures normalized by the amount of ai handled. The predicted distribution of daily exposures can be obtained by simply multiplying this normalized generic exposure distribution by the amount of active ingredient (ai) handled for the specific product being evaluated.

A default primary benchmark goal is to adequately approximate the distribution of exposure so that selected measures (i.e., means and upper percentiles) are accurate to within 3-fold. The desired degree of characterization of a scenario's exposure distribution may depend, in part, upon the relative importance of the scenario in the regulatory process. For example, lesser accuracy may be acceptable for scenarios that are less common and that result in very low exposure.

The general approach for scenario-specific test designs is to collect a variety of MUs using different subjects and a diverse set of conditions that reflect current pesticide mixing/loading and application practices in North America. Exposure will be monitored at multiple locations and the amount of active ingredient handled will be varied to cover the typical range of product handled for each scenario.

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Most scenarios in the monitoring program have been adopted by AEATF II because they have already proven to be logical and practical for use by EPA. Nevertheless, due to the variety of antimicrobial handling conditions, there could be some ambiguity as to which particular set of tasks or equipment are included in a particular handler scenario. Thus, it is very important to precisely define each scenario prior to study design. This scenario definition, in turn, permits clarity in defining the scenario target population. AEATF II will attempt to define *a priori* what handling conditions will and will not be included in each scenario.

For various reasons, a set of handler conditions (i.e., tasks or activities), although technically part of the scenario, may be excluded from the sampling process. This may occur, for example, if the conditions excluded are extremely rare or even obsolete. Such restrictions could also occasionally occur if AEATF II, in an effort to reduce the total number of MUs in the monitoring program, restricts it's testing to certain conditions believed to result in slightly higher exposure. For example, mixer/loader MUs will always involve preparation of multiple loads since this probably leads to higher exposure potential than preparing just a single load (involving an equal amount of pesticide). In another example, the mopping

scenario is restricted to the mop application technology with the highest likely exposure potential, (i.e., string mops, versus lower exposure potential technologies such as ready-to-use mop systems). When such restrictions are necessary, the scenario will be explicitly redefined to make it clear that such conditions were excluded. This provides users of the BHED™ database a clear and accurate definition of the handler-conditions the data actually represent.

The restriction of a scenario does not limit the regulatory usefulness of the resulting sample for representing the full (unrestricted) scenario. Without data for single loads, for example, regulators will simply use the (higher) exposure data from the multiple loads (restricted) scenario to represent all mixer/loader handler-days. While this might tend to over-estimate the exposure for the full scenario, it conserves valuable resources. From a regulatory perspective, overestimation of the exposure distribution is of less concern, especially given that it reduces the total number of human subjects involved in the monitoring program.

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Appendix E describes in detail the process of 'selecting' a purposive sample of conditions from the target population of all handler-days and then selecting analogous handler-days that use the surrogate chemical. Once selected, these substituted handler-days are referred to as monitoring units or monitoring events (MUs or MEs, respectively) to emphasize their specialized role in the sampling and measurement process. These correspond, in principle, to what would be termed final-stage sampling units in a population sampling context.

The AEATF II procedure for obtaining MUs is non-random. Appendix E discusses the unique aspects of the monitoring program that make purposive sampling necessary and a better choice than multistage probability sampling. The primary focus is on purposive diversity sampling. Purposive diversity sampling (Trochim, 2000) attempts to obtain a sample of handler-days that is diverse with respect to factors important to exposure. AEATF II's purposive sampling method does, however, include some aspects of 'representative sampling' (see Appendix E). Given the unique aspects of this monitoring program and the small sample sizes required, the AEATF II method is felt to be adequately representative of the target population.

For two factors, diversity is obtained as a natural part of the sampling process. These are cluster and worker. For each scenario, the total sample of MUs will be configured as clusters of MUs. Each cluster consists of a set of MUs evaluated at a different location and time period. 'Location' in this context could be a different facility (i.e., building) but may also represent a large number of conditions (known and unknown) that are associated with a change in facility (e.g. architecture, work behaviors). In addition to location, every MU will normally be a different individual. This focus on variation between subjects increases the diversity of handler-day conditions covered.

Diversity in other factors is achieved through controlling or 'scripting' some aspects of the participant worker's activities. The intent of this scripting is not to introduce artificial conditions, but merely to induce normal variations that a particular subject may not have planned to use on a particular day. Part of the research going into planning each study will be to determine what the normal range of antimicrobial use is for individuals in a day, and in scripted studies, individuals will be assigned to handle varying amounts of antimicrobial within that normal range of use. The bulk of each worker's activity remains non-scripted. While many factors could be used to diversify the sample, sample size limits the number of possible combinations of conditions. The AEATF II focuses on only those considered the most important to exposure based on reviews of existing pesticide handler exposure data (e.g., in PHED) and upon discussions with the Regulatory Agency Advisory Committee. Appendix A provides the program scope of AEATF II studies and reflects the consensus for those studies that are high priority for data generation. Two factors that could be varied to increase diversity are time or amount of active ingredient handled in these studies.

As would be true of any study using non-random sampling, the MU exposure values can only estimate a surrogate distribution of daily exposures. One cannot equate the surrogate distribution to the actual distribution in the target population using only statistical sampling theory. However, this surrogate distribution is felt to be adequate for practical regulatory purposes given the 3-fold level of accuracy specified for the benchmark parameters. While it might not be estimating the exact target population distribution, it is believed to be capturing the major aspects of it and, given the small sample sizes, is not expected to be substantially different than a same-sized cluster random sample. Interested regulatory agencies represented by the Regulatory Agency Advisory Committee are aware of these limitations of the statistical inference and have provided useful feedback on the design of BHED™.

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Sample Size Determination

The AEATF II monitoring program is not an experimental study whose purpose is to test hypotheses about the distribution of exposure or about potential determinants of exposure. Rather, its purpose is to collect sufficient data for each handler scenario to meet a specific minimum or 'benchmark' adequacy requirement. These data, possibly augmented by additional exposure data from other sources, will then be used for a variety of regulatory purposes. Benchmark adequacy requirements, based on discussion with the Regulatory Agency Advisory Committee, may differ from one scenario to another.

Benchmark Objective

The benchmark objective for each scenario is that estimates for selected exposure distribution measures expressed as normalized exposure (e.g., by pounds of active handled) be accurate to within K-fold at least 95% of the time. This specified relative accuracy level, K, could be scenario-specific. Currently, however, there is a general consensus that, for regulatory purposes, 3-fold relative accuracy (i.e., K=3) is a reasonable default for all scenarios. The standard distribution measures considered for the primary benchmark are the arithmetic mean and the 95th percentile. A more detailed discussion of benchmark adequacy and its statistical implications are provided in AHETF 2007, Appendix C.

For this objective, accuracy is determined assuming cluster sampling from a lognormal distribution as a surrogate model for the actual purposive MU sampling. As described in Appendix E, the BHED^{TM} purposive sampling recognizes larger sampling units referred to as clusters. For the mop and wipe scenarios, for example, clusters are different buildings and time periods located in the same general geographic area.

Although it is a reasonable default, 3-fold benchmark accuracy might not be required for every scenario. For example, scenarios that involve very low exposure potential will rarely be the limiting factor in a product exposure assessment and regulators may find less certainty acceptable in exposure estimates for those scenarios. When this is the case, fewer human participants would need to be monitored for such scenarios and more resources would be available for scenarios with higher exposure potential.

Page Break

Sample Size

The general method for determining the number of clusters and MUs per cluster to meet the benchmark objective under specified variability and accuracy assumptions is described in Appendix C of the AHETF governing document (AHETF, 2007). The procedure involves Monte Carlo simulation of data from the surrogate distribution, estimating the distributional parameters, and then determining the 95% bound on relative accuracy. Sample size configurations are then found that result in a 95% relative accuracy bound of 3-fold or less.

The Single-day Exposure and Long-term Mean Exposure Distributions

By definition, a particular individual handler (or ‘worker’) will appear in the target population of handler-days for all days he performs scenario-related tasks. Such multiple occurrences of a worker in the target population pose no conceptual difficulty to defining the distribution of single-day exposures. This single-day

exposure distribution merely corresponds to the likely exposure for a single handler-day selected randomly from this target population. If it were practical, the results obtained from a simple random sample of handler-days could be used to estimate the single-day exposure distribution. Unless the simple random sample is very large, however, it would rarely, if ever, contain two or more days for the same worker. Thus, having a sample of only unique-worker handler-days would not be atypical and estimating the single-day exposure distribution from such a sample is straightforward. In fact, if exposure shows any positive within-worker correlation, the intentional inclusion of repeated subjects in the sample reduces its sampling efficiency. That is, if the sample contains N handler-days but includes, by design, some days with the same subjects, then the sample size (for determining the single-day distribution) is effectively less than N. This effective sample size gets smaller as the within-worker correlation increases. If the correlation were perfect (i.e., equal to one), the effective sample size would reduce to the number of unique subjects obtained. This is the same principle that applies when sampling multiple MUs within clusters.

The AEATF II program was explicitly designed to estimate only the (total) single-day exposure distribution. This is the distribution of primary regulatory interest for the scenarios under consideration. Consequently, the diversity-oriented sampling methodology described in Appendix E purposively selects only unique subjects. There is no plan to provide BHED™ users the capability to separately estimate between-worker and within-worker components of total single-day exposure variation.

There is some regulatory interest in the distribution of long-term (or 'lifetime') mean worker exposure. From a regulatory standpoint, the long-term mean exposure is relevant to risk assessments dealing with cumulative effects from chemicals. Exposure/risk analysts estimate the distribution of intermediate- to long-term exposure (e.g., lifetime average daily exposure) by examining the distribution of long-term mean exposures multiplied by number of actual days exposed, divided by body weight (U.S. EPA Guidelines for Exposure Assessment, Federal Register 57 (104) 22888-22938, 29 May 1992).

This distribution of long-term mean exposure is different from, but related to, the distribution of single-day exposure. All the handler-days for a particular worker in the target population could be collected and the resulting exposures averaged. Such an average exposure value exists for each unique handler in the handler-day target population. In effect, this creates a target population of just unique handlers (not handler-days). Each handler in this new target population has a long-term mean exposure. A distribution of long-term means then arises conceptually by imagining selecting a worker randomly from this new target population.

One cannot directly estimate the long-term mean distribution from a sample having only a single day per worker. Some information regarding the within-

worker distribution is necessary. Such information must be obtained by either sampling multiple days per worker or by making assumptions about the degree of within-worker correlation. It is critical to note that within the practicalities of the sampling process there are two broad categories of 'within-worker' variation. These are:

Short-term, or 'repeated-measures', within-worker variation between days of the same visit to a 'location' (usually several days), and

Long-term, or 'longitudinal', within-worker variation corresponding to exposure days separated by much longer periods of time (e.g., months or years apart)

Short-term within-worker variation is expected to be much smaller than long-term variation. A worker's exposure on two sequential days at the same location should have the greatest correlation since many handler-day conditions should be similar. In contrast, exposures separated by a year or more have lower correlation since there are greater differences in location, behavioral, and other handler-related environmental conditions. It is this longitudinal variation that is most relevant to long-term (or lifetime) mean exposure. Therefore, repeated monitoring of the same individuals in the same location visit would have little value for estimating the long-term within-worker variation. Rather, it is necessary to monitor the same worker over longer periods of time spanning his typical range of possible conditions.

Designing such repeated monitoring studies to meet pre-specified benchmark objectives is not trivial. Such a program would also be more costly and complex to manage than the currently planned single-visit program. This would likely mean a reduction in the total number of scenarios that could be addressed. In addition, as pointed out by EPA's SAP (EPA 2007), participation is likely to be negatively affected if commitment to multiple periods of monitoring is required. AEATF II, in collaboration with AHETF, has determined that such additional experimental effort would be of limited regulatory value, an unwarranted drain on limited experimental resources, and an unnecessary burden on participants.

Lastly, it is important to note that methods currently exist for estimating the distribution of long-term means from just the single-day exposure distribution. Under the reasonable assumption that the single-day exposure distribution is approximately lognormal, the long-term mean distribution can be calculated if a value for the long-term within-worker correlation, R_{ww}, is assumed. R_{ww} is always between 0 and 1. When R_{ww} is near one, the long-term mean distribution is the same as the single-day exposure distribution. When $R_{ww}=0$, the long-term mean exposure distribution reduces to just a single value, the arithmetic mean of the single-day exposure distribution. When $0 < R_{ww} < 1$, the long-term mean distribution is lognormal with the same arithmetic mean as the single-day exposure distribution and variation that is a known function of R_{ww}.

If the sample sizes are sufficient to estimate the single-day exposure mean and 95th percentile to within 3-fold accuracy, then there is a practical approach for estimating the same parameters of the long-term mean distribution with similar accuracy. In their simulation studies (AHETF 2007, Section 7.5) the AHETF noted that when the value assumed for R_{ww} is close to the true (long-term) within-worker correlation, then the estimates of the mean and 95th percentile of the long-term mean distribution should also have close to 3-fold accuracy. More importantly, if the assumed R_{ww} is greater than the true R_{ww}, then the mean and 95th percentile might be overestimated by more than 3-fold, but the underestimation error is always less than 3-fold. From a regulatory perspective, overestimation of exposure is less of a problem than underestimation. Thus, a reasonable, or even conservative, value for R_{ww} can provide information about the long-term mean distribution that is quite adequate for regulatory purposes. Given such a value, the BHED™ database will provide suitable information that will be of use for long-term as well as short-term exposure assessments. Hence, there appears to be little incentive for limiting the number of scenarios and finding and committing subjects to additional monitoring just to measure within-worker variation.

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As defined in Section 16.4.1, the benchmark objective for each scenario is that selected lognormal-based estimates of the normalized (by the amount of active ingredient handled or “AaiH”), single-day exposure distribution be accurate to within K-fold, at least 95% of the time. The benchmark estimates of interest are the arithmetic mean and the 95th percentile. In principle, the value of K could be scenario-specific. In each scenario-specific data development plan will be a brief discussion of why K=3 is appropriate for that scenario, or alternatively the rationale for choosing another value of K. However, the current consensus is that for regulatory purposes, K=3 is an acceptable default value for all scenarios.

This benchmark is necessarily based on pre-data assumptions about the true nature of the exposure variation. It would be unlikely for all assumptions to be exactly satisfied for every scenario. Although slight deviations will have little or no impact, large deviations from the assumptions might result in data that deviate too far from the benchmark objective. Consequently, it is also of value to assess the benchmark requirement using the data actually obtained.

The K-fold benchmark above is specified in terms of the true variation structure and the resulting probability that certain characteristics would be observed in the data. Once the data are available, however, such probability statements are less relevant than confidence statements calculated from the actual data. Consequently, evaluation of the benchmark objectives will be based solely on confidence intervals.

To assess this benchmark goal, a 95 percent bound on relative accuracy will be calculated from confidence intervals for the arithmetic mean and the 95th percentile. For a particular parameter, θ, let T denote its estimate calculated

from the fit of a cluster sampling (variance component) model to the normalized exposure data. Further, let θ_a and θ_b denote the upper and lower limits, respectively, of a 95% confidence interval for θ. In most cases, the confidence interval, (θ_a, θ_b), will be a parametric bootstrap percentile interval obtained by resampling from a lognormal cluster sampling model. The 95 percent upper confidence bound on realized fold relative accuracy (*fRA*) is then calculated as:

$$UCL_{95}(fRA) = \text{Max} (T / \theta_a,\ \theta_b / T)$$

The values of $UCL_{95}(fRA)$ will then be compared with the pre-specified relative accuracy benchmark objective, K.

The Impact of Ignoring Clusters

As described in Appendix E, the AEATF II monitoring design involves selecting MUs in clusters. A scenario cluster is a set of MUs obtained in a single study at a particular geographic location (e.g., building) over a limited period of time (e.g. several days). Clusters are not a property of the target population, *per se*, but merely necessary artifacts of the sampling process. Exposures for MUs in the same cluster could be correlated to some degree. If so, then estimates of distributional parameters and regression analyses should accommodate this correlation. If a user ignores clusters (i.e., assumes the data are a simple random sample), then some parameter estimates may be biased and the confidence intervals may be too small. On the other hand, for the MUs of a particular scenario, such biases may be small and of little practical importance. When this is the case, analyses of the data can be simplified considerably. As an aid to regulators and other potential BHED™ users, the impact of ignoring clusters will be examined.

Estimates and confidence intervals for parameters of the normalized exposure distribution will be calculated using a model containing random cluster effects. From this analysis the variance components and intraclass correlation (ICC) and their confidence intervals will be estimated. In addition, the parameter estimates will be calculated assuming no cluster effect (i.e., assuming simple random sampling). These simplified estimates will be compared to those obtained under the cluster-sampling model. The differences obtained by ignoring clusters will then be summarized for the benefit of BHED™ users.