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# Series 875 - Occupational and Residential Exposure Test Guidelines

# Group B - POST APPLICATION EXPOSURE MONITORING TEST GUIDELINES

**Version 3.2**

**U.S. Environmental Protection Agency**
**Office of Prevention, Pesticides, and Toxic Substances**

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## DISCLAIMER

This document is a working draft for review purposes only and does not constitute U.S. Environmental Protection Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

## PREFACE

This draft Series 875-Group B (formerly Pesticide Assessment Guidelines - Subdivision K) is divided into four major parts followed by two appendices: (A) Background; (B) Guidelines; (C) Quality Assurance and Quality Control; and (D) Exposure and Risk Assessment. Part A addresses topics tangentially related to the Series 875 - Group B guidelines such as why post-application data are required and the regulatory/statutory realm. Part B is a "how-to" guide for developing study protocols and executing post-application studies. Part C provides a comprehensive overview of the QA/QC procedures required in conducting post-application monitoring studies and assessment. Finally, Part D provides information on calculating exposure and risk. Followed by these three parts are Appendix I: Data Reporting Guidelines and Post-Application Exposure, Appendix II: Evaluation and Interpretation of Results.

## ABOUT THE REVISION

**WHAT IT IS:**

Series 875 - Group B: *Post-Application Exposure Monitoring Guidelines* is a revision and expansion of the former *Pesticide Assessment Guidelines Subdivision K*. Series 875 - Group B is one of several guidelines available to assist the regulated community in designing and implementing studies required under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and/or the Toxics Substance Control Act (TSCA).

**WHO IT'S FOR:**

- Pesticide registrants and other individuals interested in post-application exposure monitoring.

**WHAT'S NEW:**

These guidelines greatly expand the scope and depth of the existing Subdivision K Guidelines. Highlights include:

- Guidance on conducting indoor/residential exposure monitoring;
- Guidance on conducting lawn/turf exposure monitoring;
- Guidance for providing activity pattern data;
- Guidance for providing detailed use information;
- Detailed Quality Assurance and Quality Control data; and
- Methodologies to develop assessments of exposure.

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# PART A

# BACKGROUND

# PART A - BACKGROUND

## PREAMBLE

This publication, Series 875 - Occupational and Residential Exposure Test Guidelines Group B: Post-Application Monitoring Test Guidelines (formerly Subdivision K of the Pesticide Assessment Guidelines), provides guidance to persons required to submit post-application exposure data under 40 CFR 158.390. Generally, such data are required under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) when certain toxicity and exposure criteria have been met. In addition, this document provides guidance to individuals interested in performing post-application exposure studies required under the Toxics Substance Control Act (TSCA) for toxics, inerts, and consumer products.

The post-application exposure guidelines are being revised because the existing guidelines (Subdivision K) no longer meet the needs of persons required to submit post-application exposure data. When the Subdivision K guidelines were first published in 1984, they were designed to establish an acceptable scientific approach to the post-application/reentry data requirements for typical agricultural exposure scenarios. Since 1984, there have been a number of changes in the Agency's data needs and requirements. First, as a result of the reregistration process, the Agency has been requiring more post-application studies. These include both occupational and residential post-application studies. Second, over the past few years, the Agency has become increasingly concerned with the expanded usage of pesticides in residential areas. Currently, there is little guidance available on conducting residential post-application studies. Third, the revisions to the Good Laboratory Practice Standards in 1989 has focused more attention on quality assurance and quality control (QA/QC). The Rejection Rate Analysis (U.S. EPA, 1993) indicated that the most common cause for rejection of studies was inadequacy or lack of QA/QC.[1] Finally, OPP and OPPT are striving to harmonize their respective post-application monitoring exposure guidance such that a single, consistent guidance document will be useful to both offices. Also, the revised guidance will harmonize, to the extent possible, with guidance issued by international organizations such as the North Atlantic Treaty Organization (NATO) and the Organization for Economic and Cooperation Development (OECD).

To support the revisions to these guidelines, EPA's Office of Research and Development (ORD) is conducting research to support the Subdivision K revision and expansion. Specifically, studies are being conducted to:

[1]The Rejection Rate Analysis was undertaken to determine the reasons for study rejection and to help improve the acceptability rate of studies submitted for reregistration by pesticide registrants.

- Develop and evaluate sampling and analytical methods for quantifying the concentration of pesticides on indoor/outdoor surfaces in and around the home;
- Develop emissions models to predict environmental concentrations;
- Provide data and models for characterizing frequently occurring activities that may lead to exposure via dermal contact/transfer (e.g., crawling on a carpet in a room that has been treated with a pesticide), inhalation, and non-dietary ingestion (e.g., children ingesting pesticide-contaminated soil); and
- Develop and test human exposure assessment models for use in providing estimates of 'central tendency' and 'high-end' exposure and dose for specific highly exposed population subgroups such as children.

This research is currently under way and is expected to continue through fiscal year (FY) 1997. During this time period, a number of outputs for each of the four areas described above will be released. Of particular relevance to the Subdivision K revisions will be the development of a manual of methods for quantifying dislodgable pesticides and consumer-use product residues on indoor/outdoor surfaces and materials. It is expected that this particular document will be issued in FY '95 as interim guidance.

A second initiative being undertaken to generate data is the formation of the Turf Task Force, which will generate exposure data to support registration and reregistration of all lawn care pesticides. The resulting database will provide a core body of knowledge that will be used in exposure assessments for mixer/loader/applicators and persons reentering treated areas. In addition, this core body of knowledge will be used to guide future studies.

To assure the quality and timely submission of the Task Force's data, the Agency plans to issue a Data Call-In notice under FIFRA section 3(c)(2)(B). In addition to exposure data, the Agency would also like to request post-application activity data, particularly for children.

## AN HISTORICAL PERSPECTIVE

Soon after the introduction of the organophosphorus (OP) insecticides in the late 1940s, specific toxic effects peculiar to some OP compounds were sometimes observed in field workers after applications of OP insecticides. These episodes were quite erratic; that is, the same pesticide might be used, at the same rate, on the same piece of ground, on the same crop for several years without any evidence of toxic effects, but in a subsequent year a number of field workers might experience toxic symptoms characteristic of OP poisoning. This made it very difficult to investigate the problem

and contributed to a number of misconceptions. Among these misconceptions were the ideas that only inhibitors (i.e., OP and carbamate insecticides) of the enzyme acetyl cholinesterase (AChE) cause reentry problems, that exposure occurred by inhalation, and that only acute effects occurred.

Because it was difficult to obtain information about the conditions leading to a reentry episode, it was difficult to arrive at a realistic model for the derivation of reentry intervals. Several models/methods were proposed, but prior to 1980 an "epidemiological" model was the primary method for the establishment of reentry intervals. For example, in the June 25, 1975 Federal Register [Vol 40, no. 123, p. 26900] it was stated: "A number of sporadic episodes of acute adverse effects in field workers have been ascribed to toxic levels of pesticide residues on plant surfaces..... Establishment of reentry intervals for a specific pesticide-crop-cultural practice combination is currently conceived as a two-step process: (1) postulating a reentry interval; and (2) testing the postulated interval in the field." This approach was not satisfactory to the Agency. At a meeting of the FIFRA Scientific Advisory Panel (SAP) February 22 and 23, 1980, the Agency presented a new model for the establishment of reentry levels and reentry intervals. This "Allowable Exposure Level" (AEL) model obviated the epidemiological method. It allowed the establishment of reentry levels and intervals from toxicity and dissipation data through the use of a correlation of "dislodgable residue" levels with exposure levels. This method addresses any class of compound and any mode of toxicity whether the effect is acute or chronic. It also makes it possible to establish reentry levels and intervals without the exposure of individuals to possibly hazardous pesticide residue levels.

The 1980 guideline draft was revised in response to public comment and to SAP advice. The revision was presented to the SAP again in May 1981. The 1981 draft was again revised, and that draft of Subdivision K was presented to and reviewed by the SAP as part of the publication of several guideline sections. The final version of Subdivision K was published in October 1984. The data discussed in Subdivision K were then codified as data requirements in 40 CFR 158.390 [originally at 40 CFR 158.140].

This present document is a revision and expansion of the existing [1984] Subdivision K. This guideline builds on the previous version; that is, the allowable exposure level (AEL) method is retained with modifications and new areas for data requirements are added. Specifically, submittal of biological monitoring data is being proposed as an optional method to set reentry intervals as part of the defense of existing pesticide registrations. Also, submission of data for human protection from pesticide treated homes, lawns, and greenhouses are being proposed.

This revised guideline will be presented for public comment in conjunction with a SAP review. Availability of the document and the date of the SAP meeting will be published in the

Federal Register. After any necessary revisions/responses, the final version will be published along with notification of its availability to the public. By 1995, interim guidance will be available. To finalize these guidelines [TBA: What must be done]

## EVIDENCE OF POST-APPLICATION/REENTRY EXPOSURE

[Note: The term re-entry interval is obsolete. Subsequent versions of this document will use terminology considered with the Worker Protection Standards.

There is nationwide concern over reentry exposure. Reporting of pesticide-implicated illnesses and injuries is mandatory in California. Thus, that state has the most complete record of suspected and confirmed effects attributed to pesticide exposures (as reviewed in U.S. EPA 1984). In 1977 California physicians reported 1,518 cases of occupational illness or injury resulting from pesticides; 12 percent of these cases involved field workers. Approximately one-fourth of the field worker cases were of a systemic nature, with the remainder being injuries to the skin, eyes, or both (U.S. EPA 1984). Reported occupational injuries from pesticide exposure in 1987 numbered 1,595 (580 confirmed cases, 391 probable, and the remainder possible or unlikely), with approximately one-half of a systemic nature. However, total reports did not show a clear trend in frequency between 1982 and 1987. Also, 28 percent of the occupational reports filed in 1987, involved exposure to residues in agricultural fields or on commodities (Maddy et al. 1990).

Krieger and Edmiston (n.d.) analyzed and ranked pesticides in California according to reported occurrences of systemic injury from 1982 through 1986. They noted that the highest incidence was associated with parathion use, which accounted for 18 percent of the total reports, almost twice that of the second-ranked pesticide, mevinfos. Fifteen of the twenty highest ranked pesticides were cholinesterase-inhibiting insecticides, including methomyl, methamidophos, dimethoate, methidathion, and carbofuran.

U.S. EPA (1984) reported several case studies of field reentry poisoning incidents to demonstrate the serious nature of the poisoning symptoms and the number of workers involved. Over 63,000 pesticide-related incidents were reported to poison control centers in 1988, two-thirds of which were from insecticides (Litovitz et al. 1988). Organophosphates caused the most fatalities. Wasserman and Wiles (1985) estimated that more than 300,000 pesticide-related illness and injury incidents occur nationwide on an annual basis.

[TBA: Paragraph on instances where the Agency has requested post-application agricultural and residential exposure data. Some instances include EBDCS, captan, and benomyl.]

## LEGISLATIVE AUTHORITY

### Legislative basis

FIFRA provides a statutory framework under which EPA, primarily through a registration process, regulates the sale, distribution, use, and disposal of pesticides. As the standard for registration of a pesticide, FIFRA requires that the pesticide, when used in accordance with widespread and commonly recognized practices, will not cause unreasonable adverse effects on human health or the environment (7 U.S.C. section 136a(c)(5) and (7)). A similar standard applies to the reregistration of existing pesticide products and Agency approval of experimental use of unregistered pesticides (7 U.S.C. sections 136b(g)(2) and 136c). FIFRA defines "unreasonable adverse effects on the environment" as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of [the] pesticide" (7 U.S.C. section 136bb).

For the Agency to make well-informed "unreasonable adverse effects" determinations, FIFRA gives EPA broad authority, before and after registration, to require specific testing by registrants and/or applicants and submission of the resulting data to the Agency (7 U.S.C. sections 136 a,b, and c). Registrants and/or applicants are under a continuing obligation to provide the Agency with adequate information about their products to demonstrate that the products meet the statutory standard for registrability and to report any additional information that may affect the Agency's determination (7 U.S.C. sections 136a(c)(2)(B), 136b(b), and 136d(a)(2).

### EPA's Role in Providing Guidance

The Data Requirements for Registration (40 CFR 158) specify the types of data and information generally required to make sound regulatory judgements under FIFRA for each pesticide proposed for experimental use, registration, amended registration, or reregistration with respect to its potential for causing unreasonable adverse effects.

These data requirements, in support of pesticide registrations, have evolved over time through a series of legislative initiatives, regulations, and policy directives. In 1975, registration regulations were promulgated that established the basic requirements for registration of pesticide products. From 1975 to 1981, pursuant to FIFRA section 3(c)(2), EPA made available several subparts of the "Guidelines for Registering Pesticides in the United States" as draft guidance. These guidelines specifically described the kinds of data that were required for registration.

Subsequently, EPA reorganized the guidelines to limit the regulation to a concise presentation of what the data requirements were and when they were required. On October 24, 1984 the regulation was issued and codified in 40 CFR 158 (49 FR 43881).

In addition to the regulation, guidelines were issued in 1983 as a series of documents titled the "Pesticide Assessment Guidelines." The Guidelines describe acceptable protocols, test conditions, and the data that must be reported for each test requirement. The Guidelines were set forth as separate Subdivisions as follows:

- Subdivision D (Product Chemistry);
- Subdivision E (Wildlife and Aquatic Organisms);
- Subdivision F (Hazard Evaluation: Human and Domestic Animals);
- Subdivision G (Product Performance);
- Subdivision I (Experimental Use Permits);
- Subdivision J (Hazard Evaluation: Nontarget Plants);
- Subdivision K (Reentry Exposure);
- Subdivision L (Hazard Evaluation: Nontarget Insects);
- Subdivision M (Biorational Pesticides (since revised under the title "Microbial and Biochemical Pest Control Agents");
- Subdivision N (Chemistry: Environmental Fate);
- Subdivision O (Residue Chemistry); and
- Subdivision R Spray Drift.

Since 1984 a new Guideline document, Subdivision U: Applicator Exposure Monitoring, has been published. In addition, several position documents and addenda to the guidelines have been published. The Agency has also published standard evaluation procedure documents which give further guidance in a number of disciplinary areas.

Currently, the Office of Prevention, Pesticides, and Toxic Substances (OPPTS) is harmonizing its pesticide and toxics guidance (i.e., the "Pesticide Assessment Guidelines) with similar international guidance such as that issued by OECD and NATO. The purpose of harmonizing these guidelines into a single set of OPPTS guidelines is to minimize variations among the testing procedures that must be performed to meet the data requirements of EPA under the Toxic Substance Control Act (15 U.S.C. 2601) and the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136, *et seq.*). A goal of guideline harmonization is to reduce the data collection burden on industry as the results of a study conducted following harmonized guidelines may be used by a number of regulatory organizations/

countries. In addition, harmonizing OPPTS Guidelines with those of the OECD will enable the Agency to achieve compliance with the OECD's Mutual Acceptance of Data Doctrine.

The harmonized OPPTS Test Guidelines are arranged into eight series as follows, each of which is broken down into a number of Groups:

- Series 810 - Product Performance Test Guidelines;
- Series 830 - Product Properties Test Guidelines;
- Series 835 - Fate, Transport, and Transformation Test Guidelines;
- Series 840 - Fate and Transport Field Studies Test Guidelines;
- Series 850 - Ecological Effects Test Guidelines;
- Series 860 - Residue Chemistry Test Guidelines;
- Series 870 - Health Effects Test Guidelines;
- **Series 875 - Occupational and Residential Exposure Test Guidelines**
  - Group A - Applicator Exposure Monitoring Test Guidelines
  - **Group B - Post Application Exposure Monitoring Guidelines;**
- Series 880 - Biochemicals Test Guidelines; and
- Series 885 - Microbial Pesticide Test Guidelines.

Eventually, each of the existing Pesticide Assessment Guideline Subdivisions will be republished as a harmonized OPPTS Guideline.

The guidance being drafted in this document is Group B of Series 875 which includes the former Pesticide Assessment Guidelines - Subdivision K. Group A Guidelines of this Series are the existing Subdivision U Guidelines.

## REGULATIONS AND POLICIES

In conducting post-application exposure monitoring studies, the study investigator needs to be cognizant of certain Agency regulations and policies that could impact his investigation. For instance, research being conducted on human subjects must conform to the requirements of the "Common Rule." Investigations being conducted to fulfill the requirements of 40 CFR 158.390 must be carried out following the requirements of the Good Laboratory Practices and must comply with the requirements of the Worker Protection Standards. Highlighted below are Agency regulations and policies that a study investigator must consider in pursuing post-application exposure monitoring.

Protection of Human Subjects

***Common Rule*** - The Federal government has established common requirements for the protection of human subjects involved in research conducted or funded by a number of Federal Departments and Agencies including EPA and USDA (56 FR 28002; June 18, 1991). These requirements are known informally as "the common rule." EPA has adopted the common rule as regulations; they are codified at 40 CFR 26. The Agency is now drafting an order (EPA Order 1000.17 Human Subject Research) for implementing the policy set forth at 40 CFR 26; it is expected to be finalized by [TBA -- When???]

***FIFRA*** - In addition to the common rule, FIFRA also provides requirements for the protection of human subjects. Pursuant to FIFRA section 12(a)(2)(P), it shall be unlawful for any person "to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test;"

***Worker Protection Standard*** - On August 21, 1992 EPA published the Worker Protection Standard Final Rule (ref. 2) under the authority of FIFRA (U.S. EPA, 1992a). These regulations (codified at 40 CFR 156 and 170) were promulgated to govern the protection of workers from agricultural pesticides. The provisions of the Worker Protection Standard are directed toward the working conditions of two types of employees: those who handle agricultural pesticides (e.g., mix, load, apply, clean or repair equipment, act as flaggers, etc.) and those who perform tasks related to the cultivation and harvesting of plants on farms or in greenhouses, nurseries, or forests that may have been treated with pesticides (e.g., scouting, irrigation workers, and harvesters). The Worker Protection Standard includes provisions intended to: (1) eliminate or reduce exposure to pesticides; (2) mitigate exposures that occur; and (3) inform employees about the hazards of pesticides.

In conducting any field study, the investigator must insure that the applicable provisions of the Worker Protection Standard regulations are being fulfilled. Generally, hazard information must be available for all workers, appropriate protective clothing must be provided, and decontamination sites and emergency assistance must be available. See Part C (QA/QC) for specific guidance on protecting human subjects involved in post-application monitoring studies.

Good Laboratory Practices

The FIFRA Good Laboratory Practice (GLP) Standards are regulations that were promulgated to insure the quality and integrity of data submitted to the Agency (U.S. EPA, 1992b). "EPA

originally published FIFRA GLP standards in the **Federal Register** of November 29, 1983 (48 FR 53946), which were codified at 40 CFR part 160....These regulations were promulgated in response to investigations by EPA and FDA during the mid-1970s that revealed that some [toxicological] studies had not been conducted in accordance with acceptable laboratory practices" (U.S. EPA, 1992b). In 1989 EPA revised the GLPs to: (1) include the environmental testing provisions currently found in the TSCA GLP standards and; (2) apply to all data submitted to support registration/reregistration/special review of pesticides under FIFRA. "In summary, the FIFRA GLP standards will allow EPA to ensure the quality and integrity of all data submitted in support of pesticide product research or marketing permits" (U.S. EPA, 1992b). Part C of this document (Quality Assurance/Quality Control) provides a detailed explanation of how to comply with the FIFRA GLPs.

### Agency Policies

[TBA: Paragraph on pollution prevention/risk reduction/use of fewer pesticides; exposure and risk to infants and children.]

## THE GUIDELINE REQUIREMENTS – AN OVERVIEW

EPA requires pesticide post-application exposure data when it needs to determine: (1) a reentry interval (i.e., the length of time required before persons could enter a pesticide-treated site without appreciable risk); or (2) whether a pesticide could be used without appreciable risk in a residential setting. Reentry intervals are required for highly toxic pesticides that have use types likely to result in significant dermal and inhalation exposure to persons entering treated fields or treated homes. The decision to require post-application exposure data is made by examining the toxicity and exposure criteria detailed at 40 CFR 158.390.

To determine a reentry level or whether a pesticide could be used in a residential setting, information is needed on the rate at which a specific pesticide dissipates over time (see Part B – Chapters 2, 3, 4, and 5); the amount of pesticide an individual is exposed to (see Part B – Chapters 6 and 7); and the toxicity of the pesticide (see Part B – Chapter 1). Other information that may be considered to refine the exposure and risk estimates include: activity data (see Part B – Chapter 10) and dermal absorption estimates.

**Determining When/If Exposure Studies Are Needed**

Under the "Data Requirements for Registration" described at 40 CFR 158, reentry protection data requirements (40 CFR 158.390) are "conditionally required (CR)." Conditionally required data requirements are those that must be satisfied when certain criteria are met. In the case of the reentry protection data requirements, such data are required if the following toxicity and use-type criteria are met.

*Toxicity*

The Agency requires that registration of pesticides with acute dermal, inhalation, and oral toxicity properties corresponding to Toxicity Category I (see 40 CFR 156.10) should be supported by the establishment of reentry intervals (40 CFR 158.390). These acute toxicity criteria include:

- Acute dermal: less than 200 mg/kg;
- Acute inhalation: less than 200 $mg/m^3$ (for a one-hour exposure); or
- Acute oral toxicity: less than 50 mg/kg (body weight).

However, in practice the Agency is now requiring post-application exposure studies for pesticides corresponding to toxicity category I or II. This change will be formally adopted through rulemaking. The above criteria are based on the toxicity of the technical pesticide and its toxic alteration products. Use of the technical product is necessary because persons reentering treated sites will normally not be exposed to the formulated product or to its diluted form as applied, but rather to a "weathered" or environmentally modified and dissipated residue, which no longer is composed of the same mixture or ratio of components present in the formulated product.

*Use Type*

Use types, where post-application exposure data are required, are those that are characterized by the high likelihood of dermal or inhalation exposure of persons who enter sites included in these classes. Dermal exposure will generally arise from contact with treated foliar, fruit, or soil surfaces; inhalation exposure will normally arise from respiration of volatilized pesticide residues and residues adhering to particulate matter which has become airborne. The Agency believes that these use types constitute the most likely conditions for significant human exposure in reentry situations.

The Agency recognizes that other reentry exposure situations may occasionally occur that would not meet either the toxicity or use type criteria but which could potentially result in adverse

acute or chronic effects to persons entering treated sites. In these cases, the Agency will consider the requirement for reentry intervals and supporting data on a case-by-case basis. Similarly, there are likely to be cases where the toxicity and use type criteria are met but exposure is not likely to occur. The Agency has included in 40 CFR 158 procedures for waiving the reentry interval requirement in such cases. Toxicity and use criteria are described in detail in Part B -- Chapter 1.

**ISSUE: Could modelling ever be used instead of the toxicity and exposure criteria to determine whether or not these studies need to be done?**

## Types of Studies and Information Required

At a minimum, dissipation, exposure, and toxicity data are needed to determine a reentry interval and/or to assess risk. Dissipation may occur on foliage, soil, or indoor surfaces. The Agency may require one or more of the following studies to determine the dissipation rate, depending on the use of the pesticide: Foliar Dislodgable Residue (FDR) Dissipation Study; Soil Residue Dissipation (SRD) Study; or an Indoor Surface Residue (ISR) Dissipation Study.

Exposure may occur via the dermal or inhalation routes. To determine human exposure, EPA may require Dermal Exposure or Inhalation Exposure studies. Alternatively, study investigators may choose to determine human exposure through Biological Monitoring.

Toxicity data are needed in conjunction with the dissipation and exposure data to estimate the reentry interval or to ensure no appreciable risk from use in residential settings. No new toxicological studies are required under 40 CFR 158.390. Rather, the toxicological data needed are derived from studies required under 40 CFR 158.340. These data requirements are described in Subdivision F: Hazard Evaluation - Human and Domestic Animals.

Finally, estimates may be refined by submitting dermal absorption data and/or detailed use information. Such information will allow the Agency to avoid using "worse-case" estimates.

Description of Required Studies

*Dissipation Studies*

**Foliar Dislodgable Residue (FDR) Dissipation Study.** FDR studies assess the dissipation rate of pesticide active ingredients that can be transferred from foliar surfaces (e.g., agricultural crops, turf, and garden plants) to human skin by analyzing foliar samples collected at various post-application time intervals.

**Soil Residue Dissipation (SRD) Study.** SDR studies assess the dissipation of pesticide residues in soil by extracting and measuring residues in soil collected at specified intervals post-application.

**Indoor Surface Residue (ISR) Dissipation Study.** ISR studies characterize dissipation of pesticide residues from indoor surfaces as a function of time by sampling and analyzing surface residues at various time intervals following application.

*Measurement of Human Exposure*

**Dermal Exposure (passive dosimetry).** Passive dosimetry studies assess potential dermal doses to humans by analyzing pesticide residues on dosimetry patches or clothing worn by study participants during reentry activities.

**Inhalation Exposure.** Inhalation monitoring studies establish potential inhalation levels during post-application activities by analyzing air samples collected via personal sampling pumps, passive monitors, high-volume samplers, or other techniques.

**Biological Monitoring.** Biological monitoring assesses internal dose by measuring either body burden or enzyme activity in selected tissues or fluid, or from the amount of pesticide or its metabolites eliminated from the body.

*Other Data*

**Human Activity Data.** Human activity data define the activity patterns that affect exposures. These data include site-specific and test subject-specific information.

**Toxicity Data.** Toxicity studies quantify adverse biological effects based on specific exposure conditions and doses.

**Detailed Use Information.** The submission of detailed use information (e.g., typical use of the pesticide such as pounds applied) and its associated cultural practices would allow more precise evaluation of exposure.

## Exposure Scenarios and Exposed Populations

Once a study investigator determines (using the toxicity and exposure criteria at 40 CFR 158.390) that reentry data are required, he must then determine specifically which studies need to be done. To do this, it may be useful to develop representative exposure scenarios. The following elements of an exposure scenario should be considered: (1) the sites and patterns of pesticide use; (2) the potentially exposed populations; (3) significant exposure routes; and (4) the duration over which exposure is likely to occur (i.e., acute or chronic exposures).

***Sites, Patterns, and Conditions*** - Exposure may occur at either indoor or outdoor locations. Potential outdoor sites include agricultural fields; public parks and recreational areas; golf courses; residential lawns; other widespread spraying operations (e.g., mosquito or med-fly control); spray drift from nearby outdoor applications; and swimming pools, hot tubs, lakes and ponds. Indoor sites include greenhouses; residences; schools and hospitals; restaurants; commercial buildings and manufacturing facilities; and barns and other farm buildings. Usage patterns at outdoor sites include various types of agricultural practices; treatment of turf and gardens; and use of antimicrobial agents in swimming pools, hot tubs, lakes and ponds. Indoor uses that can result in exposures include greenhouse applications; crack and crevice treatments; pesticide foggers (i.e., flea bombs); broadcast spray applications; vapor strips; moth repellents; residual termiticides; pet products (i.e., flea collars, dips, and shampoos); disinfectants; and indoor plant applications. A secondary source of indoor exposure is lawn and garden pesticides that are inadvertently "tracked in" to the home. Preliminary findings of ongoing research have indicated that children of agricultural families have a higher potential for exposure to pesticides from "track-in" than children of non-agricultural families (Fenske, 1993).

***Exposed Populations and Routes*** - Potentially exposed populations can include members of the general population (i.e., residential exposures), subsets of the population (i.e., farmworkers or golfers), or sensitive populations such as infants and children. The route(s) by which these populations are exposed to a specific pesticide active ingredient is dependent

on its chemical nature, use patterns, and site of application. Inhalation exposure may result from pesticides that remain suspended in the ambient air, volatilize after application, or are resuspended by activities. Inhalation monitoring studies are necessary to evaluate exposure via this route. Dermal exposure may occur from indirect contact with pesticides that dislodge from treated surfaces (i.e., plant leaves, or indoor surfaces), or from direct contact with antimicrobial agents used in swimming pools, and other water bodies. Foliar, soil or indoor dislodgable residue studies and dermal exposure assessments are required for evaluating these exposures. Biological monitoring may also be used. Non-dietary ingestion exposure may occur as a result of inadvertent ingestion of pesticide-contaminated soil or dust, or pesticide residues that dislodge from treated surfaces onto the surface of the hands or objects (i.e., toys) and are ingested as a result of hand-to-mouth or object-to-mouth activities. Soil/dust ingestion studies and other measures of non-dietary ingestion exposure may be used to assess these exposures.

*Exposure Duration* - The length of time over which exposures occur can have a significant impact on the magnitude of exposure and risk. Health effects are typically indexed to the duration of exposure. Acute exposures are those that occur over a relatively short time period (i.e., hours or days). Chronic exposures occur over longer time periods (years or a lifetime). For example, acute pesticide poisonings can result from relatively brief exposure periods, whereas carcinogenic slope factors used in risk assessment assume long-term exposures. The exposure period is frequently dependent on the factors described above (i.e., site, use patterns). For example, for recently treated lawns, the potential for acute exposures among young children may be especially significant. Children may be acutely exposed to lawn chemicals via inhalation (children's breathing zones are closer to lawn surfaces), and inadvertent ingestion (hand-to-mouth and object-to-mouth activity). Dermal exposure is also a potentially significant route, especially if the child is not fully clothed (i.e., wearing only a diaper or a pair of shorts). In contrast, indoor treatments with residual pesticides may result in low-dose exposures over longer periods of time. This is caused in part by the tendency for indoor pesticides to dissipate more slowly and the higher percentage of time that individuals (especially young children) spend inside the home.

*Exposure Scenarios* - Representative pesticide exposure scenarios may be constructed by considering the four factors described above (i.e., sites and use patterns, potentially exposed populations, exposure routes, and duration). The construction of these scenarios may assist the user in selecting appropriate methods for evaluating pesticide exposures. Examples of some representative exposure scenarios include, but are not limited, to the following:

- Treatment of an agricultural crop; potential acute dermal exposure among farmworkers as a result of harvesting/scouting/maintenance operations;
- Outdoor pesticide usage in a public park; potential acute exposure among the general population using the park (especially children); potential for dermal contact with soil and foliage, inhalation exposure depending on time lapse before reentry, and soil ingestion;
- Use of lawn care products; outdoor acute inhalation/dermal/ingestion exposure, especially among children;
- Antimicrobial agents in swimming pools; potential acute dermal, inhalation (if pesticide includes volatile components), and incidental ingestion among adults and children. Exposure may also occur via buccal/sublingual, orbital and nasal, and aural exposure routes, and via sexual organs and anal routes;
- Residential use of garden care product; potential chronic non-dietary ingestion exposure indoors as a result of "track in" of soil and dust; family members, especially children exposed;
- Indoor termiticide used in a pre-school; potential chronic dermal, inhalation, and non-dietary ingestion exposure among children;
- Pet care products applied to pets; chronic dermal exposure with pesticide treated surfaces and direct skin contact, potential non-dietary ingestion exposure from hand-to-mouth contact, and inhalation of volatile components; and
- Vapor strips used indoors; chronic inhalation exposure to all household residents.

Example Scenarios and Studies That Might be Required

Listed in Table A-1 are a number of representative exposure scenarios along with the types of studies that might be required under 40 CFR 158.390.

## USE OF THE GUIDELINES

The information provided in this Background section is intended to provide the reader with an understanding of why post-application data are required and how to determine which studies need to be performed. The next sections of this document -- Part B - Guidelines, Part C - QA/QC, and Part D - Exposure and Risk Assessment -- provide the actual "how-to" guidance on conducting and implementing post-application exposure studies.

Each of the "Guidelines" in Part B is labelled by an 875 number. This is in keeping with the OPPTS initiative to develop harmonized guidelines and numbering, as described earlier in this Background section. In addition to the Guideline of interest (e.g., Guideline 875.2500 - Inhalation Exposure Monitoring), the study investigator must at a minimum also consult Guideline 875.1000 - General Provisions, Part C - QA/QC, and Part D - Exposure and Risk Assessment.

**TABLE A-1: Studies/Data Required for Various Exposure Scenarios**

| EXPOSURE SCENARIO | REQUIRED STUDY | | | | | | |
|---|---|---|---|---|---|---|---|
| | FDR | SDR | ISR | DE | IE | BioM | USE |
| Grape Harvesting | | | | | | | |
| Application of Lawn Chemicals | | | | | | | |
| etc. [To be Completed] | | | | | | | |

KEY: FDR = Foliar Dislodgable Residue Dissipation Study (see Guideline 132)
SDR = Soil Dislodgable Residue Dissipation Study (see Guideline 132)
ISR = Indoor Surface Residue Dissipation Study (see Guideline 132)
DE = Dermal Exposure (see Guideline 133)
IE = Inhalation Exposure
BioM = Biological Monitoring
USE = Use and Agricultural/Residential Practice Information

## REFERENCES FOR PART A

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# PART B

# GUIDELINES

# PART B - CHAPTER 1
# GUIDELINE 875.1000 - GENERAL PROVISIONS

## 1.1 PURPOSE AND SCOPE

These guidelines describe the reentry protection data requirements (40 CFR 158.390) that may be required in support of registration. These data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects, and environmental fate of pesticides.

## 1.2 GENERAL REFERENCES

**ISSUE: What would be good references?**

## 1.3 DEFINITIONS

Terms used in Series 875 - Group B have the meanings set forth at 40 CFR 152.3 and at 40 CFR 158. In addition, for the purposes of this subdivision:

- "Airborne residue" means residue of a pesticide, including vapors, aerosols, and airborne particulates, that remains suspended in the air after pesticide application or is caused to become suspended in the air at a treated site during a normal human activity;
- "Allowable exposure level" or "AEL" means the maximum amount of combined dermal and inhalation exposure which is considered not to cause unreasonable adverse effects to people entering a previously treated site. An AEL will generally be based on animal toxicity studies and adjusted by means of an appropriate safety factor;
- "Dermal exposure" means the process by which pesticide residues are deposited onto the clothing and skin of people entering a previously-treated site. The term also refers to a measure of the amount of residue deposited by such exposure. External dermal exposure differs from "dermal dose" which is the amount actually reaching the skin. Neither is usually equivalent to the amount of residue absorbed into the body through the skin;

- "Direct exposure method" means a procedure for measuring the quantity of pesticide residue transferred to a person's skin or respiratory tract. This method would involve, but not be limited to, measuring residues on dermal patches or respirator filters. This method excludes indirect exposure methods, such as quantification of pesticide residues in blood, urine, or tissues, and excludes measurement of physiological changes, such as changes of blood enzyme activities;
- "Dislodgable residue" means that portion of pesticide residue on a surface that is available for exposure via human activities involving contact with the surface. The term also includes residue that can be dislodged by dissolving in moisture (dew, rain, perspiration) and which then can contaminate skin, respiratory tissues, hair, clothing, etc., of people entering the treated site. The surfaces involved include, but are not limited to, foliage, agricultural produce, and soils. The foliar "dislodgable residue" method in Iwata et al. (1977) is one specific form of the generic term used herein;
- "Dissipation curve" means a graphical representation of pesticide residue levels plotted against time of sampling, or the mathematical representation of such a data.
- "Early reentry" means the entry of people into a site previously treated with a pesticide prior to the expiration of any established, pertinent reentry interval;
- "Inhalation exposure" means the process by which pesticide residues are inhaled by a person in a treated site. The term also refers to the quantity of residue sorbed by respiratory tissues by such a process. This term is synonymous with pulmonary or respiratory exposure, and is not necessarily equivalent to the amount of residue which would be absorbed into the body through the pulmonary system;
- "Personal protective equipment" means special clothing, hats, shoes, gloves, respirators, or other risk mitigation devices attached to or covering people and intended to reduce human exposure to pesticide residues. This term refers to items that normally would not be used in the absence of pesticide hazards and that would provide greater protection to people than normal attire.
- "Proposed reentry interval" means a reentry interval proposed by an applicant as adequate for human protection;
- "Reentry" means the entry of one or more people into a site subsequent to pesticide application;
- "Reentry interval" means the length of time that must elapse after pesticide application before people who are not using personal protective equipment may enter the treated site without risk of any unreasonable adverse effects due to exposure to pesticide residues. This term is synonymous with "reentry time" [cf. 40 CFR 170.2(a)];

- "Reentry level" means the maximum level of pesticide residues at a treated site that is not likely to pose unreasonable adverse effects on people entering the site without personal protective equipment;
- "Residue(s)," "pesticide residue(s)," and "residue(s) of a pesticide" mean active ingredient(s), toxic impurities of the pesticide, and toxic alteration products of the active ingredient that remain at the site of application or that remain on items that are subsequently removed from the site;
- "Site" means a specific agricultural area such as a field, grove, vineyard, or orchard;
- "Surrogate," "surrogate of a pesticide," or "pesticide surrogate" means a chemical compound or a mixture of compounds other than the pesticide being investigated which could be used to quantify human exposure to that pesticide. The surrogate could be an active ingredient of a pesticide previously registered for that use;
- "Task" means a human work activity performed according to current commonly-recognized practice, or any other human activity that could result in exposure to pesticide residues at the site;
- "Typical end-use product" means a pesticide product that is representative of a major formulation category (e.g., emulsifiable concentrate, granular product, wettable powder) and contains the active ingredient of the registration applicant's product; and
- "Use type" means a grouping of crops or plants with similar potential for exposure during reentry activities.

[TBA: Residential - specific definitions]

## 1.4 REQUIREMENT FOR POST-APPLICATION EXPOSURE AND SUPPORTING DATA

A reentry interval and the supporting data discussed in this Series are required by 40 CFR 158.390 to support the registration of each end-use product that meets one or more of the toxicity criteria specified below, and that has a use type that could be included in the use classifications specified below.

### 1.4.1 Toxicity and Exposure Criteria

As delineated at 40 CFR 158.390, reentry protection data are required if the following conditions are met:

"(i)(A) The acute dermal toxicity of the technical grade of active ingredient is less than 200 mg/kg (body weight); or

(B) The acute inhalation toxicity of the technical grade of active ingredient is less than 200 $mg/m^3$ (for a one-hour exposure); or

(C) The acute oral toxicity of the technical grade of active ingredient is less than 50 mg/kg (body weight); or

(D) Neurotoxic, teratogenic, or oncogenic effects or other adverse effects as evidenced by subchronic, chronic, and reproduction studies would be expected from entry of persons into treated sites; or

(E) The Agency receives other scientifically validated toxicological or epidemiological evidence that a pesticide or residue of a pesticide could cause adverse effects on persons entering treated sites. In the last situation, reentry intervals and supporting data may be required on a case-by-case basis.

(ii) And if: end-use product is to be registered for:
(A) Application to growing crops, such as to or around horticultural and agronomic crops that are field- or orchard-grown.

(B) Application to outdoor tree or nursery operations.

(C) Application to turf crops and commercial applications to turf.

(D) Application to parks and arboretums; or (E) application to aquatic crops."

However, the Agency is currently using the following criteria. These criteria have not been formally adopted but are generally accepted and are expected to be formally proposed in the near future.

- The acute dermal $LD_{50}$ of the technical grade of the active ingredient (TGAI) is less than 2000 mg/kg (i.e., Toxicity Categories I and II - see 40 CFR 156.10); or

- The acute inhalation $LC_{50}$ of the TGAI is less than 2 mg/L and the TGAI has a vapor pressure greater than $10^{-4}$ torr at 25°C if used outdoors (note: failure to meet the acute inhalation criteria would negate the need for inhalation exposure data if the pesticide did not pose any significant chronic concerns); or

- The TGAI is found to be a developmental toxicant (Guideline 83-3, 83-6);

- Other adverse effects have been observed in any of the following toxicity studies: carcinogenicity (Guideline 83-2), neurotoxicity (Guideline 82-6, 82-7), reproduction (Guideline 83-4), and chronic feeding (including immunotoxicity testing), (Guideline 83-1); or

- Epidemiological/poisoning incident data indicates that adverse effects result from post-application exposure;

- Exposure data are required to demonstrate a negligible exposure scenario if the registrant requests a waiver for chronic testing data (Guideline 83-1, 83-2);

- Pesticide will be applied to crops where human tasks such as cultivation, pruning, harvesting, etc. will involve post-application exposure to pesticide residues; or

- Pesticide will be applied to nonagricultural outdoor sites such as home lawns where human exposure would occur; or

- Pesticide will be applied to indoor sites, domestic, industrial, or agricultural, where human post-application exposure could occur (note: this would require the development of inhalation exposure data such as indoor or personal air monitoring data as well as indoor surface residue dissipation data and activity dependent transfer analysis data necessary to estimate dermal exposure).

### 1.4.2 Waivers

**General waiver.** An applicant for registration may request a waiver from the requirement to submit some or all of the data required by 40 CFR 158.390 and described in this subdivision provided that written evidence that such data are inapplicable to the specific pesticide or product are submitted. Detailed information on requesting waivers may be found at 40 CFR 158.45.

**Waiver for no substantial exposure.** The applicant may provide a description of sites and human reentry activities revealing that no substantial human exposure to pesticide residues can be reasonably foreseen. If the applicant also requests a waiver from the requirement to provide a reentry interval on a particular product label, the Agency will review the request and the descriptions submitted. If the Agency agrees with the submitted rationale, it will grant a waiver.

**Waiver for other specific reasons.** The applicant may request a waiver from submittal of certain data required by 40 CFR 158.390 and discussed in this subdivision, if evidence that specific properties or characteristics of the pesticide or product preclude the requirement for such data are submitted. Such properties or characteristics could include, but are not limited to, the composition, degradation rate, toxicity, and such other chemical and physical properties of a specific pesticide or product that are fundamentally different from the factors considered by the Agency in the establishment of the data requirements of 40 CFR 158.390.

### 1.4.3 Formulators' exemption

As provided by 40 CFR 158.50, an applicant for registration of an end-use product who purchases and legally uses a registered product to formulate the end-use product is not usually required to submit or cite data discussed in Series 875 - Group B. Such a purchased product must be registered and labeled for manufacturing use or for the same use as the end-use product being formulated by the applicant. This is consistent with the Congressional intent as set forth in sec. 3(c)(2)(D) of FIFRA, which provides that:

> "No applicant for registration of a pesticide who proposes to purchase a registered pesticide from another producer in order to formulate such purchased pesticide into the pesticide that is the subject of the application shall be required to: (i) submit or cite data pertaining to such purchased product; or (ii) offer to pay reasonable compensation otherwise required by [3(c)(1)(D) of FIFRA] for the use of any such data."

Because studies required by 40 CFR 158.390 and discussed in these Guidelines would ordinarily be conducted by the basic manufacturer, pesticide formulators would not often be expected to conduct such tests themselves to develop data to support their individual products. They may do so if they wish, but they may merely rely on data developed by the manufacturing use producer.

[TBA: Sentence on what happens when the basic registrant fails to support the chemical.]

**ISSUE: What about chronic effects not covered by TLV or PEL?**

**1.5 GENERAL STUDY DESIGN** [TBA: This section will present the factors that must be considered in designing a study. Topics will include: exposure scenarios, exposure duration.]

**1.6 GENERAL REPORTING REQUIREMENTS**

In brief, reporting of study results must follow the provisions described under the Good Laboratory Practices (GLP) at 40 CFR 160.185. Generally, the GLP provisions provide information on the format of submitted studies. Other formatting requirements are listed under the Data Requirements for Registration at 40 CFR 158.32. Units of measurement should be in the metric system.

**1.7 COORDINATION WITH OTHER REQUIREMENTS IN 40 CFR PART 158**

The applicant should determine whether studies conducted to meet the requirements of 40 CFR 158.390 can be coordinated with studies required by other sections of 40 CFR 158, such as 158.640 discussed in Subdivision G (Product Performance); 158.540 discussed in Subdivision J (Hazard Evaluation: Nontarget target Plants); 158.290 discussed in Subdivision N (Chemistry Requirements: Environmental Fate), and 158.240 discussed in Subdivision O (Chemistry Requirements: Residue Chemistry). The studies should be coordinated with the data gathered to meet the requirements of 40 CFR 158.340 discussed in Subdivision F (Hazard Evaluation: Humans and Domestic Animals) and with information from Subdivision I (Experimental Use Permits). The applicant should also be cognizant of the labeling implications of this Series in relation to Subdivision H (Label Development). In addition, some of the studies might be usefully coordinated with those required for supporting a tolerance or temporary tolerance petition under the Federal Food, Drug and Cosmetic Act.

**1.8 TOXICITY DATA REQUIRED**

The toxicological data submitted by registration applicants to evaluate the toxicity of a pesticide to humans and domestic animals as required by 40 CFR 158.340 should be used to determine an allowable exposure level (AEL) for use in proposing reentry intervals. Those data are

described in the following sections of Subdivision F. Detailed information on using those data to determine the AEL is provided in Part D - Chapter 2: Calculation of Reentry Levels and Reentry Intervals of Series 875 Group B.

| | |
|---|---|
| Acute oral toxicity | Guideline 81-1 |
| Acute dermal toxicity | Guideline 81-2 |
| Acute inhalation toxicity | Guideline 81-3 |
| Primary eye irritation | Guideline 81-4 |
| Primary dermal irritation | Guideline 81-5 |
| Dermal sensitization | Guideline 81-6 |
| Acute delayed neurotoxicity | Guideline 81-7 |
| Subchronic oral toxicity | Guideline 82-1 |
| Subchronic dermal toxicity | Guideline 82-2,-3 |
| Subchronic inhalation toxicity | Guideline 82-4 |
| Subchronic neurotoxicity | Guideline 82-5 |
| Chronic toxicity | Guideline 83-1 |
| Oncogenicity | Guideline 83-2 |
| Teratogenicity | Guideline 83-3 |
| Repro. and fertility effects | Guideline 83-4 |
| Combined chronic tox./oncogen. | Guideline 83-5 |
| Mutagenicity | Guideline 84-2 |

# PART B - CHAPTER 2
# GUIDELINE 875.2100 - FOLIAR DISLODGABLE RESIDUE (FDR) DISSIPATION

## 2.1 INTRODUCTION

After application, pesticide active ingredients dissipate at rates dependent upon their physical chemical properties and use characteristics. Pesticide residues that remain in treated foliage (e.g., agricultural crops, turf, or gardens), and have a tendency to be dislodged on contact, may be a source of exposure among individuals who reenter treated areas. Residue dissipation studies are necessary to evaluate potential reentry exposures at various time intervals. Typically, these studies have been used to set reentry intervals for harvesters. Foliar dislodgable residues are particularly useful where a transfer coefficient is available to relate measured residues to dermal exposures for a particular crop and activity.

The requirements of 40 CFR 158 described in this section address measurements of pesticide residues that are deposited on and remain on foliar surfaces and pose a potential risk to individuals reentering those treated areas.

## 2.2 PURPOSE

Foliar dislodgable residue dissipation data are necessary to develop exposure/risk assessments and establish reentry intervals (REIs) for conditions where the pesticide is applied on the foliage of a crop. The following discussion provides guidance on selecting sampling intervals, sampling techniques, and residue dislodging techniques. In addition, guidance on appropriate QA/QC procedures, sample storage and analysis are provided.

## 2.3 WHEN REQUIRED

Dissipation data for dislodgeable residues on foliage are required when the toxicity and/or use criteria as stipulated in 40 CFR Part 158.390 have been met.

## 2.4 SAMPLE COLLECTION

**NOTE: See Part C (QA/QC) for background information (e.g., climate, sampling for maximum potential exposure) that must be considered in selecting study sites.**

**ISSUES: Are triplicate samples enough?**

### 2.4.1 Test Substance

Studies should be conducted using the typical end-use product(s) of the active ingredient. Pesticide products which could potentially result in the highest concentrations should be used unless adequate justification is provided. The end-use product should be applied at the maximum allowable rate using the equipment recommended for that end-use product and use scenario. If multiple applications are recommended for the product to be efficacious, then the minimum allowable time interval between applications should be used when conducting the study. The potential accumulation of residues from multiple applications should be considered.

It should be noted that there are end-use products whose metabolites or breakdown components of the active ingredient are of toxic or hazardous concern. These products should be addressed on a case-by-case basis.

### 2.4.2 Sites

- Number [TBA]
- Location [TBA]
- Substitution [TBA]

**ISSUE:** **OREB does not have a written policy on which crop scenarios may be substituted for other crop scenarios. For setting tolerances, EPA has established a policy on crops that may represent other crops (see 40 CFR 180.34). For instance, data generated for apples may be used to represent pears.**

**OREB is now exploring this issue.**

### 2.4.3 Method of Application [TBA]

### 2.4.4 Timing of Application [TBA]

### 2.4.5 Sampling Intervals

Sampling regimens should be designed to adequately characterize dislodgable-residue dissipation from leaf surfaces. Sampling intervals at the beginning of a study should be relatively short and then increase with time. For example, it may be appropriate to take samples as soon as the spray has dried or the dust has settled, and then at 4 hours, 1/2, 1, 2, 5, 7, 14, 21, 28, and 35 days after application. Baseline or control samples should also be taken immediately prior to the test chemical application. If residues are expected or measured on the control samples from prior applications or from subsequent applications to nearby sites, the sampling from a control site should continue at various concurrent intervals with the treated samples. If sample analyses reveal residues above the reentry level, sampling and analysis should continue until a level at or below the reentry level (restricted entry level) is measured for 2 or 3 consecutive samples.

### 2.4.6 Sampling Technique

A mechanical sampling device such as the Birkestrand leaf punch (Birkestrand Co., South El Monte, California) or some comparable device should be used depending on leaf size. The general procedure involved is presented in Iwata et al. (1977) and Knaak et al. (1989). Leaf punch samples should represent approximately 400 $cm^2$ of surface area (includes area on both sides of leaf) to ensure that the sample is representative of the study site. Insufficient surface area samples may not be representative of a study site because the sample procedures may have sampled either "hot" residue spots or areas where the residue levels were very low. If leaf size prevents using a leaf punch, sufficient numbers of samples should be collected to obtain approximately 400 $cm^2$ (or more) of leaf surface area (two sides) per replicate (Iwata et al. 1977).

Where possible, the diameter of the leaf punch should be about 1.8 to 2.5 cm. Using the largest diameter leaf punch possible, triplicate leaf samples, representing approximately 400 $cm^2$ of surface area per sample for double-sided leaves (minimum 40 randomly collected leaf discs), should be taken per test plot from various heights along a row (Knaak et al. 1989) or around a tree canopy (Gunther et al. 1973, Iwata et al. 1977) at every sampling interval. If leaf size requires the use of a smaller diameter punch, the number of leaf discs per sample must be increased commensurately to maintain the same approximate leaf area per sample. The cutting edge of the sampler must be cleaned between each replicate sample to minimize the potential for cross contamination.

For leaves that are not large enough for leaf punch sampling (i.e. turf), valid alternative means for relating residue level to leaf surface area must be utilized. One example would be to generate a relationship between mass of leaf samples and surface area. In situations where determining the leaf surface is not practical, reporting residue levels based on ground surface area or sample weight is permissible. Sufficient documentation must be submitted to the Agency to enable it to judge the validity of the method. For detailed information on lawn and turf sampling, see Chapter 5.

### 2.4.7 Other Sampling Considerations [TBA]

### 2.4.8 Dislodging Solutions

To remove any dislodgable residues from the sampled leaf surfaces prior to analysis, a residue dislodging solution such as the surfactant solution of sodium dioctylsulfosuccinic acid (American Cyanamid's Sur-Ten, four drops of a diluted 1:50 in water in 100 mL water, or similar products such as aqueous dilutions of Aerosol OT-75 or NEKAL WT-27) should be utilized, as described by Iwata, et al. (1977). This procedure, when coupled with an appropriate transfer coefficient, produces a reasonable estimate of the dislodgable pesticide residue that may be transferred by contact to a worker's skin. Applicants are advised to adhere as closely as possible to the Iwata et al. (1977) methodology. Sample residues should be dislodged (i.e., leaf discs washed with surfactant solution) as soon as possible after collection (i.e., preferably in the field within 2 hours of collection), unless the investigator can demonstrate that longer storage periods do not alter the proportion of the dislodgable residues present on freshly collected foliage. The procedure outlined by Iwata et al. (1977) should serve as the standard method, i.e., mechanically shaking at least 100 mL of the dislodging solution with the foliage sample for approximately 30 minutes.

## 2.5 SAMPLE STORAGE

Appropriate measures for maintaining sample integrity in the field, as well as during transmittal to the laboratory and storage prior to analysis should be utilized. These include, but are not limited to, using airtight storage containers that will not adsorb residues, refrigerating or freezing samples, and providing protection from direct sunlight. See Part C for further details on sample storage.

## 2.6 SAMPLE ANALYSIS

Pesticide residues should be dislodged from leaves as described above (Section 2.4.8). Suitable methods for extraction, cleanup, separation, and quantification should be validated and utilized for the parent pesticide and any environmental transformation products of interest to the Agency with respect to toxicity. (See Part C for details.) Laboratory and field recovery experiments must be conducted to ensure the stability of the active ingredient (and metabolite) in the dislodging solution. See Part C for further details on sample analysis.

## 2.7 CALCULATING DISSIPATION RATES

Refer to Part D of this document for a description of the calculations needed for estimating dissipation rates for foliar dislodgable residues.

## 2.8 DATA PRESENTATION

Analytical results are to be presented in terms of milligrams or micrograms of residue per square centimeter of leaf surface (mg or $\mu g/cm^2$). All calculations are to be based on double-sided leaves or an equivalent total sample surface area for samples like pine needles or grass. Refer to Appendix I for information on Data Reporting.

## REFERENCES FOR CHAPTER 2

Gunther F.A., Westlake W.E., Barkley J.H., Winterlin W., and Langbehn L. 1973. Establishing dislodgable pesticide residues on food. Bull. Environ. Contam. and Toxicol. 9:243-249.

Iwata Y., Spear R.C., Knaak J.B., Foster R.J. 1977. Worker reentry into pesticide-treated crops. I. Procedure for the determination of dislodgable residues on foliage. Bull. Environ. Contam. and Toxicol. 18: 649-655.

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# PART B - CHAPTER 3
# GUIDELINE 875.2200 - SOIL RESIDUE DISSIPATION (SRD)

## 3.1 INTRODUCTION

Whenever a pesticide or its degradation products are toxic and they are deposited on, incorporated into, or diffuse into soil at the application site, and the potential for exposure exists due to contact with of soil, such exposure should be quantified. Soil can be a significant source of exposure for activities involving work in soil or in close proximity to it (i.e., harvesting root crops or mechanical cultivation).

## 3.2 PURPOSE

If exposure to soil is likely, soil residue dissipation data along with concurrent dermal exposure monitoring data may be necessary to develop exposure/risk assessments and establish reentry intervals (REIs). The following discussion provides guidance on selecting sampling intervals, sampling techniques, sampling locations, and soil preparation techniques. In addition, guidance on appropriate QA/QC procedures, sample storage and analysis are provided.

## 3.3 WHEN REQUIRED

Data for the dissipation of residues on soil are required when the criteria as stipulated in 40 CFR Part 158.390 have been met.

## 3.4 SAMPLE COLLECTION

**NOTE: See Part C (QA/QC) for background information (e.g., climate, sampling for maximum potential exposure) that must be considered in selecting study sites.**

**ISSUE: Are triplicate samples enough?**

### 3.4.1 Test Substance

Studies should be conducted using the typical end-use product(s) of the active ingredient. Pesticide products which could potentially result in the highest concentrations should be used unless adequate justification is provided. The end-use product should be applied at the maximum allowable rate using the equipment recommended for that end-use product and use scenario. If multiple applications are recommended for the product to be efficacious, then the minimum allowable time interval between applications should be used when conducting the study. The potential accumulation of residues from multiple applications should be considered.

It should be noted that there are end-use products whose metabolites or breakdown components of the active ingredient are of toxic or hazardous concern. These products should be addressed on a case-by-case basis.

### 3.4.2 Sites

- Number [TBA]
- Location [TBA]
- Substitution [TBA]

### 3.4.3 Method of Application [TBA]

### 3.4.4 Timing of Application [TBA]

### 3.4.5 Sampling Intervals

Sampling regimens should be designed to adequately characterize residue dissipation from soil. Sampling intervals at the beginning of a study should be relatively short and then increase with time. For example, it may be appropriate to take samples as soon as the spray has dried or the dust has settled, and then at 1/2, 1, 2, 5, 7, 14, 21, 28, and 35 days after application. Baseline or control samples should also be taken immediately prior to the test application and from a control site at various concurrent intervals with the field samples. If sample analyses reveal residues above the reentry level, sampling and analysis should continue until a level at or below the reentry level (restricted entry level) is measured for 2 or 3 consecutive samplings.

### 3.4.6 Sampling Technique

Soils should be collected from the surface layer (not more than the upper 1 cm) in all test plots. Appropriate sampling techniques include sweeping surface soil dusts or excavation of soil from the upper 1 cm layer, using templates as described by Berck et al. (1981) and Zweig et al. (1985), respectively. The vacuuming method described by Spencer et al. (1977) is acceptable for sampling surface soil dust.

Triplicate samples should be taken from areas where the maximum potential for exposure is anticipated. In other words, samples are to be collected from areas expected to have the highest residue levels (e.g., around the base at the drip line). Sampling devices shall be decontaminated to prevent cross contamination between each replicate sample.

Fine materials should be separated from soil samples without grinding to yield a particle size of 147 microns or less (e.g., 125 microns #120 mesh) for analysis. Larger materials tend to be problematic; therefore, they are not to be retained for analysis. [TBA: A discussion of why larger materials are problematic.] A mesh screen can be used to sieve fine materials away from more coarse components. Soil samples should be sieved either immediately after collection or after thawing but while still partially frozen yet malleable or workable. Aliquots of the fine materials should also be dried to determine the percent water in each sample.

### 3.4.7 Other Sampling Considerations [TBA]

## 3.5 SAMPLE STORAGE

Appropriate measures for maintaining sample integrity in the field, as well as during transmittal to the laboratory and storage prior to analysis should be utilized. These include, but are not limited to, using airtight storage containers that will not adsorb residues, refrigerating or freezing samples, and providing protection from direct sunlight. For more detailed information, see Part C.

## 3.6 SAMPLE ANALYSIS

Suitable methods for extraction, cleanup, separation, and quantification should be validated and utilized for the parent pesticide and any environmental transformation products of interest to the Agency with respect to toxicity (see Part C for details). Examples of the latter include the various oxon analogs of phosphorothionate insecticides and the MBC conversion product of benomyl.

Analytical sensitivity must be low enough to describe residue dissipation over at least the portion of the proposed reentry interval during which soil residues contribute substantially to the reentry hazard. Whether wet or dried soil was analyzed must also be reported, along with the measured percent moisture.

## 3.7 CALCULATING DISSIPATION RATES

Refer to Part D of this document for a description of the calculations needed for estimating dissipation rates for soil dislodgable residues.

## 3.8 DATA PRESENTATION

Residues are to be reported as parts per million (ppm) of dry soil and if appropriate in terms of micrograms per square centimeter ($\mu g/cm^2$) of the surface area from which the soil sample was obtained. The surface areas from which the samples were collected (e.g., 1 sq ft) should always be presented, along with the percent water or wet soil weight of each sample. For further details regarding data reporting, see Appendix I: Data Reporting Guidelines.

## REFERENCES FOR CHAPTER 3

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# PART B - CHAPTER 4
# GUIDELINE 875.2300 - INDOOR SURFACE RESIDUE (ISR) DISSIPATION

## 4.1 INTRODUCTION

Historically, concerns associated with the use of pesticides have focused primarily on agricultural environments. However, in recent years the use of pesticides in indoor and residential environments has escalated, initiating a cause for increased attention to pesticide exposures in these environments. It is estimated that over 90 percent of United States households use a variety of pesticides including disinfectants, insecticides and pet collars (Godish, 1985). This large percentage of pesticide usage warrants attention as most individuals spend a significant period of time indoors. It is estimated that on a daily basis an employed adult spends 15 hours per day at home and a small child spends 21 hours per day (on a daily basis the total time an individual spends indoors is approximately twenty-two hours) (Lewis, 1989) (Refer to Section 2.11, Activity Pattern Information)

As a result of increased concern and lack of knowledge regarding the nonoccupational use of pesticides, the EPA conducted the Nonoccupational Pesticide Exposure Study (NOPES), which measured the levels of 32 pesticides in residences. The study demonstrated that air levels of many pesticides were significantly higher indoors than outdoors (U.S. EPA, 1990). The Committee on Urban Pest Management noted that 5000 health-related incidents involving pesticides were reported occurring in homes in the U.S. from 1966 to 1979 (National Academy of Sciences, 1980). According to the National Center for Health Statistics (NCHS, 1982-1991), residential pesticide poisoning resulted in 97 deaths between 1980 -1988 (Appleton, 1993).

The scope of the indoor environment encompasses a variety of non-agricultural settings in which human activities or properties are threatened by pests such as insects, microbes, rodents, fungi or weeds. Examples of such areas where pest control is of interest are homes and apartments, greenhouses, farm buildings, health care facilities, schools and day care centers, and restaurants and food preparation establishments. Treated areas typically include the floors, carpets, furniture upholstery, cabinets, counter tops etc. of areas such as offices, kitchens, living rooms and bedrooms.

Indoor surface and airborne residues may be generated from a variety of pesticide uses such as foggers, broadcast spray applications, crack and crevice treatments, vapor strips, moth repellents, residual termiticides, pet products, disinfectants, and indoor plant applications. According to the National Research Council (1993), the active ingredients found in most household products are cholinesterase-inhibiting compounds (i.e., organophosphates or carbamates). These residential

pesticide products are primarily insecticides containing active ingredients such as chlorpyriphos, propoxur, diazinon, malathion, and DDVP.

Another concern has been expressed about exposures to preservatives found indoors. For example, studies conducted with pentachlorophenol (PCP), a wood preservative commonly used to treat logs for home construction in the United States, show measurable contamination of PCP in household dust and in blood samples of building occupants (Godish, 1985). Another consideration is the exposure to volatile compounds off-gassing from products used indoors (i.e., preservatives used in paints).

Outdoor-applied pesticides may also be tracked or transported indoors where they become a secondary source of exposure to the building occupants. Secondary sources of indoor exposures may occur from homeowner or commercially-applied lawn products (herbicides, insecticides, and fungicides); garden pesticides; agricultural or community spray drift; and fungicide-treated lumber. Transfer of lawn pesticides to indoor carpets by foot traffic was experimentally demonstrated by Nelson et al. (1988). Pesticides are used on playground equipment and in swimming pools to which children may potentially be exposed. Also, persons who come in contact with pesticides as a result of their occupation may transport pesticide residues into the home (i.e., work clothing washed with other clothing, children touching contaminated clothing, etc.). It has been noted that people who reside in close proximity to agricultural areas may be exposed to higher pesticide residues in the ambient air (Maybank et al., 1978). [TBA - Telone Exposure Assessment Methodology] Although EPA is cognizant of the existence of secondary exposure sources and the fact that humans, especially infants and children, are subject to these secondary sources, it recognizes that it is difficult to quantify these exposures due to limited data. Nevertheless, these secondary sources should not be overlooked when evaluating total human exposure.

Exposure to pesticides used in and around indoor and residential settings may occur via multiple routes of exposure – dermal, inhalation or non-dietary ingestion. Dermal post-application exposure results when the skin contacts contaminated dust or surfaces, such as carpets, vinyl tile flooring, counter tops, upholstery, etc. Humans may be exposed to dust, vapors and aerosols via the inhalation route (See Part B - Chapter 7 - Inhalation Exposure Monitoring for techniques used to assess inhalation exposure, including indoor exposure). Oral exposure (non-dietary ingestion) may result from hand-to-mouth or object-to-mouth activity (especially for children), or through the consumption of contaminated food (including contamination while preparing, serving, and eating meals and snacks), and ingestion of dust or soil (See Part B - Chapter 8 for information on non-dietary exposure assessment techniques).

Due to pesticide poisoning incidents involving children and the significant differences in the potential for pesticide exposures between adults and children, it is necessary to focus specific attention on the assessment of pesticide exposures to children. In 1992, data compiled from the Poison Control Centers indicated that approximately 63,000 exposures to pesticides occurred in children under the age of 6 years old (Litovitz and Holm, 1992). As previously mentioned, a large proportion of residential use pesticides are cholinesterase-inhibiting insecticides. These chemicals can produce effects such as drooling and frequent urination which may not be easily recognizable as resulting from pesticide intoxication because they resemble common behavioral patterns in children (Berteau et al., 1989).

As a follow-up to the NOPES study (which suggested house dust may be a potentially important source of exposure for infants and toddlers), the EPA conducted the Household Infant Pesticide Exposure Study (HIPES). HIPES (now referred to as "Methods to Monitor Potential Exposure of Young Children to Pesticides in the Residential Environment") was conducted to evaluate methods which can be utilized in monitoring infant and toddler exposure to pesticides in the home, and to obtain preliminary data for assessing inhalation and non-dietary ingestion as a route of exposure for infants and toddlers (Lewis, 1991). The study demonstrated that 23 of the 31 targeted pesticides were detected, 20 of which were detected in house dust.

Fenske et al. (1990) measured chlorpyrifos concentrations in a carpeted apartment following treatment and found that the chlorpyrifos vapors measured in the infant's breathing zone (25 cm above the carpet) were significantly higher than in the sitting adult's breathing zone. It was suggested that although open windows provided dilution of air 1 m above the carpet, the treated carpet was a source of volatilized chlorpyrifos and concentrations near the floor were not as diluted (Fenske, et al. 1990). This is a concern for infants and toddlers who may come into contact with these residues when crawling or playing on the floor.

The exposure potential for children (inclusive of infants and toddlers) to indoor pesticides is greater than for adults because of several physiological, behavioral and metabolic factors. The following are some examples:

- Children have a higher surface area to body weight ratio than adults;
- The rate at which air is respired in children is less than adults;
- Children spend a significant amount of time crawling, playing or lying on the floor; consequently, pesticides may be absorbed by exposed skin if the contacted surface is contaminated.

- Children have increased mouthing activity and a lesser awareness of hygiene (i.e., eating food that has been dropped onto the floor, not washing hands after playing in dirt/soil) and as a result, it has been estimated that the risk of exposure to indoor and outdoor contaminants in soil and dust may be up to 12 times higher for children than adults (Hawley, 1985);
- The breathing zone for children is usually closer to the floor than adults;
- Infants may wear less clothing than adults while at home, i.e., wearing a diaper while crawling on the carpet, resulting in a greater surface area for potential exposure; and
- Children, particularly infants, spend more time in the home than adults.

[TBA: A comparison chart]

These factors along with other metabolic parameters and the stages of growth and development may make children more susceptible to passive indoor and residential exposures. It should be noted that knowledge in this area of exposure science is deficient and substantial research is required if exposures to this segment of the population are to be adequately assessed.

## 4.2 PURPOSE

The purpose of this section of the guidelines is to provide interim guidance for measuring indoor surface and airborne residues in indoor environments following pesticide application. Indoor surface and airborne residue data are necessary for EPA to estimate exposure to the general population. Many of the regulatory decisions made by EPA are based on the quantitative assessment of risk to human health. The indoor exposure monitoring measurements will be utilized in the exposure assessment, which is an integral component of EPA's risk assessment. As required by the FIFRA, 1988 (as Amended), it is the responsibility of the registrant to demonstrate that the pesticide, when used in accordance with label requirements, will pose no unreasonable risk to human health or the environment. The submission of actual data will reduce the uncertainty used in exposure assessments and improve the Agency's ability to accurately characterize risk and variability.

In addition, indoor surface residue data are necessary to quantify the transfer of dislodgable residues from surfaces to the skin. If indoor surface residue measurements are collected concurrently with human exposure measurements, a transfer coefficient may be determined that will estimate the amount of surface area that an individual contacts per unit time for the activity monitored.

Further research is needed to adequately assess exposure to pesticide products employed in indoor and residential environments. As research efforts progress, this section of the guideline will be revised accordingly.

[TBA: Specific ORD research that applies]

## 4.3 WHEN REQUIRED

Indoor surface residue data are required when the toxicity and/or use criteria as stipulated in 40 CFR Part 158.390 are fulfilled.

## 4.4 SAMPLE COLLECTION

**NOTE: See Part C (QA/QC) for background information (e.g., climate, sampling for maximum potential exposure) that must be considered in selecting study sites.**

### 4.4.1 Test-substance

Studies should be conducted using the typical end-use product(s) of the active ingredient. Pesticide products which could potentially result in the highest concentrations of indoor surface and/or airborne residues should be used unless adequate justification is provided. The end-use product should be applied at the maximum allowable rate using the equipment recommended for that end-use product and use scenario. If multiple applications are recommended for the product to be efficacious, then the minimum allowable time interval between applications should be used when conducting the study. The potential accumulation of residues from multiple applications should be considered.

It should be noted that there are end-use products whose metabolites or breakdown components of the active ingredient are of toxic or hazardous concern. These products should be addressed on a case-by-case basis.

### 4.4.2 Sites for Conduct of Tests

- Number - It is recommended that a minimum of (XXX) representative sites (i.e., rooms) be utilized for exposure monitoring;
- Location - The sites chosen (i.e., sampling locations within buildings, within rooms, and between rooms) should be representative of those typically treated with the pesticide, and the environmental conditions expected in the intended use area. Variability in the surface types (i.e., stain-resistant carpet, hardwood flooring), surface conditions (i.e., old (worn), new), ventilation and air filtration, room size, etc. should also be considered; and
- Substitution - Indoor surface and airborne residue data from one site may be substituted for data from another site when surface characteristics and ambient conditions are similar.

ISSUE: Number of Sites?? Three has been the traditional number used.

### 4.4.3 Method of Application

There are several methods used in the application of indoor and residential pesticides. For example, pesticide foggers such as flea bombs; spot or crack and crevice treatments; vapor strips for flying insects; broadcast spray applications; moth repellents; termiticides; pet products such as flea collars, dips and shampoos; disinfectants; and indoor plant applications are among the most commonly used indoor pesticides. The application method typical for the selected product should be used. In many cases a product is labelled for several uses, in which case, initially, the use scenario representative of the highest risk due to exposure should be tested. Refer to Part C, Quality Assurance/Quality Control for additional information about application.

ISSUE: Would it be appropriate to discuss the preference of selecting one method over another when both are available (i.e., Fogger versus crack and crevice treatment)?

### 4.4.4 Timing of Application

Studies should be conducted under ambient conditions which are similar to those encountered during the intended use season. Ambient conditions (i.e., temperature, relative humidity, barometric pressure, ventilation etc.) should be monitored through out the course of the study. Ventilation, among other factors, affects the accumulation, decay, transformation, transport (between rooms and media), and transferability (from media to body) of airborne and surface residues; consequently, the time of application (i.e., summer versus winter) can impact the quantity of dislodgable indoor surface and airborne residues. For instance, studies have demonstrated that relatively nonpersistent insecticides will remain within structures protected from sunlight and ventilation for several weeks (Leidy et al., 1993). (Refer to Part C, Quality Assurance/Quality Control)

### 4.4.5 Sampling Considerations

[More detail TBA]

Indoor surface residue measurements should be collected for a sufficient duration at appropriate intervals necessary to characterize residue dissipation as a function of time to a level below that corresponding to the AEL. This is essential in determining if a reentry interval is needed. This can influence the registration/ reregistration of a product (i.e., establishment of a reentry interval for a residential product may result in a recommendation for product cancellation). It is recommended that a minimum of XXX be collected at each site at each time interval.

Surface sampling should be conducted in conjunction with air sampling. (Refer to Chapter 7.) A minimum of XXX air samples should be collected in each room at each designated time interval. Stationary air samplers should be placed inside and/or outside of the treated area as applicable. Air samples should be collected at 25 cm above the floor (infant's breathing zone) and at one other height; either a nominal seated height of 1 m or standing height of 180 cm should be chosen based on the nature of the residue and room ventilation. Control (untreated) samples should be collected from the test site prior to application of the pesticide. Sufficient fortified control samples (spikes) should be prepared at each sampling interval. These fortified controls should be packaged, transported, stored and analyzed concurrent with the indoor surface and/or inhalation residue samples. Refer to Part C, Quality Assurance/Quality Control for additional information about sampling.

ISSUE: Minimum number of replicates for indoor and airborne concentration measurements. Some industrial hygiene guidance demonstrates that less than 6 samples results in a large degree of uncertainty about the exposure distribution. Taking more than 10 samples provides additional refinement to the estimates but the marginal improvements are small compared to the cost associated with the additional samples (See Hawkins, N.C., et. al. "A Strategy for Occupational Exposure Assessments."

ISSUE: Number of post-application sample collection intervals and the duration of the kinetics study (e.g., 10 intervals over 35 days).

### 4.4.6 Sampling Techniques

Several methodologies of assessing exposures to pesticides used indoors and around residential settings have been developed. These guidelines will provide an overview of the current methodologies of measuring indoor pesticide surface or dislodgable residues, as expressed in the published literature. Research is relatively new and is continuing in the area of indoor/residential exposure monitoring, and any guidance provided herein should be considered interim. Due to the lack of sufficient data to adequately endorse a specific sampling technique, EPA will not require the performance of exposure studies using a specific technique, but a minimum acceptable criteria for conducting these studies will be provided. It will be at the discretion of the study investigator to select the methodology which is most suitable for measuring human exposure for the use(s) intended. In addition, the study investigator is encouraged to propose new methodology to estimate human exposure and to validate existing methods. However, it should be noted that the selected technique must satisfy specific performance criteria as detailed in Part C, Quality Assurance/Quality Control.

The following list briefly describes some of the sampling methodologies currently described in the literature. For a more detailed explanation of the sampling methodologies, refer to the EPA Document Number EPA 736-S-94-0001 entitled, "Methodologies for Assessing Residential Exposure to Pesticides", and published literature. It should be noted that for each of the subsequent sampling techniques, the residues should be transported on ice to the laboratory for extraction and analysis after sampling. (Refer to Part C, Quality Assurance/Quality Control.)

***Polyurethane Foam Rollers (PUF)*** - The Polyurethane Foam (PUF) roller sampler was designed to measure dislodgable residues from contaminated surfaces which a child may contact during various activities (i.e., crawling) (Hsu et al., 1990). A dry PUF ring (3" length, 3.5" outside diameter, 1.9" inside diameter) is secured on a 7.2 lb stainless steel roller (8" length x 2" outside diameter). The

PUF ring is rolled over a surface once in both directions at the rate of 10 cm/second, exerting a pressure of 7300 Pa, comparable to that of a toddler standing or crawling, (6900 Pa - crawling and 8600 Pa - standing). After the two rolls, the PUF ring is slit and removed from the roller for analysis. The exposed rollers must be carefully handled to avoid contamination. To simulate the moistness of human skin, the PUF may be moistened with water.

*Drag Sleds* - The Dow Drag Sled technique has been developed to estimate the transfer of pesticide from the contaminated surface to the skin (Vaccaro et al., 1991). The technique consists of dragging a weighted (8 pound) 3" x 3" plywood block on which a removable denim patch is attached. After dragging the sled once over a 3" x 4' carpet strip (sample area equal to one square foot) at 6-8 cm/second, the denim cloth is removed for analysis. Tape is used to indicate areas where samples have been taken so the same area is not sampled again. The denim pad is removed after each drag.

*Vacuum Cleaners* - In an effort to measure pesticides in house dusts, a potential reservoir or secondary source, a standard home vacuum cleaner was used to collect samples from four residential houses. Roberts and Camann (1989) used cotton gloves to sample pesticide-bearing dusts in and on carpets. The gloves and house dust were analyzed simultaneously to determine the reliability of the glove test in demonstrating the level of pesticide residues in house dust. In addition, a High Volume Surface Sampler (HSV3 – previous model HSV2) was designed to collect dust from carpets. It is a specially designed vacuum device with a stainless steel sampling train (Roberts et al., 1991). A cyclone with a cut-point of 5$\mu$m particle diameter at a flow rate of 20 cfm is used to separate the larger particles for collection.

*Coupons* - The "Gunther/Iwata" coupon approach is one of the methods used for sampling the amount of total dislodgable residues. Coupons simulating materials commonly found in indoor settings (i.e., carpet, tile, hardwood, glass, etc.) are placed near or on the surfaces that they represent. A sufficient number of coupons is placed at each location to provide triplicate samples for each sampling interval and field spikes. The coupons are collected at appropriate time intervals (i.e., before application, immediately after application, 2 hrs., etc.) and an appropriate solvent is used to extract residues. Clean forceps should be used to pick up each coupon to prevent contamination between coupons.

*California Cloth Roller* - A percale cotton/polyester bedsheet is placed on the surface and covered with a sheet of plastic (Ross et al., 1991). A foam covered roller is rolled over the plastic bedsheet ten times backward and forward without additional pressure. After 20 passes, the percale cloth is collected and analyzed.

***Wipe Samples*** - Residues which can be transferred from the treated surface as a result of contact can be measured using wipe sampling. This technique is conducted using moistened cotton gauze pads to sample a standardized area (e.g., one square foot). This is a relatively simple technique which can be conducted on a variety of surfaces. The number of times which the surface should be wiped is not consistent. For example, NACA recommends a single wipe in one direction using a weighted-block. A 1 kg lead weight is attached to the sampling pad to apply uniform pressure (Curry and Iyengar, 1992). Whereas, research has shown that when 2 wipes are done (sampled area wiped twice using two pads in two directions and applying maximum pressure by the hand) the second wipe can yield almost as much residue as the first wipe (Naffziger et al., 1985). To minimize variability in results certain factors should be considered (standardizing the sampling material, standardizing the area to be wiped, outlining the boundaries of the surface to be wiped with tape or a template, wiping the sample area once with firm even pressure, collecting samples in triplicate checking the moisture content of the wipe). As with the previous techniques, samples should be collected at sufficient intervals to establish a dissipation curve.

***Hand Press*** - The hand press method is similar to the wipe sampling technique with the difference being the sampling medium (hands (with or without gloves) versus cotton gauze pads). The palm of the hand (excluding fingers) is pressed sequentially over the designated testing area. This technique has also been used to validate the PUF roller technique (Hsu et al., 1990).

## 4.5 SAMPLE STORAGE

Indoor surface residue samples and extracts should be stored in a manner which will minimize the loss of pesticide between collection and analysis. Refer to Part C, Quality Assurance/Quality Control for additional information on storage of samples.

## 4.6 SAMPLE ANALYSIS

Dislodgable pesticide residues should be extracted from the sampling medium (i.e., denim weave cloth) as soon as possible. Laboratory and field recovery experiments should be conducted to ensure the stability of the active ingredient in the extracting solution and to determine the recovery rates for the active ingredient. Care should be taken not to contaminate samples (i.e., clean forceps after each sample). (Refer to Part C, Quality Assurance/Quality Control)

## 4.7 CALCULATING DISSIPATION RATES

Refer to Part D of this document for a description of the calculations needed for estimating dissipation rates for indoor surface residues.

## 4.8 DATA PRESENTATION

Indoor surface residues may be reported as mg or $\mu$g of pesticide active ingredient per $m^2$ (unit area) of surface area sampled. Refer to Appendix I: Data Reporting Guidelines for detailed information on data presentation.

**REFERENCES FOR CHAPTER 4 [To be completed]**

[References]

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# PART B - CHAPTER 5
# GUIDELINE 875.XXX - LAWN SURFACE RESIDUES/TURF DISLODGABLE RESIDUE DISSIPATION

## 5.1 INTRODUCTION

Each year, approximately 70 million pounds of pesticide active ingredients are applied to turf [TBA: Reference]. Of this quantity, an appreciable amount is used for private lawns treated by residents and/or the commercial lawn care industry. These statistics have generated considerable public concern over potential exposure and health effects, especially for children entering recently treated areas. In the past, EPA has evaluated exposures to turf pesticides by modifying methodologies used for agricultural workers. Due to the intensity of contact with crops by workers in the agricultural environment, it was believed that estimates of exposure to turf pesticides derived from agricultural contact rates would err on the side of caution. However, as private sector research on exposure to turf pesticides has progressed and public concern over exposure to children has escalated, EPA has recognized the need to revisit its approach.

Increasingly, data designed to better characterize exposure to turf pesticides will be required in the Registration, Reregistration, and Special Review processes. However, previous guidance on conducting reentry exposure studies (Subdivision K of the Pesticide Assessment Guidelines, October, 1984) lacked information on conducting these studies in the residential environment. Therefore, this section is intended to provide interim guidance for the development of reentry exposure data for turf pesticides. Recognizing that research in this field is currently underway, this section will be subject to revision. Additional final guidance is scheduled for 1997.

## 5.2 PURPOSE

Lawn surface residue measurements are necessary for exposure assessment and for calculating the dissipation rate of pesticide residues that are potentially available for exposure. As in the agricultural setting, tracking the dissipation of pesticide residues allows for the determination of appropriate reentry times. If the reentry times are excessive (i.e., more than X hours), it is unlikely that the pesticide can be used on residential turf. Further, for turf pesticides, tracking residue dissipation provides valuable information for posting and notification requirements, where applicable.

ISSUE: Feasibility of reentry intervals for residential settings.

## 5.3 WHEN REQUIRED

Lawn surface residue data are required when the conditions set forth in 40 CFR Part 158.390, Notes (1)(A, B, C, D, or E) have been met.

## 5.4 SAMPLE COLLECTION

NOTE: See Part C (QA/QC) for details on test-substance, sites for conduct of tests, substitution of sites, method of application and timing of application.

### 5.4.1 Test Substance

The test substance used for lawn surface residue measurements for a particular pesticide must be considered carefully. Pesticide products which could potentially lead to the highest concentrations of lawn surface residues should be used unless adequate justification is provided. Factors to consider include (but are not limited to): formulation, irrigation practices (i.e., "watering in"), and concentration of active ingredient after spray dilution. For example, several researchers have found that lawn surface residues are greater following applications of liquid formulations than after granular application. Therefore, for a pesticide available in several different formulations, a liquid formulation (e.g., emulsifiable concentrate) should be chosen for testing. Furthermore, it has been demonstrated that "watering in" immediately after application moves pesticide residues into the thatch where they are less available. Therefore, a product for which "watering in" is not prescribed for efficacy should be used for testing. Similar to "watering in," applying a pesticide in a large volume of water may carry the residues into the thatch. Therefore, products which can be applied in a minimal amount of water should be used.

**ISSUE: Effect of "watering in." Also, even if it's on the label, does this practice routinely take place? What about the effects of regional differences in types of grass and climate (i.e., relative humidity and frequency of watering?**

Whatever products are chosen for testing, they should be applied at the maximum label rate and, where multiple applications are recommended, the minimum time interval between applications should be used. Finally, the minimum volume of diluent recommended on the label should be used.

### 5.4.2 Sites for Conduct of Tests

- Number - Studies should be conducted at a minimum of XX sites.
- Location - Sites should be representative of the climatic conditions expected in the intended use area and during the intended use season. In addition, sites should be representative with respect to turf species and density;
- Substitution - In certain cases, data from one site (when available) may be substituted for data from another site when surface characteristics are generally similar or nearly identical.

**ISSUE: How many samples are necessary to represent the surface; how large an area needs to be samples?**

### 5.4.3 Method of Application

The application method/equipment typical for the selected test substance should be used. Further, the application method/equipment typical for the intended end user (private resident versus commercial lawn care applicator) should be used.

As stated previously, the label maximum application rate must be used with the minimum time interval between multiple applications. Spray applications should be conducted using a minimal volume of diluent.

### 5.4.4 Timing of Application

As stated previously, the testing should be conducted during the intended use season or under climatic conditions that are essentially identical to those encountered during the intended use season. Weather forecasts should be studied to avoid initiating the testing immediately (e.g., 24 hours) before a precipitation event.

### 5.4.5 Sampling Considerations

In order to develop dissipation curves, lawn surface residue samples should be collected over an appropriate period of time. The first samples should be taken immediately after pesticide application (time 0 samples). The time intervals for the sampling scheme should be relatively short in the beginning and should lengthen as the study progresses. At each sampling interval, sufficient samples [TBA: number of samples] should be collected from multiple regions within the area of treated turf to account for differences in turf density, pesticide application variation, and environmental factors. In addition, control or background samples should be collected from the test plot prior to application of the test substance. Sufficient control samples should be collected so that fortified controls (spikes) can be prepared at each sampling interval. These fortified controls should be packaged, transported, stored, and analyzed concurrent with the lawn surface residue samples. For detailed information on QA/QC considerations, refer to Part C, Quality Assurance/Quality Control.

### 5.4.6 Sampling Techniques

The measurement of lawn surface residues is a relatively new area in the field of exposure assessment. The various techniques that have been employed by researchers since the early 1980's are mostly modifications of agricultural dislodgable residue techniques or techniques being developed for indoor surface sampling. Presently, EPA does not have sufficient information to recommend one sampling technique as a better measure of human exposure over the others. Therefore, as interim guidance, the Agency will briefly describe all available techniques and leave selection of a technique to the study investigator. Study investigators should be aware; however, that because method research is continuing, a study of the most recent published literature should be conducted before selecting a particular method. Study investigators will also need to consider that the selected method must satisfy specific performance criteria as detailed in Part C, Quality Assurance/ Quality Control.

The following is a brief description of each of the available methods. Detailed descriptions of these methods may be found in the published literature and in "Methodologies for Assessing Residential Exposure to Pesticides," (EPA 736-S-94-0001).

***Dislodgable Residue Technique*** - In the Dislodgable Residue Technique, grass clippings are obtained either directly from the treated plot or from a turf plug or core sample that has been obtained from the treated plot. The grass clipping samples are immediately stored on ice and then transported to the laboratory where they are weighed and then extracted by washing multiple times using a detergent/surfactant solution (e.g., 0.2 ml of 2 percent Sur-Ten Solution in 50 ml of water). Prior to the study, multiple grass clipping samples must be obtained from the test plot in order to establish a correlation between leaf surface area and weight. This correlation is established by weighing grass clippings that have been placed on a template of known surface area. Multiple surface areas (and therefore, multiple weights) must be tested to establish the correlation. The weights tested should bracket the anticipated sample size for the dislodgable residue testing. While determining the weight/surface area correlation, it may be necessary to correct for moisture losses occurring while grass leaves are being arranged on the templates. Refer to Part B - Chapter 2 for further information on foliar dislodgable residue dissipation study techniques.

ISSUE: Should a discussion of sampling thatch and soil be inserted at this point? Reference Chapter 3 for soil sampling.

***Cheese Cloth Wipe Technique*** - There are various approaches to wipe techniques for determining lawn surface residues. One technique described in the published literature involves a person scuffling forward and backward over a designated area of treated turf. More specifically, the sampler dons a pair of boots. The boots are then covered; first with protective plastic and then with multiple layers of cheese cloth that have been moistened with distilled water. The sampler then scuffles forward and backward over a 1 $m^2$ area for a specified amount of time (e.g., 1 minute). The cheese cloth is then removed from the sampler, the excess, unexposed material is cut away, and the remainder is transported, on ice, to the laboratory for extraction and analysis.

***Polyurethane Foam Roller Technique*** - The Polyurethane Foam Roller (PUF roller) device was developed to simulate the contact of a child's skin with a contaminated surface. Originally, the device was designed and tested on indoor surfaces (e.g., vinyl flooring). More recently, the design of the PUF roller has been altered to facilitate use on turf. In general, the PUF roller device consists of a PUF ring (8.9 cm outside diameter x 8 cm long) that is fitted around an aluminum or stainless steel

roller. This roller is attached to the end of a wheeled, forked handle. The device is weighted (via the stainless steel roller or weights attached to the forked handle) in order to exert a pressure of 7300 Pa while rolling (approximating the pressure of a crawling or standing child). The roller is pushed over a specified area of treated turf to sample for surface residues. After sampling, the PUF ring is transported, on ice, to the laboratory for extraction and analysis.

***California Cloth Roller*** - As is the case for the PUF roller, the California Cloth roller was originally designed to measure residues that may be dislodged by a child in contact with indoor surfaces. However, this sampling technique may be applied to turf with minimal modifications. In general, a sheet of percale cotton/polyester cloth is placed over a specified area of the treated lawn. A sheet of protective plastic is then placed over the cloth. When the sheets are in place, a weighted foam covered roller (similar to a baker's rolling pin) is rolled over the entire covered area 10 times. The percale cloth is then collected and transported to the laboratory, on ice, for extraction and analysis.

***Drag Sled Technique*** - As with the two roller techniques, the drag sled method (also called the Dow sled) was originally designed for sampling indoor surfaces. However, it has also found application in outdoor grassy areas. This technique consists of dragging a weighted plywood block through a fixed area of treated turf. The block is 9 $in^2$ in area and contains a removable denim pad attached to the underneath side. The weight placed on the block (usually a lead ball) can be varied but the original testing (as with the roller techniques) has focused on the pressure exerted by a crawling or standing child. After sampling, the denim pad is removed and transported, on ice, to the laboratory for extraction and analysis.

As previously stated, the Agency cannot recommend one technique over another at the present time. However, with the research currently underway, the Agency will continually improve its ability to discuss the pros, cons, and uncertainties associated with each method. For example, recent comparisons (research to be published) of several of the above methods have indicated that the drag sled may remove more pesticide residue from a surface (floors) than the PUF roller and both techniques may remove more residue than human skin. During this study, logistic problems with the California Cloth Roller were noted. As research on the above methods (especially as they apply to lawn surface residue sampling) is an ongoing effort within EPA and the chemical industry, the importance of reviewing the most recent published literature before selecting a method cannot be over emphasized.

**ISSUE: Should a discussion of track-in be inserted here?**

## 5.5 SAMPLE STORAGE

Lawn surface residue samples and extracts may be stored in a manner which will minimize deterioration if appropriate QA/QC samples are prepared (see Part C, Quality Assurance/Quality Control).

## 5.6 SAMPLE ANALYSIS

Dislodgable pesticide residues should be extracted from grass clipping and other sampling materials (cheese cloth, PUF, denim, . . .) as soon as possible. Appropriate clean up procedures should be applied to all extracts and the pesticide residues quantified by the best available method. Control samples should be prepared for each step of the analytical process (extraction, clean up, and analysis) to check for contamination, interferences, and/or loss of analyte (see Part C, Quality Assurance/Quality Control).

## 5.7 CALCULATING DISSIPATION RATES

Refer to Part D of this document for a description of the calculations needed for estimating dissipation rates for lawn surface residues.

## 5.8 DATA PRESENTATION

Lawn surface residues should be reported as mg or $\mu$g of pesticide active ingredient per $m^2$ or $cm^2$ of lawn sampled. These data should be reported in tabular form for each sampling interval. In addition, the best fit dissipation curve should be plotted (typically log-linear) with lawn surface residues presented on the Y-axis and time on the X-axis. Also, if the dislodgable residue technique is used, the weights of various surface areas of grass clippings should be reported in tabular form followed by the regression analysis conducted to establish the surface area to weight correlation.

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# PART B - CHAPTER 6
# GUIDELINE 875.2400 - MEASUREMENT OF DERMAL EXPOSURE

## 6.1 INTRODUCTION [TBA]

## 6.2 PURPOSE

Measurement of dermal exposure using passive dosimetry techniques is necessary to estimate dermal dose. In addition, dermal exposure data may be used to calculate transfer coefficients when monitored concurrently with dislodgeable residue data. Dermal exposure data and dislodgeable residue data should be collected for the same application/site. Each of these studies should be viewed as a component of an exposure study.

## 6.3 WHEN REQUIRED

Exposure criteria are met if there is a high likelihood of dermal exposure among persons who enter treated sites. Dermal exposure can arise from contact with treated vegetation, soil, or other surfaces.

> ISSUE: Should dermal exposure data always be required to be monitored concurrently when dislodgable residue data are collected?

## 6.4 SAMPLE COLLECTION METHODS [TBA: Discussion on pros and cons of the various methods]

**ISSUE: Should the Agency base its assessments on exposure outside of clothing or dose inside of clothing (or require both sets of data). The locations of dosimeters will depend on that decision.**

**ISSUE: Should all methods be considered to be of equal validity? If not, what guidance should be provided by the Agency?**

### 6.4.1 Patch Dermal Dosimeter

**ISSUE: For post-application exposure studies, do we need to distinguish between dust and liquid?**

A comprehensive review of the "patch" sampling methodology is available in Durham and Wolfe (1962), Wolfe (1976), and Davis (1980).

**Liquids:** Pads to be used for estimating dermal exposure to liquids may be constructed from papermaking pulp or a similar material, approximately 1 mm thick. Hereafter, this material will be referred to as alpha-cellulose. A good grade of alpha-cellulose will absorb a considerable amount of spray without disintegrating. Typically, it should not require preextraction to remove substances that interfere with residue analysis. This should, however, be determined before exposure tests using such pads begin. Acetanier P-FA (produced by ITT Rayonier, Incorporated) has been found to be satisfactory for this use. It is available only in 500- pound bales, but 4-pound samples of 10-inch square sheets are available for free (shipping not included) if an investigator wishes to compare it to other potential dermal dosimeter materials before choosing an appropriate pad material. Another material, that is satisfactory and more readily available in small lots, is preparative chromatography paper (17 Chrom), available in sheets from Whatman Incorporated. [TBA - Paragraph on the construction of patches for solid formulations.]

**Attachment and location of patches:** Pads should be attached, according to the exposure situation, to collect residues representative of those impinging on all regions of the body. Normally, a complete set for each exposure period will consist of 10 to 12 pads.

Pads should be attached to the outside of a worker's clothing or skin at the following locations: top of the shoulders, in back of the neck just below the lower edge of the collar, on the upper chest near the jugular notch, in back of the forearms, and in front of the thighs and lower legs. If the workers are engaged in some activity that is likely to result in extraordinary exposure to regions of the body that are not well represented by the usual pad locations, extra pads must be included to assess such exposure.

**ISSUE: What patch locations are appropriate (e.g., Subdivision U locations)?**

If the determination of actual penetration of work clothing is desired in the field study, additional pads can be attached under the worker's outer garments. Because workers often wear upper and lower outer garments made from different types of cloth, pads should also be attached under both garments, particularly in regions expected to receive maximum exposure. Care must be taken to ensure that any pads under clothing are near, but not covered by, pads on the outside of the clothing. Inside pads must be centered under seams as well as under unseamed material, because seams are often the areas of maximum penetration.

Pads may be attached to the skin or clothing using strips of masking tape along two edges of a pad. Some investigators have utilized specially designed harnesses or lightweight vests fitted with open-fronted pockets to hold the shoulder, chest, and back pads. Others have simply attached the pads to clothing with safety pins. These alternative attachment methods have been used successfully and are acceptable. The pads should be evaluated for potential contamination or losses from/to adhesives or holders.

**ISSUE: Are safety pins acceptable or should patches be taped to the skin?**

**Removal and handling of patches:** The procedure for handling exposed pads will depend on the stability of the pesticide(s) being studied. If the environmental data indicate that the pesticide is stable on moist exposure pads, then method (a) described below may be used. This method is advantageous because it requires less time-consuming manipulation of the exposed pads in the field.

If the material is found to be unstable or if the investigator elects not to perform the stability testing with moist pads, then method (b) should be employed. Method (b) may also be employed by choice.

(a) Stable residues. Place the pad in a prelabeled protective envelope or bag in a manner that avoids both cross-contamination with its holder and loss of contamination to the envelope. Group all bags containing exposed pads from one exposure of a single test subject together. Care should be taken to not contaminate the pads in handling.

(b) Unstable residues. Remove the tape or other material used to attach the pad to the test subject. If a dosimeter holder was not used, a template of a convenient size (25 $cm^2$ has been employed with success) may be needed to trim away material contaminated by the tape. Discard the protective backing and place the sample obtained in a wide-mouth jar or other appropriate container with a convenient volume of a suitable solvent. Other methods may be utilized if they are thoroughly documented in any submission and ensure the integrity of the samples from time of collection through analysis.

### 6.4.2 Whole Body Dosimetry

Total body dosimeters can be defined for the purposes of this document as any article of clothing (including socks) that is useful for monitoring dermal exposures. Several options are available to investigators. Standard total body dosimeters that are generally accepted include commercially available socks, long sleeved cotton tee shirts, and thermal underwear bottoms and tops (WHO, 1982; Abbott et al. 1987). Whole body "Union" type suits or lightweight coveralls are only marginally acceptable to measure exposure to clothing because penetration may occur when over-saturated. Investigators can select the particular articles of clothing from a wide variety of commercially available choices (e.g., sizes, suppliers, fabrics, elastic waist and ankle bands, etc.). Test subjects should wear total body dosimeters underneath typical work clothing.

Durability and availability should be considered by investigators as key issues when making selections. The standard dosimeters mentioned above should be capable of withstanding the mechanical forces (e.g., abrasion, snagging, tearing, etc.) exerted upon them as a result of the routine activities of the test subjects. Such post-application activities may include, but are not limited to, harvesting, maintenance operations, scouting, and planting. Physical durability is critical; if dosimeters are not intact at the end of an exposure interval, they are useless.

Availability of the garments selected as the total body dosimeters is another critical issue. Investigators must be careful to purchase sufficient quantities of garments to ensure that all dosimeters used in a study for measuring a particular type of exposure are of the same type (e.g., fabric blends) and from the same production lot, if possible. Obtaining dosimeters from the same or similar production lots is critical because it allows direct comparison of exposure results. Also, blanks and spiked samples should be used to evaluate contamination and recovery rates by production lot or batch. [TBA: reference]

**Required facilities:** The need for various facilities is self-evident in the discussion of whole body dosimeters. Test subjects must be afforded privacy when donning and removing the garments used as whole body dosimeters. Changing rooms must remain pesticide residue free during preparations for a field trial.

**Removal and sectioning of whole body suits:** Upon completion of an exposure interval, investigators must be careful to ensure the integrity of the samples. Proper sample collection procedures are critical. Investigators must be especially careful to avoid cross contamination of the exposed dosimeters. Typically, test subjects will be required to wear total body dosimeters underneath their normal work clothing to simulate the adsorptive/absorptive surfaces of bare skin protected by normal work clothing. Because this is the case, test subjects' normal work clothing will act as a protective "filter" through which the pesticide residues must pass prior to being retained by the dosimeter. As a result, test subjects' clothing must be treated by investigators as being a potential source of cross contamination. Investigators should develop sample collection procedures that minimize cross contamination. For example, to obtain a representative sample, test subjects may be asked to: (1) wear rubber gloves while removing their outer clothing; (2) discard the initial pair of rubber gloves and replace them with a clean pair; then (3) remove and section the total body dosimeter and place it into sample storage containers. At a minimum, whole body dosimeters must be sectioned by investigators into arms, torso, and legs.

The Agency recognizes that communication between test subjects and investigators is critical. This is never more apparent than when total body dosimeters are collected. Investigators, therefore, are required to be able to communicate clearly with test subjects. Interpreters should be available, if needed. As an example, total body dosimeter samples can easily be invalidated by cross contamination through several mechanisms, including but not limited to, the following examples: (1) test subject places sample on floor or chair in changing room; (2) test subject touches sample wearing rubber gloves used to remove outer clothing; or (3) outside surfaces (i.e., highest anticipated residue levels or nonprotected "skin") of test subject's outer clothing contact surfaces of dosimeter.

Postexposure changing facilities potentially can be highly contaminated with the pesticide(s) being studied because it is normal for test subjects to become dirty during their work activities. Contamination in changing facilities can occur when dirt and dusts retained by the workers' clothing and shoes are shaken off during sample collection procedures.

### 6.4.3 Hand Rinse/wash

ISSUE: Is handrinse/wash an acceptable sampling method (see Fenske and Lu, 1993)? With respect to monitoring hand exposure by hand rinses, the Agency is concerned about the inadequacy of associated field recovery techniques that initiate with spiking the rinsate. Such methodology fails to account for the ability of the dosimeter to trap or retain residues under a variety of environmental and/or physiological conditions. In addition, there is a failure to account for extraction efficiency of the solvent for removing residues from the hand. These deficiencies in generating adequate field recovery may produce an underestimation of actual hand exposure. The use of light weight cotton glove dosimeters, which may be directly spiked for field recovery determination, minimizes these problems when used for exposure monitoring. The Agency recommends that the registrant address these concerns when selecting and developing a hand exposure monitoring methodology.

ISSUE: Can wipe samples of the hands or other locations be used? What fluids should be used for these samples (note: use of solvents may increase dermal absorption).

ISSUE: Should removal efficiency studies be required?

Hand rinse sampling has been used historically for monitoring dermal hand exposure. Several types of solutions can be used, ranging from various types of aqueous surfactant solutions to neat isopropanol or ethanol. Investigators are free to select which types of solutions can be used. Investigators, however, must also be careful to consider the physical/chemical properties of the pesticide(s) being studied. For example, if a pesticide is water soluble, then an aqueous surfactant solution should be used as opposed to a neat alcohol. Sufficient quantities of hand rinse solutions should be prepared prior to field trials to avoid the chance of cross contamination during solution preparation in the field.

Water used for preparing aqueous solutions should be distilled and deionized; however, deionized or distilled water is sufficient if no alternatives exist. Water, used in the preparation of the aqueous surfactant solutions, may be purchased from commercial vendors. If commercial water is

used, investigators should try to obtain sufficient quantities from the same lot and supplier. If the water used in a study is tapwater purified by the performing laboratory (i.e., distilled and/or deionized), the equipment used to prepare the water must be described in the report. Investigators must be careful to use the same water source throughout all phases of a study. Several commercially available surfactants can be used to prepare hand rinse solutions (e.g., Sur-Ten, Aerosol OT-75, and Nekal WT-27). In general, hand rinse solutions should be diluted and otherwise prepared in a manner congruent with that described for the foliar dislodgable residue solutions (see Part B, Chapter 2).

Neat alcohols (e.g., isopropanol or ethanol) may also be used as hand rinse solutions. The same factors described above regarding the purchase/preparation of water for use in the aqueous hand rinse solutions also apply to alcohols. Investigators must use pesticide grade solvents if neat alcohols are to be used as hand rinse solutions.

**Sampling procedure:** Investigators use a wide array of techniques to obtain hand rinse samples. Some investigators opt for minimal mechanical agitation while others routinely employ it in their sampling methods. The Agency, however, recommends that mechanical agitation be used. Various procedures can be used to introduce agitation and therefore, theoretically, mechanical removal of residues from the skin's surfaces (Durham and Wolfe, 1962). These procedures can include, but are not limited to (1) a hand rinse procedure in which test subjects wash their hands in a routine fashion, or (2) a procedure in which hands are placed in individual bags containing a hand rinse solution and are then shaken vigorously for at least 2 minutes. All field procedures must be carefully documented in any submission to the Agency.

ISSUE: Add paragraph on appropriate sampling intervals (e.g., lunchtime).

### 6.4.4 Sampling Gloves

Gloves provide investigators with a better alternative technique for monitoring dermal hand exposure. As with the total body dosimeters described above, a wide variety of cloth gloves are commercially available. Several key issues must be considered by investigators when selecting a glove for use as a field dosimeter.

Durability and availability should be considered by investigators as key issues when making selections. Physical durability is critical; if the gloves are not intact at the end of an exposure interval, they are useless. The standard dosimeters should be capable of withstanding the mechanical forces (e.g., abrasion, snagging, tearing, etc.) exerted upon them as a result of the routine activities of the test subjects. Such post-application activities may include harvesting, maintenance operations, scouting, and planting. While white "pall bearers" gloves have a number of advantages as hand dosimeters, they lack the physical strength for some activities. Various knit nylon gloves (sometimes labelled "pickers gloves") are a more rugged alternative.

Availability of the selected gloves is another critical issue. Investigators must be careful to purchase sufficient quantities of gloves to ensure that all dosimeters used in a study for measuring a particular type of exposure are of the same type (e.g., fabric blends) and from the same production lot, if possible. Obtaining gloves from the same or similar production lots is essential because it allows direct comparison of exposure results.

**Removal of sampling gloves:** Upon completion of an exposure interval, investigators must be careful to ensure the integrity of the samples. Proper sample collection procedures are critical. Investigators must develop sample collection procedures that prevent cross contamination. For example, to obtain a representative sample, test subjects should peel the gloves away (i.e., turn inside out) from both hands, then place the gloves into a sample storage container(s).

| ISSUE: "Jazzercize" routine should be discussed as a monitoring technique. |
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### 6.4.5 Fluorescent Tracer Technique

Dermal exposure can be quantified directly and non-invasively by measuring deposition of fluorescent materials. The use of fluorescent compounds can be coupled with video imaging measurements to produce exposure estimates over virtually the entire body (Fenske et al., 1986a, 1986b). This requires pre- and post-exposure images of skin surfaces under longwave ultraviolet illumination, development of a standard curve relating dermal fluorescence to skin-deposited tracer, and chemical residue sampling to quantify the relationship between the tracer and the chemical substance of interest as they are deposited on skin. Advances in hardware and exposure quantification procedures have resulted in a second generation imaging system (Fenske et al., 1993). Imaging

analysis has been applied primarily to pesticide mixers and applicators (Fenske, 1988; Methner and Fenske, 1993a, 1993b), but has also been applied to workers handling treated lumber (Fenske et al., 1987) and to children contacting turf following pesticide applications (Black, 1993), and to greenhouse reentry workers (Archibald, 1993).

Ideally, this method can provide improved accuracy in dermal exposure assessment, since it measures actual skin loading levels. In practice, however, it has several important limitations: (1) use of a tracer requires the introduction of a foreign substance into the production system; (2) the relative transfer of the tracer and chemical substance of interest must be demonstrated during field investigations, (3) additional quality assurance steps may be required during field studies, including range-finding and the evaluation of potential tracer degradation due to sunlight; and (4) when protective clothing is worn, separate studies may be required to determine the relative fabric penetration of the tracer and the chemical substance of interest. In studies of protective clothing performance, patch sampling is likely to be more sensitive than video imaging, although not necessarily more accurate (Methner and Fenske, 1993a; Fenske, 1993).

## 6.5 SAMPLE STORAGE

Appropriate measures for maintaining sample integrity in the field, as well as during transmittal to the laboratory and storage prior to analysis should be utilized. These include, but are not limited to, using airtight storage containers that will not absorb residues, refrigerating or freezing samples, and providing protection from direct sunlight.

## 6.6 SAMPLE ANALYSIS

NOTE: Part C (QA/QC) contains a comprehensive review of sample analysis procedures.

## 6.7 DATA CALCULATIONS AND INTERPRETATION

ISSUE: The following items will be discussed in Part D.

A. Standard Body Surface Areas
B. Transfer Coefficient Calculations
C. REI Calculations
D. Fluorescent Tracer Interpretation [Fenske]
E. Use of recovery data to correct field sample residue levels

## 6.8 DATA PRESENTATION

[TBA]

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# PART B - CHAPTER 7
# GUIDELINE 875.2500 - INHALATION EXPOSURE MONITORING

## 7.1 INTRODUCTION

Post-application inhalation exposure to pesticides is of potential concern in a variety of use scenarios including, but not limited to, the following: typical agricultural uses, residential uses (indoors and turf), in commercial and industrial settings, and for various atypical pesticide use patterns. After application of a pesticide, the residues are available for distribution throughout the environment. Pesticide residues can become an inhalation hazard or risk to people who enter areas after an application through a variety of mechanisms. These mechanisms can be typically defined by: the environmental fate and transport characteristics of the pesticide active ingredient/end-use product; the ambient climatological conditions; the conditions of the application site (e.g., soil type); and target crop. Airborne pesticide residues can exist in the environment as one or a combination of three physical states/forms. These include the following: gas; vapor; and airborne particulates.

The quantification of airborne pesticide residues is the primary focus of this chapter. Additionally, the consideration of the physical/chemical properties of the specific pesticide is also of utmost importance. The discussion presented in this chapter provides specific guidance on the following: monitoring equipment; sampling media/holders; selection criteria for equipment; monitoring techniques; technique validation outside the scope of the QA/QC chapter; and field operations.

## 7.2 PURPOSE

The purpose of this chapter is to describe suggested techniques and strategies for quantifying potential inhalation exposure levels through either personal or area monitoring. In order to do this in an effective manner, any environmental fate/transport data should be utilized in the development of an effective sampling strategy. The resultant, potential inhalation exposure data are necessary to develop exposure and risk assessments for specific pesticide/end-use-product scenarios. Additionally, as a result of the risk assessments, Restricted-Entry Intervals (REIs) for pesticide labels are to be developed.

## 7.3 WHEN REQUIRED [TBA]

## 7.4 SAMPLE COLLECTION AND STORAGE METHODS

### 7.4.1 Monitoring Equipment

Several approaches are available for establishing potential inhalation exposure levels. These approaches can be classified based on the types of equipment that are available to an investigator and the nature of the exposure scenario. For example, it would be typical to monitor potential inhalation exposure during agricultural harvesting operations using a personal sampling pump, while establishing potential inhalation exposure levels in a treated room in a residence may lend itself to the use of a stationary monitoring device (area samples). Available types of monitoring equipment are described below.

**Personal Sampling Pumps:** Several brands of battery powered, personal monitoring pumps are considered to be satisfactory for use in estimating a worker's inhalation exposure. These pumps consist of a NiCad battery powered motor which operates a diaphragm pump for intervals averaging up to 8 hours. For the Agency to consider a particular type of pump acceptable, it must be capable of producing an airflow of at least 2 to 4 liters/min. Its batteries should also be capable of sustaining maximum airflow for at least 4 hours without being recharged. Acceptability should also be judged based on the ability of the pump to maintain a specified flow rate, within a specified tolerance (i.e., $\pm$ 10%) at the expected pressure drop across the filter and sampling cartridge (if used) for the full duration of sampling (with an increased pressure drop due to loading on the filter). The sample flow rate is only important if it will fail to collect a sufficient sample over a specified time period to exceed the quantifiable limit (QL) of the analytic finish. This can be calculated in advance to show the lower limit of detection for an air concentration given the flow rates, collection efficiency, and QL. Too high of a sample rate may result in sample losses or artifact formation. Note that several low flow pumps are commercially available (i.e., maximum average flow rates of $<1$ L/min); these will not be considered as acceptable alternatives for monitoring respiratory exposure to pesticides in an aerosol (mist, dust, or other particulate form). [TBA: Rationale for this]

**High Volume Pumps:** A typical example includes the model TF1A manufactured by Staplex, Inc. High volume air samplers consist of an electric powered fan that draws air through some type of filter (e.g., various filter fibers, polyurethane foam, or activated charcoal) at average flow rates of 20-50 $ft^3$/min (CFM). These should be used with caution so not to modify the sampled environment by scavenging/cleaning the air conditions. That use is probably not appropriate for residential settings.

**Passive Monitors:** Passive monitors such as the 3M badge (e.g., 3M Company Model 3500) are commonly used by industrial hygienists and other health and safety personnel to monitor ambient

levels of workplace gases and vapors. These should be used with caution, as they are only capable of collecting the vapor phase, and would miss residues in the aerosol phase or that are adsorbed onto particulate matter or resuspended dust. Also, diffusion-based systems may not be appropriate for stationary operation in locations with limited air flows due to the need for an adequate face velocity. The Agency does not object to investigators using this technology provided that extensive documentation and validation data are submitted. It is recommended that the manufacturers of these devices be consulted for technical assistance when validating uses of these devices.

**Alternate Technologies:** Investigators are encouraged to develop novel approaches for monitoring potential inhalation exposure levels and/or ambient air concentrations. Alternate technologies may consist of redefining the application of existing technologies or the development of a new technology appropriate for this purpose. Specific examples of an alternate technology may include: real-time gas chromatography; modification of various remote sensor technologies, commonly used in industrial safety engineering; or the use of immunoassay techniques. If investigators opt to use alternate technologies, they must provide thorough documentation to justify their adaptation/implementation of the chosen technique.

**7.4.2** Sampling Media/Holders [TBA: Pictures or figures of the various media]

Many devices are available for containing the different types of media used for entrapping pesticides during personal air monitoring. These devices range from spill-proof microimpingers equipped with membrane filters for separate collection of large particulates to simple glass tubes that contain solid sorbents. Most of these devices and their uses have been described by Linch (1974). Polyurethane foam plugs have recently become popular for monitoring pesticide exposure, and several types of devices to hold these plugs have been described by Lewis et al. (1980) and Davis et al. (1982). Filter cassettes may also be used for monitoring pesticide exposure, using a variety of filter membranes.

A host of different media are available for trapping pesticides in air. The most suitable media for a particular investigation will depend on the pesticide(s) being studied. Ideally, the media should entrap a high percentage of the pesticide(s) passing through it, and should allow the elution of a high percentage of the entrapped pesticide residues for analysis. The pesticide(s) should be recovered without any conversion to other reaction products, if possible. Also, the media should not significantly restrict airflow. Media that have proved effective for trapping pesticides have been reviewed by Van Dyk and Visweswariah (1975) and Lewis (1976). Examples include filters, sorbent tubes, various impinger solutions, polyurethane foam, and the XAD-2 sorbent which is used for many PAH applications. Different types of sampling media placed in series are acceptable (e.g., filter

cassette backed up by a sorbent-containing tube to trap vapors). This may be required because of the physical/chemical properties of the pesticide(s) being monitored. The registrant should present data to support the use of a method that will not collect both the vapor and aerosol phases (and residues on particulate matter). A backup tube should be the "standard approach" to prevent or determine if there are losses during the sampling.

**Sorbents:** A wide variety of sorbent resins are available for use as inhalation monitoring media. These sorbent tubes typically are small diameter glass tubes, approximately 10 cm in length, that are filled with resin and are open at both ends (i.e., to allow air flow through the resin). These devices are almost exclusively used in conjunction with a personal sampling pump. Commercially produced tubes are available with the following common resin types: XAD; Chromsorb; Tenax; Silica; Alumina; Charcoal; and Florisil (e.g., SKC and MSA). The wide variety of tube/resin combinations available make the selection and procurement of resins appropriate for specific pesticides relatively easy. Flow rates for these devices are typically on the order of 0.1 to 1 liters per minute (Lpm). Excessive flow rates can result in early breakthrough or low collection efficiency, which must be validated. Sample holders for these types of monitoring tubes are also readily available from the same manufacturers. Sample holders typically consist of a fitting for attachment to the flexible tubing of the personal sampling pump, rubber grommets to hold the tube in place and that allow air to flow through the tube, and an alligator type clip to affix the device to the test subject during sampling.

**Filters:** Filters (i.e., filter paper for the purposes of this guideline section, unless otherwise defined) are available from commercial sources. Filters can be utilized to trap airborne residues, using either personal monitoring pumps or high-volume stationary sampling devices. Commercially available filters are available in a wide variety of matrices. Common types include: cellulose, glass fiber, thin layers of polyurethane foam (PUF), and impregnated charcoal in a variety of thicknesses and dimensions (i.e., diameter/surface area). Filters for use in conjunction with personal sampling pumps typically have flow rates of 1 to 4 Lpm. Flow rates as high as 40 or 50 cfm can be used for filters with high-volume air samplers. Investigators typically do not have to develop a mechanism for attaching filters to the air samplers unless they make the filters themselves. For personal sampling, 37 mm filter cassettes are widely used and consist of a three piece plastic ring "sandwich" in which the filter resides. These devices can be used as open-faced (i.e., the actual diameter of the filter) or closed-faced (i.e., air flow constricted through a 4 mm diameter orifice which protrudes through the third piece of the filter cassette "sandwich"). [Note: When used as an open-faced device the third piece of the filter cassette is added after sampling to seal the cassette and is not utilized during sampling.] Filters are usually attached to the high volume air samplers using a manufactured threaded or snap-on arrangement.

**Polyurethane Foam (PUF):** PUF is a matrix that can come in several physical configurations. The commonly available plugs are similar to the resin tubes or flat pieces of filter paper described above (i.e., cylinder shaped PUF devices are typically 1 to 2 inches in diameter and 2 to 3 inches in length). [Note: PUF is described above for filters because in that application it is commonly used as a flat, thin piece of material through which air is drawn across the height, and not the diameter, of the sampler.] PUF devices are commonly used in both personal and stationary monitoring devices. These matrices are placed in some type of cylindrical holder which can either be in-line with other devices or open-faced. Air is drawn through the length of the matrix. Flow rates for personal sampling are typically 1 to 4 Lpm while flow rates for stationary samplers can be as high as 25 cfm.

**Particulate Sizing Device (e.g., cyclones):** In some instances the primary post-application inhalation hazard will be from airborne dusts/particulates generated when pesticides are adsorbed onto surfaces and then distributed by an environmental force (e.g., wind blows pesticide laden particles into air). Under conditions where inhalation exposure from dusts is possible and more likely than a gas or vapor exposure (e.g., strawberry or tomato harvesting in San Joaquin Valley), the Agency reserves the right to require that respirable dust levels be measured on a case-by-case basis. Respirable dusts (i.e., dust particles $< 10$ $\mu$m in aerodynamic diameter) can be separated from the total available dusts using a cyclone. The cyclone is a device that was developed based on the principles of momentum and centrifugal force. Airborne dust particles are drawn into a vertically positioned cylindrical apparatus where the airflow occurs in a circular motion. As dust particles move about the cylinder in a circular motion, the lighter particles (i.e., respirable dusts) move to the top and are collected on a filter paper contained in a cassette. The heavier particles drop to the bottom of the cylinder and are discarded. Total dust levels can be measured using these techniques.

Size separation is now often achieved using inertial impactors, rather than with cyclones. However, there is some question about the desirability to limit the size fraction too low, given the potential for ingestion of large particles that are trapped and cleared in the upper airways.

ISSUE: Should particulate samplers only be used by exception? What are sufficient reasons for using them?

**Trapping Solutions (e.g., impingers/diffusers):** The use of trapping solutions to capture airborne residues of specific chemicals is an accepted technique. Trapping solutions are placed in a impinger or diffuser and ambient air is drawn through the solution. As the bubbles pass through the solution, pesticide residues are dissolved into or otherwise held in solution. A variety of trapping solutions have been used. Some common examples include, but are not limited to, the following: ethylene glycol; weak acids/bases; common organic solvents (e.g., hexane, xylene and acetonitrile); and various buffer solutions. For inhalation exposure monitoring, these solutions are commonly used in conjunction with personal sampling pumps operating at flow rates near the 1 Lpm range. Solution holders typically consist of a simple (sometimes calibrated) glass cylinder fitted with a fritted glass or threaded plastic impinger which allows the sampled air to bubble through the trapping solution. Tubes are commonly 20 to 25 mL in volume and are filled to approximately 80 percent of their total volume during sampling to ensure that the sampled air will bubble through a sufficient volume of trapping solution. Additionally, these diffusers are commonly outfitted with a diffuser head that maximizes the amount of bubbles created as air is drawn through the trapping solution (i.e., flat piece with a multitude of frits in it through which the sampled air stream is pulled during pump operation). In contrast to their broad utility, they are subject to internal spillage (resulting in ingestion of the solution by the pump) and glass breakage, and must be used with care. Trapping solutions have limited applicability to the residential environment, given the potential for spilling solutions.

**Grab Sampling:** Grab sampling is not typically utilized for this type of ambient air monitoring. However, in rare instances it may prove to be useful. Grab sampling involves drawing a volume of air into a sample collection bag. The sample is retained and analyzed or residues are trapped on a sorbent and analyzed at a later date. Several sample collection bags are commercially available for the collection of these samples. They are of known volume and are typically made from some sort of polymeric material such as mylar or a high strength polyethylene. Flow rates are not applicable for these types of samples. Grab sampling is usually done over a very short period of time (even instantaneously), and represents only a brief snapshot of the exposure. This is in contrast with other sampling devices that collect samples over longer periods of time (e.g., hours).

**Alternate Technologies:** Investigators are encouraged to develop novel approaches for monitoring potential inhalation exposure levels and/or ambient air concentrations. Alternate technologies may consist of redefining the application of existing technologies or the development of a totally new technology appropriate for this purpose. Specific examples of an alternate technology may include: various novel textiles as filter devices; solid-phase extraction techniques; and sample collection tubes which can be placed in-line for virtually real-time GC analysis. If investigators opt for the use of alternate technologies, they must provide thorough documentation to justify their adaptation/implementation of the chosen technique.

### 7.4.3 Selection Criteria

Selecting a proper method for monitoring inhalation exposure depends on factors such as: (1) the typical agricultural and commercial practices involved, (2) the scenario that mimics the maximum potential for exposure, (3) the durability of the dosimeters, and (4) the trapping efficiency and chemical/physical properties of the pesticide; (5) airborne concentration; and (6) sampling duration.

**Cultural/Commercial Practices**: Understanding the conditions under which the pesticide is used and the practices associated with its use, enables the Agency to determine the monitoring methods. For example, an impinger may not be the best method for evaluating exposure for strawberry pickers because the work requires these individuals to repeatedly lean over. This would cause the impinger trapping solution to spill or be sucked into the personal sampling pump. On the other hand, impingers may be appropriate for certain tree fruit harvesters because they are not required to lean over. Submissions to the Agency should clearly document the typical agricultural and commercial practices associated with a pesticide's use.

**Maximum Exposure Scenario**: Determining the agricultural and commercial practices associated with a pesticide's use is necessary to define the maximum potential exposure scenario. The Agency requires that studies be performed using scenarios that present the maximum potential for exposure yet are still representative of typical agricultural and commercial practices. Maximum exposure scenarios are typically defined by specific sites or regions in which an operation is conducted for a particular use pattern (e.g., harvesting citrus fruits treated with an organophosphate insecticide may have higher associated exposure levels in California than Florida due to environmental differences or subtle differences in practice). The study scenario must, however, be representative of typical use patterns. Historically, it has been demonstrated that the dermal exposure route contributes more to total body burdens than the inhalation exposure route for activities in areas that have been treated with pesticides. As a result, most exposure scenarios should be defined by the potential for dermal exposure (See Part B: Chapter 6 and Part C: Quality Assurance/Quality Control). The maximum potential for exposure must be identified and used as the study scenario for all studies unless otherwise directed by the Agency for the anticipated major route of exposure. As an example of the selection of the major inhalation exposure scenario, consider a theoretical broad spectrum insecticide that is volatile and easily hydrolyses (i.e., the degradates are toxicologically insignificant) and is used to treat both pome (e.g., apples in Washington or Virginia) and citrus fruits (e.g., oranges in California). The maximum inhalation exposure potential for this scenario is the California citrus use for several reasons including: (1) the arid environment (i.e., dry and dusty) in which there is great potential for adsorption to fine dust particles that may be respirable, (2) more persistent residues due to the low humidity (in contrast to apple growing regions where humidity is typically high and

less hydrolysis is likely to occur), and (3) the typically warmer climate may contribute to higher airborne concentrations of the pesticide as more residues volatilize into the air.

**Durability of Sample Matrices:** Monitors must remain intact throughout the duration of an exposure interval to ensure the integrity of the sample. Monitors must be designed and used in a manner that is consistent with (1) the monitor's surviving the exposure interval intact (2) obtaining a representative sample, and (3) not interfering with the normal work functions of the test subjects. If a monitor should leak, spill, tear, or otherwise disintegrate during the exposure interval, the investigator should make every effort to preserve the sample, unless the integrity of the sample is compromised. If the sample is compromised, it must be identified as such and, in most cases, should be voided. For example, monitors can be reaffixed to clothing or replaced with a fresh, unexposed monitor as long as the appropriate notations are made in the study records.

**Selection Criteria Matrix:**

| | |
|---|---|
| **ISSUE: Additional information will be added here.** | |

### 7.4.4 Monitoring Techniques

Two basic techniques are available for monitoring inhalation exposure: personal and stationary or area sampling. Personal monitoring can be done using battery powered pumps or passive monitors. Stationary or area monitoring can be done using high volume air samplers, battery powered pumps, or passive monitors. These techniques are described below. Investigators must determine and justify their selections of specific sampling methods, the appropriate sampling medium, conditions for storage of samples, and analytical procedure. Investigators should make selections based largely on the pesticide(s) being studied.

**Personal Monitoring:** The Agency considers battery powered, personal monitoring pumps to be the most effective method for measuring respiratory exposure. Study protocols should typically be designed using this method unless otherwise indicated by the Agency. The sampler should be clipped to the collar so the intake is near the nose or mouth (or breathing zone) and the intake is oriented downward to avoid direct deposition.

**Passive monitors:** Can provide an alternative means of measuring inhalation exposures. The 3M Company, for example, manufactures passive monitors that have been validated for a variety of volatile chemicals including some pesticides. As a rule, however, passive monitors should not be used as the primary monitoring method unless: (1) a method involving the use of a personal sampling pump could not be validated, or (2) the Agency has been consulted. Passive monitor manufacturers will typically develop and validate protocols both for the use of their monitors while sampling (e.g., specification of exposure intervals) and for their analysis. These protocols must be adhered to and supplied with any submission to the Agency. Deviations from these protocols must be justified in subsequent submissions to the Agency. Whenever passive monitors are used, the Agency must be consulted prior to initiating the study to determine whether or not the proposed quality control regimen is acceptable.

**Stationary/Area Monitoring:** Area monitoring can provide useful information to the Agency. This information is especially helpful when attempting to correlate personal exposures and workplace environment airborne contaminant levels (i.e., to develop a predictive model). Area monitoring will be required by the Agency on a case-by-case basis. If area monitoring is required, high volume air samplers should be placed within the desired treated area. Samples should be collected in areas that are typical of the working environment of the test subjects. For example, if workers are reentering a treated field to harvest strawberries, samples should be collected from the center of that field and from at least four other locations, preferably at the cardinal compass points from the center location. Sample locations should be separated equidistantly from one another. The samplers should be spaced at equal distances along one or the other axis and from the field borders (see Figure 7-1).

ISSUE: Figure 7-1. Sample Locations to be added here.

ISSUE: Develop standard sample height criteria for indoor air sampling (e.g., 25 and 100 cm).

ISSUE: Need to determine where to sample on surfaces relative to the application(s), and if spatial samples are to be composited or analyzed independently to evaluate spatial variation as a function of application type.

Protocols should be designed to maximize the duration of the sampling interval. Airflow rates should be recorded at the initiation and termination of the sampling intervals, with the average being

used in all calculations. Intervals where the sampling process has been interrupted should be described in submissions to the Agency (e.g., fueling portable gasoline powered generators to operate air samplers, changing filters, checking flows, etc.). Note that the duration of the sample collection intervals is directly proportional to the breakthrough/volatilization capacity of the filter of choice. Additional sampling points may be required by the Agency on a case-by-case basis.

Personal sampling pumps can also be used to monitor airborne contaminant levels using a protocol similar to that described for the high volume air samplers. Personal sampling pumps are most effective for area monitoring when used in an indoor environment compared to the high volume air samplers because of their lower flow rate and the dilution factor associated with outdoor sampling. See the guidelines describing Personal Monitoring Using Battery Powered Pumps and Area Monitoring Using High Volume Air Samplers for further assistance in designing a study using battery powered pumps for area monitoring.

High volume air samplers are commercially available. The Agency recognizes that logistical support for these devices is difficult; in contrast to personal monitoring pumps, placement of high volume air samplers can be problematic. Prefield analytical method development will determine the maximum sampling interval for the type of filter selected. Study protocols should reflect these intervals. Air samplers should be operated as continuously as possible throughout any sampling interval. In other words, the length of the sampling intervals should be maximized.

Passive monitors can also be used to monitor volatile airborne contaminant levels using a protocol similar to that described for the high volume air samplers. Passive monitors are restricted to gaseous (gas or vapor phase) pestidices. Passive monitors will provide the best results when used to monitor for pesticide(s) for which they have been validated by the manufacturer since the manufacturers of these devices are typically more familiar with their characteristics. See the guidelines describing Personal Monitoring Using Passive Monitors and Area Monitoring Using High Volume Air Samplers above for further assistance in designing a study using passive monitors for area monitoring.

[TBA: Additional information will be added here concerning specific requirements for monitoring indoor, outdoor and atypical scenarios.]

### 7.4.5 Technique Validation

[TBA: include items not specifically in the scope of the QA/QC section.]

**Breakthrough/Volatilization Trials:** Development of an inhalation exposure monitoring method should include three phases: (1) selection of the types of monitor(s) to be considered for validation, based on literature review, Agency recommendations, experience, etc.; (2) performance of a rangefinder breakthrough/retention (i.e., volatilization) study to narrow the selection process; and (3) final selection based on a definitive breakthrough/retention study. Breakthrough/Trapping (Retention) efficiency studies are required to validate inhalation exposure monitors prior to field trials. While it would be desirable to know the trapping efficiency of media using aerosols or particulates of the pesticide(s) being studied, no completely satisfactory procedure is currently available for this type of testing. Investigators are strongly urged to develop an acceptable procedure. Melcher et al. (1978) may provide an appropriate methodology for combining certain pesticides and dosimeters.

Unless aerosols or particulates can be introduced to test the collecting medium when pesticides having very low vapor pressures are used, investigators will have to determine the retention efficiency of fortified media rather than the trapping efficiency. This can be done by directly fortifying the matrix with a large enough quantity of the pesticide(s) (e.g., 10x to 100x the QL) in the smallest feasible volume of volatile organic solvent possible (e.g., $\mu$L quantities of acetone). Investigators should then allow an adequate amount of time for the solvent to evaporate prior to initiating airflow across the fortified sample(s). Air should be drawn through the fortified dosimeters at flow rates similar to that to be used in the field trials for similar periods of time, and under similar climatic conditions.

To ensure that collected pesticide residues are not lost from the medium during sampling, investigators should also test for breakthrough. This can be done by analyzing for any residue that is collected by a trap placed in the airflow downstream to the monitor being tested. This is exemplified by the "back section" of packing in the sampling train described by Melcher et al. (1978). Tests must be performed at high enough residue levels (e.g., 100x to 1000x QL) to accurately determine the percentage of breakthrough that will occur. According to standard industrial hygiene practice, if the back-up section contains more than 20 percent of the concentration in the front part of the tube, then the sample should be discarded [TBA: reference]. Low concentrations make it more difficult to accurately quantitate breakthrough levels because anticipated levels would approach the QL or the LOD. As with the storage stability study regimen previously described, rangefinder samples should be fortified at two levels (e.g., 10x and 100x the QL).

Retention samples are inhalation monitors that have been fortified and allowed to dry for a sufficient quantity of time (i.e., spiking solution solvent evaporation to prevent volatilization due to coevaporation with solvent), then had air drawn through them for a period of time and flow rate similar to that anticipated in the field study under similar conditions. Breakthrough samples are blank (i.e., not fortified) dosimeters that have been placed in line between the fortified dosimeters and the pump (i.e., personal sampling pump or high volume air sampler) to entrap residues volatilized through the fortified dosimeters. Exposed samples are inhalation monitors that have been fortified and allowed to dry as above, then exposed to identical environmental conditions (i.e., all tests done concurrently) as the breakthrough/retention samples with the exception of having air drawn through them. Exposed samples are required in order to determine volatilization and other dissipation or degradation effects from inhalation monitors due to environmental conditions, without having had air drawn through them. As stated above, breakthrough/retention studies should be performed under conditions similar to those anticipated in the field studies. Laboratory incubators can be used to simulate field temperature and humidity conditions. If environmental conditions are anticipated to change during sampling intervals, then a worst-case scenario (i.e., most chances for volatilization/degradation) should be simulated; e.g., relative humidity typically drops drastically in the San Joaquin Valley of California as the sun rises. Worst-case scenarios should be supported by investigations based on the physical/chemical characteristics of the pesticide(s) being studied.

**Equipment Maintenance:** [TBA]

**Monitor Calibration:** When electronic sampling pumps are employed, it is necessary to check the flow at the beginning of the exposure period and again at its end. Several types of equipment are available for calibrating personal sampling pumps, including bubblemeters, magnehelic gauges, and rotometers. All equipment used to calibrate personal sampling pumps, must be traceable to a primary standard such as a bubblemeter. In other words, secondary standards such as a rotometer can be used, but the results must be modified to reflect the true airflow rates calculated from the comparison of a secondary to a primary standard. If flows change during the exposure interval, the mean flow rate should be used for all calculations.

A typical high volume air sampler is calibrated using a manometer or other similar device. In general, airflow is proportional to the type of filter that has been selected. The more resistance a filter provides to the sampler the lower the airflow and the higher the strain on the device. Sampler flow rates are not adjustable, and fluctuate only based on the nature of the filter material. High volume air sampler flow is usually recorded from a rotometer or other indicator on the device as an "observed flow," which then must be compared to a device-specific calibration curve to calculate a "true air flow." Calibrations of flow indicators should be performed either before or after the

exposure interval. Calibration curves will not vary unless the rotometer or other flow indicator adjustments are altered. The kits used to calibrate high volume air samplers are usually supplied by the sampler manufacturer. The Agency considers these kits to be a primary standard.

### 7.4.6 Field Operations

**Field Phase Operations:** The intake tube of any pump-powered sampler unit should be positioned so that the opening is downward. This is to avoid the collection, via direct drift, of large droplets that are not normally drawn into the nostrils. The intake tube should be placed as near as possible to the nose level of the test subject (i.e., within the breathing zone of the worker). Placing the collection media on the worker's lapel is commonly used. The height of the intake tube is especially important when taking samples indoors where walls or ceilings are being sprayed. For the study subject's comfort and safety, it is necessary to ensure that the pumps, hoses, and samplers are secured to minimize movement and the potential for snagging. High volume air samplers are mechanical devices. Therefore, they can be expected to break down during use or otherwise malfunction in some other way (e.g., overheating, rotometer/indicator adjustment changes, power supply failures, etc.). Investigators should anticipate these occurrences and take the appropriate precautions. High volume air samplers should be maintained according to the manufacturers' specifications. Maintenance and calibration logs should be kept on each sampler where appropriate. High volume air sampler operation must be monitored during the sampling intervals. If samplers break down or otherwise obviously malfunction during operation, the devices should be replaced and the sampling intervals should continue, if possible. The investigator should use any means available to obtain field samples when malfunctioning equipment is involved unless the integrity of the sample is compromised. If questions regarding the integrity of the sample cannot be answered, the sample should be discarded.

**Sample Collection:** Sample collection procedures are critical in ensuring the integrity of the sample upon completion of any exposure interval. Every means available to the investigator should be utilized to prevent cross contamination of the sample (e.g., changing rubber gloves between test subjects and cleaning equipment used to remove exposed sample matrices from test subjects). As mentioned above, investigators can use several types of dosimeters to measure inhalation exposure, including: various fibers filter (held in open-faced 37mm cassettes); polyurethane foam; high volume air sampler filters; various resins (e.g., XAD, silica gel, etc.) or activated charcoal; and passive monitors. The above list is not meant to be all inclusive; however, the variety of dosimeters cited demonstrates the need for investigators to carefully consider how the exposed monitors will be stored after an exposure interval ends.

Filters held in open-faced cassettes should be sealed with the remaining unused portion of the cassette after the exposure interval. This procedure should be similar to those commonly employed by industrial hygienists. Solutions should be decanted out of impingers and into appropriate storage vessels (e.g., 25 mL glass liquid scintillation vial with Teflon®-lined cap) with as few steps as possible to minimize the cross-contamination potential (e.g., do not use a pipette to transfer solutions). Investigators must also consider the possibility of breakage during transit and storage, as well as the absorptive/adsorptive properties of the pesticide(s), when selecting a storage vessel for impinger solutions (e.g., a plastic storage vessel and the associated leaching possibilities for various pesticides).

Polyurethane foam filters should be stored in a manner similar to that used for the impinger solutions (i.e., similar storage vessels may be used). Note that in dusty environments polyurethane foam filters may tend to contain significant quantities of particulate contaminants after the exposure interval. If this is the case, investigators should collect the filters, along with any residual particulates that may have been lost due to the mechanical forces exerted during sample collection.

High volume air sampler filters should be handled and stored in a manner similar to that proposed for the impinger solutions and polyurethane foam filters. The volume of a solution contained in an impinger or the volume of a polyurethane foam filter sample will be substantially less than the storage volume required to contain a high volume air sampler filter, which is on the average approximately 4 inches in diameter and has an average thickness of 1 to 10 mm. Therefore, storage vessels larger than those used for the polyurethane foam and impinger solution samples should be used.

A wide variety of resins can be used to monitor inhalation exposure. Essentially, all resins used for this purpose are contained in similar devices during the sample collection period (i.e., a glass tube with holes in both ends). When the sampling interval is completed, exposed resins can be stored in one of two ways: (1) by capping both ends of the container tubes and storing them until analysis or (2) by emptying the resins contained in the tubes into a vessel in the field and storing it until analysis. Passive monitor manufacturers often supply devices to store the exposed monitors until analysis. If this is the case, investigators should follow the manufacturer's instructions. If no sample storage devices are supplied with the passive monitors, then investigators should utilize some sort of storage medium that will prevent pesticide dissipation from the exposed dosimeters.

Investigators must account for the logistical problems associated with their monitors of choice to ensure that sample collection procedures do not compromise the integrity of a study. Standard Operating Procedures (SOPs) should be developed and used by investigators who routinely employ

various monitoring devices in their exposure studies. In summary, the Agency wants investigators to use the simplest but most appropriate monitors possible in order to protect the quality of the data they receive.

## 7.6 SAMPLE ANALYSIS [Reference QA/QC]

## 7.8 CALCULATIONS

To calculate inhalation exposure, it is necessary to obtain or define the following information: level of exertion; airborne pesticide concentration or residue levels; duration of typical exposure interval. The equations and other guidelines required to complete these calculations are included in Part D.

## 7.9 DATA PRESENTATION

The final results for respiratory exposure should be reported in any submission to the Agency as the mean residue per liter or cubic meter of air drawn through the sampling media (if sampling pumps are employed). These results should be corrected for recovery values which vary $> 10$ percent resulting from extraction, and storage. The number of separate exposures giving rise to the mean and the range of the exposures should also be specified. If any exposures are below the quantitative limit of the method used for analysis, the number of such exposures should also be specified. To calculate mean residue per liter of air sampled, any samples that contained residues below the limit of quantification should be considered to have contained half this limit. Also, samples should not be considered valid if the final airflow, where appropriate, through the sampling medium was found to be less than 25 percent of the initial airflow. The total time worked during the sampling period and the total quantity of active ingredient handled during the sampling period must be reported. The residue and the total quantity of air drawn through each individual sample should also be submitted to the Agency.

## REFERENCES FOR CHAPTER 7 [TBA]

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# PART B - CHAPTER 8
# ASSESSMENT OF NON-DIETARY INGESTION EXPOSURE

**ISSUE: The assessment/evaluation of non-dietary ingestion (e.g., children licking hands or a toy that may be contaminated with pesticides) is a relatively new area of concern with respect to the pesticides program. Although exposure via this route may be less than via the dermal route, internal dose may be more significant because limited dermal penetration will not be a factor. Eventually, this section will provide more guidance that will enable investigators to assess non-dietary ingestion. The Office of Research and Development is currently conducting research to support this area of exposure assessment. For the time being, this topic is an issue that needs further exploration.**

**TBA: Specific research that ORD is doing.**

# PART B - CHAPTER 9
# GUIDELINE 875.2600 - ASSESSMENT OF DOSE THROUGH BIOLOGICAL MONITORING

## 9.1 INTRODUCTION

Biological monitoring provides the basis for estimating an internal dose by measuring pesticide and/or metabolites compound concentrations in selected tissues, fluids, or bodily wastes (feces and/or urine). Pesticide and metabolite compound concentrations can also be estimated by measuring evidence of reaction of the pesticide and/or metabolite compounds with various biochemical sites of interaction. Dose responses associated with short biological half-lives (e.g., blood levels) may be an appropriate measure of current or very recent exposures; dose responses associated with long biological half-lives may be appropriate measures of integrated exposure over an extended period of time (ACGIH, 1990). The most appropriate type of biological monitoring should be chosen based on an understanding of the pharmacokinetics of the pesticides, whether recent or long-term exposures are to be captured by the monitoring technique.

Biological monitoring is sometimes directed at defining evidence of the reaction of the pesticides with its biochemical target, such as an enzyme, rather than the pesticide level itself. In other words, pesticide exposure can be estimated based on an indicator property rather than through direct quantification. These biochemical targets, therefore, constitute internal dosimeters as measures of exposure. This type of monitoring may not only provide a measure of internal dose, but can also provide a direct measure of the potential of a given exposure for adverse effects. Thus, if the toxicology of the pesticide is understood, in addition to the correlation between the extent of affected biochemical targets and overall health status, one can utilize such measurements for medical surveillance of workers and as the basis for expedient implementation of preventive or mitigating risk reduction measures.

Biological monitoring of biochemical targets has a long history of use in occupational settings. Correlations between levels of exposure to various industrial chemicals and covalent adducts between the chemical, or its metabolite, and hemoglobin have been reported (Tannenbaum and Skipper, 1984, Pereira and Chang, 1982). Specific examples of industrial chemicals for which this approach has proved useful include ethylene oxide (Calleman et al., 1978), chloroform (Pereira and Chang, 1982), and aniline (Neumann, 1984).

One example of this type of biological monitoring with regard to pesticides is the use of cholinesterase levels in the blood as an indicator of worker exposure to organophosphate pesticides

(Peoples and Knaak, 1982). Early attempts to correlate levels of cholinesterase inhibition with concentrations of pesticides and/or their metabolites/analog compounds in blood were generally not successful (Bradway et al., 1977, Roan et al., 1969, Drevenkar et al., 1983), however, because of the wide variability in cholinesterase levels among individuals (Popendorf and Leffingwell, 1982). Lessons from these early efforts suggest that baseline pre-exposure cholinesterase levels should be established for all workers for which this type of data is collected. This is especially important if post-exposure cholinesterase levels are used to compare to enzyme activity levels at which a worker is to be removed from further exposure.

Hemoglobin is a useful internal dosimeter because (1) it contains reactive nucleophilic amino acids (histidine and cysteine), (2) hemoglobin is present in the body in large amounts relative to other reactive receptors, and (3) the life span of hemoglobin and its adducts is about 18 weeks in humans, providing a stable marker for exposures experienced within that time frame. Besides *in vivo* measurements, reaction constants for various pesticide(s) with hemoglobin can be determined *in vitro*, and may be used with data on the concentration of the adduct to estimate the internal dose to an exposed individual. This type of analysis has been performed for ethylene oxide. A correlation was established between external exposure and the amount of covalent adduct formed per gram of hemoglobin for sterilizer workers (Calleman et al., 1978).

Pesticide elimination may also be used as an indicator of pesticide exposure. The most common way in which elimination of a pesticide and/or its metabolite/analog compounds has been measured is by urine analysis. Such measurements can potentially allow determination of internal dose and may also be used for medical surveillance to identify workers who are at high risk. The presence of the parent compound or known urinary metabolites has been used for almost four decades as an indicator of exposure to a number of pesticides, including paraquat (Swan, 1969), arsenic (Gollop and Glass, 1979, Wagner and Weswig, 1974), parathion (Lieben et al., 1953, Durham and Wolfe, 1962), chlorobenzilate (Levy et al., 1981), the phenoxy acid herbicides (Kolmodin-Hedman et al., 1983), and organophosphate pesticides (Kutz and Strassman, 1977). Besides being used as an indicator of exposure, urinary metabolites have been used to confirm poisoning cases involving pesticides, including those involving organophosphates and carbamates (Davies et al., 1979). Such studies have noted the relationship of the pesticide(s) and/or metabolite/analog compounds in urine to exposure. Typically, no accurate quanitification of exposure was able to be made from these data, partly because of a lack of adequate understanding of the pharmacokinetics of the pesticides. In addition to urine analysis, breath analysis may be useful for monitoring very recent exposures to volatile nonpolar pesticides, particularly some fumigants. Pesticides and/or the metabolite/analog compounds may also be monitored through fecal analysis even though there is by comparison

relatively little literature on this approach. Analysis of sweat as a biological monitoring media for pesticides has some potential, but is severely limited by potential contamination from the skin of exposed workers. Based on methodological considerations and ease of use, the main focus in monitoring the elimination of pesticides will be on urine and exhaled air as the two preferred media.

**NOTE: Additional information is available on biological monitoring in Eller, P.M. 1984. NIOSH Manual of Analytical Methods. National Institute of Occupational Safety and Health, Cincinnati, Ohio. It will also be cited in Part C, QA/QC.**

## 9.2 PURPOSE

The purpose of biological monitoring is to measure internal pesticide doses and to assess the potential for a specific pesticide dose to result in an adverse effect.

## 9.3 WHEN REQUIRED

The Agency does not routinely require registrants to submit biological monitoring data. However, if a registrant believes that the limitations of biological monitoring described above can be overcome for a particular pesticide and chooses to monitor worker exposure using biological monitoring, the Agency will evaluate the resulting data and, if judged to be adequate, will incorporate the results into the risk assessment process. If a registrant decides to undertake a biological monitoring study, the registrant must verify that adequate pharmacokinetic data exist to effectively interpret the data in a meaningful way, or must simultaneously conduct studies to provide the missing pharmacokinetic data. Prior to initiating a biological monitoring study, registrants must receive Agency approval of the specific study protocol.

Biological monitoring studies may be considered/proposed by registrants as an alternative to passive dosimetry at both outdoor and indoor sites if each of the following criteria (1 through 4) below is satisfied. Biological monitoring studies will be required by the Agency for a specific pesticide when each of the criteria (1 through 5) below is satisfied:

Criterion 1 – The toxicological evaluation of a pesticide product indicates that the use of the product may pose an acute or chronic hazard to human health.

Criterion 2 -- Exposure is likely to occur during use or following use (post-reentry time period).

Criterion 3 -- Data that would allow the Agency to estimate the magnitude of exposure for a particular work activity with an acceptable degree of confidence are not available (i.e., surrogate exposure estimates are not available).

Criterion 4 -- The pharmacokinetics of a pesticide and/or metabolite/analog compounds (i.e., whichever method is selected as an indicator of body burden or internal dose) is understood well enough that a back-calculation to actual dose is possible.

Criterion 5 -- Passive dosimetry techniques are determined not to be applicable for a particular exposure scenario (e.g., for extremely volatile pesticides such as some fumigants or prolonged immersion or saturation of the skin with a nonvolatile pesticide).

## 9.4 SAMPLE COLLECTION

| NOTE: See Part C (QA/QC) for details on sample collection QA/QC for Biological Monitoring. |
|---|

### 9.4.1 Exhaled Air

| NOTE: What would be the utility of exhaled air monitoring? |
|---|

Sampling of exhaled air should be conducted in a manner that adequately accounts for the considerations shown in Table 9-1. Sampling techniques and equipment for collecting exhaled air have been reviewed by Wilson (1986). Control samples (field blanks) should be collected in the field in an uncontaminated area prior to reentry activities. The sampling procedure should be explained to and practiced with the worker prior to reentry activities. All samples should be collected while the worker is at rest; hyperventilation and forced exhalation should be avoided prior to sampling. Containers for sampling mixed-exhaled air must be large enough to accommodate whole breath

**Table 9-1. Methodological Issues in Sampling, Storage, and Analysis of Exhaled Air, Blood, and Urine**

| Issue | Exhaled Air | Blood | Urine |
|---|---|---|---|
| **SAMPLING** | | | |
| Suitable determinants | Volatile, stable, hydrophobic compounds | Any | Any (although most convenient for polar determinants) |
| Specimen characteristics | End-haled versus mixed-exhaled air; mode of respiration (nose-mouth breathing) | Whole blood, plasma, serum, cells, clotted blood | Spot specimen, timed specimen |
| Invasiveness | Noninvasive | Invasive | Noninvasive |
| Collection period | Instantaneous (single breath) or short-term (multibreath sample) | Instantaneous | Short-term (2 to 24 hours) |
| Special qualification of health personnel | Need to be well informed on technique | Medical staff required to obtain sample | Minimal training required |
| Infection protection | Sterile mouthpiece | Sterile needle | Clean container |
| Container requirements | Air tight | | |
| | Made of material that does not react or absorb determinant | | |
| | 25-50 ml for end-exhaled air; more than 1 L for mixed-exhaled air | Depends on method | 50 ml or more |
| Precautions | Proper timing of sample collection required | | |
| | Sample only persons with normal pulmonary function; normal breathing (avoid hyperventilation; use low resistance apparatus); sampling apparatus made from nonabsorbing material; methodology should account for condensation | Venus blood preferred (versus capillary blood, which is only appropriate in limited cases); proper anticoagulant; dry syringe | Sample only persons with normal renal function |
| Potential sources of contamination | Ambient air | Skin exposure, cleaning solutions, syringe, needle, anticoagulant | Cross contamination from exposed hands, hair, clothing (sampling after shower and clean clothes preferred) |
| Health hazards | Respiratory infection | Hepatitis, HIV | Minimal |

**Table 9-1. Methodological Issues in Sampling, Storage, and Analysis of Exhaled Air, Blood, and Urine (Continued)**

| Issue | Exhaled Air | Blood | Urine |
|---|---|---|---|
| **TRANSPORTATION AND STORAGE** | | | |
| Potential sources of contamination | Ambient air or container | Container | |
| Source of deterioration | Temperature changes (leading to leaks, condensation on surface of container), light | Hemolysis, bacterial decomposition, light | Bacterial decomposition, light |
| Other transport issues | Avoid temperature changes | Low temperature required | Large volume and weight of samples |
| Storage temperature | Room temperature | Refrigerated or frozen (after separation of serum and plasma) | Refrigerated or frozen |
| **ANALYTICAL** | | | |
| Cleanup procedure | None | Complex | Some |
| Possible interferences | Condensation | Protein binding, conjugation, and chelation (impact dependent on analytical method) | |
| Method | Sensitive and specific onsite analysis desirable | Sensitive and specific | |
| **DETERMINANTS REQUIRING SPECIAL CONSIDERATIONS** | | | |
| Parent chemical | Avoid contamination during sampling procedure | | |
| Volatile chemicals | Use airtight containers; avoid condensation | Use airtight containers with controlled head space | |
| | | Anaerobic collection | Rapid collection |
| Solvents | Avoid contact with rubber and some plastics | | |
| | Mouthpieces, container, stopcock | Container, stoppers | |
| Metals | NA | Contamination free needles | Avoid contamination |
| Enzymes | NA | Low temperature | NA |
| Photosensitive chemicals | Dark containers | | |

Source: ACGIH 1990.

volume. It is recommended that samples be collected by having the worker inhale through the nose and exhale by mouth into a plastic bag or other container via a glass tube connector of sufficient width to present minimal resistance. Narrow tubing or use of a stopcock should not be used unless alternatives are not readily available; thus, the equipment should not be designed so that workers exhale into restricted diameter adsorption tubes. Containers for sampling end-exhaled air can be smaller (50 ml). All containers and collection equipment should be designed properly and should be nonreactive and nonadsorptive. To obtain a representative measurement, single breath samples should be collected in triplicate. Droz et al. (1988) recommended that the measured concentration in an exhaled air sample should be normalized to a concentration of 5 percent carbon dioxide ($CO_2$) to help eliminate any effect due to the resistance of the sampling device.

### 9.4.2 Blood

Sampling of pesticides or their metabolites in blood should be conducted in a manner that accounts for the considerations summarized in Table 9-1. Blood may be sampled using venous blood or capillary blood from fingers or ear lobes, except under the restriction that capillary blood is not an acceptable media when more than 0.5 mL of blood is needed for an adequate method sensitivity (i.e., to obtain a quantification limit that is low enough to be meaningful), when samples collected in the workplace are to be analyzed offsite (because of the risk of external contamination), or when a specimen is being analyzed for volatile chemicals (because of loss by evaporation) (ACGIH, 1990).

Venous blood should be collected in sealed containers; if headspace exists in the sample containers, it must be analyzed separately from the blood. For example, for each 10 ml of unclotted blood, the sample container should contain one of the following anticoagulants designated as appropriate by consultation with the laboratory: 20 mg of potassium oxalate or sodium oxalate, 50 mg of sodium citrate, 15 mg of disodium-EDTA, or 2 mg of heparin. The anticoagulant of choice should have been dispersed along the bottom wall of the tube and then dried. Immediately after sample collection, the sample tube should be rotated gently to thoroughly mix the blood with the anticoagulant. A variety of bood collection devices are commercially available. Investigators should be careful to adhere to the manufacturers' guidelines and protocols when using the equipment (e.g., vacutainer tubes).

Because prior exposures to some pesticides may have a significant impact on blood levels, baseline blood samples should be taken prior to exposure of an individual under reentry conditions. A brief history should be taken from each participant relating to known prior exposures to pesticides for at least the last 2 weeks, including reentry into potentially treated fields (ACGIH, 1990).

In addition, a number of precautions should be taken relating to blood monitoring: (1) medical staff should take appropriate precautions to protect both the study participants and staff from exposure to infectious agents (such as HIV); (2) samples should not be drawn from body parts that are known to be contaminated (e.g., from a spill onto skin); (3) prior to drawing blood, the collection site (e.g., arm, finger) should be washed with detergent and water, dried, and then washed with isopropyl alcohol; (4) appropriate precautions should be taken so that other chemicals do not contaminate the sample; (5) during analysis, samples should be well mixed prior to removing an aliquot for analysis to avoid errors because of sedimentation; and (6) analyses should account for the fact that some determinants can be present in free, conjugated, and protein-bound forms (samples analyzed for total determinant require appropriate acid or enzymatic hydrolysis prior to analysis) (ACGIH, 1990).

### 9.4.3 Urine

Sampling of pesticides and/or their metabolites/analog compounds in urine should be conducted in a manner that accounts for the considerations summarized in Table 9-1. The collection of all urine specimens by workers should be logged in at the time of the collection in the field. Specimens should be collected at the beginning of the day of reentry activities (just prior to reentry), during a break in the middle of reentry activities, at the end of the work day, and later that evening, based on the pharmacokinetics of the pesticide--the time of collection for this last sample must be recorded by the worker. Continuous, sequential, and 24-hour specimens require an adequate collection volume until the beginning of the next day. If feasible, workers should remove contaminated clothing and wash their hands thoroughly before specimen collection so as not to inadvertently contaminate the specimens. Ideally, the second and third samples should be collected after showering and changing of clothes to minimize the likelihood of extraneous contamination. The workers sampled should be provided with readily sealable containers (i.e., that prevent spillage) of approximately 500 ml volume that are either prepackaged, prerinsed with an appropriate solvent, or heated to 250°C (if glass) for 1 to 2 hours to guarantee lack of contamination. Specimens collected for measurement of volatile chemicals should be collected in a 50-ml container which must be completely filled with the specimen and immediately sealed to minimize losses. In such cases, the laboratory should also withdraw a headspace sample by syringe for analysis. The specimen containers should be able to withstand the pressure changes caused by changes in temperature during transportation and storage without loss of headspace or specimen.

## 9.5 SAMPLE STORAGE

Once the field samples have been collected, the next step in the process is to transport the samples to the analytical laboratory and store them until analysis. Samples should be transported on either wet or dry ice, as appropriate, to minimize analyte dissipation. After arrival at the analytical laboratory, samples should be kept in freezer storage, except as noted below (i.e. air and whole blood samples). Because of the diverse nature and properties of potential biological monitoring indicators, some analytes may exhibit unusual behavior under these storage and transport guidelines. If investigators deviate from the aforementioned guidelines because of the unusual physical/chemical characteristics of the analyte(s) of interest, the rationale must be documented in any submission to the Agency.

All exhaled air samples should be transported and stored in the same way as ambient air samples; in the dark at room temperature to prevent photolysis of samples. Precautions should be taken during sample analysis for the high content of water vapor in exhaled samples, which may condense on the surface of the container and contain a significant portion of the chemicals in the sample that are water soluble or of low vapor pressure (ACGIH, 1990).

All blood samples should be treated with a minimum of agitation and temperature changes during transportation and storage to minimize the extent of hemolysis (ACGIH, 1990). If the analysis is to be done on separated serum, the collected venous blood should be allowed to clot in collection containers that are not treated with anticoagulant. The clot is then removed about 10 minutes after collection and the serum is withdrawn by syringe (ACGIH, 1990). Whole blood samples should never be frozen; for overnight storage, refrigeration at 4°C is usually satisfactory. For longer storage, samples should be centrifuged and the plasma should be removed for storage. Field blanks and other appropriate control samples (e.g., field spikes) should be included in the analysis (ACGIH, 1990). All urine specimens should be stored frozen after the specific gravity is measured.

If biological monitoring media are to be stored after exposure, a stability test for the analyte(s) of interest should be documented in conformance with the medium-specific storage precautions noted above. See Part C, QA/QC for more information regarding procedures for initiating a stability study. In short, fortified media must be stored under the same conditions that will be used for field samples. In addition, the storage stability samples are to be handled and analyzed by the same methods that will be employed for field samples.

## 9.6 SAMPLE ANALYSIS

The selection of analytical procedures will depend on the particular chemical being studied. Consequently, this decision is left to the discretion of the investigator. The selected procedure should be capable of producing recoveries in the range of 70 to 120 percent with a coefficient of variation of in-set/batch duplicates of 20 percent. The amount of test substance should be reported as a cumulative total for each collection period.

Urine samples should be well mixed before aliquots are taken for chemical analyses. The investigator should consider determining creatinine levels as a way of monitoring completeness of urine collection samples. Creatinine should be measured using a colorimetric method known as the Jaffe Reaction, in which creatinine reacts with alkaline picrate to produce an intense red color (Tietz, 1976). Specific gravity can be read using a densitometer; this analysis should be performed as soon after collection as possible (and before sample storage) before irreversible sedimentation of solids occurs in the samples. Most clinical laboratories can perform these two analyses at relatively low cost. Specimens showing physiologically impossible low levels of creatinine or specific gravity should be viewed as having been tampered with and should be either discarded or reported with an appropriate footnote.

## 9.7 CALCULATION OF ESTIMATED EXPOSURES

| ISSUE: Calculations specific to Biological Monitoring need to be added here, or the reader needs to be referred to Part D. | |
|---|---|

## 9.8 DATA PRESENTATION

| ISSUE: What types of data presentation should be required for Biological Monitoring? | |
|---|---|

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# PART B - CHAPTER 10
# GUIDELINE 875.2800 - HUMAN ACTIVITY PATTERN MONITORING/ASSESSMENT

## 10.1 INTRODUCTION

**ISSUE: An introductory section needs to be added here.**

## 10.2 PURPOSE

The purpose of collecting human activity pattern data is to obtain realistic data to support the risk assessment process, to evaluate the range (distribution) of activities related both to contact and transfer (frequency, magnitude, and duration) and product use (and user information). To accomplish this in an effective manner three types of activity pattern data must be reported within each submission to the Agency. The first type of data pertain to the study region while the other data are use-site and test-subject specific. The purpose of the regional data is to justify the selection of a region for the conduct of a study. The second type of data are intended to support the selection of specific study sites within the region of interest. Each of these types of data must be closely integrated with the data that are also to be collected as part of the Detailed Product Use Information requirements as described in Chapter 11. The third type of required activity data provide specific information concerning the biomechanical attributes of each test subject in a study (i.e., the way each study test subject performs specific tasks which are monitored in a study). These data are useful in explaining differences in exposure values between individual test subjects and for determining how biomechanics affect resultant exposure levels.

## 10.3 WHEN REQUIRED

Unless otherwise directed, activity pattern data must be included as part of every study submitted to the Agency that is completed for regulatory purposes under 40 CFR 158. The only exceptions will be for broad spectrum chemicals for which there may be several scenarios of interest to the Agency and for extremely specialized studies required by the Agency to support particularly novel and/or specialized uses of a specific pesticide. [Note: These exemptions will be granted only on a case-by-case basis by the Agency for specific pesticides.]

## 10.4 DATA COLLECTION

As described above, three approaches are important in identifying appropriate activity data. The first relates to the selection of a region for a specific pesticide study. The second details the site selection process within each particular study region. The third approach involves a more basic evaluation of the test subject's activities by using a biomechanical approach to exposure assessment. Each of the types of approaches and the corresponding required data are explained below in detail.

### 10.4.1 Regional Selection of Study Site

To represent the use of a specific pesticide, regions must be carefully selected, and selections must be adequately justified in submissions to the Agency. Regional variations must be addressed in submissions to the Agency as these are critical in determining the representativeness of a dataset. Regions may be delineated using a variety of characteristics including, but not limited to, the following:

- Geography;
- Climate;
- Growing Regions (e.g., San Joaquin vs. Napa Valleys in CA);
- Cultural Practices;
- Soil Types;
- Agricultural Statistics (e.g., production profiles of target crop); and
- Pesticide Sales/Usage in a Region.

It is recommended that investigators utilize several resources when attempting to determine regions for the conduct of studies. Some significant resources include, but are not limited to, the following:

- Local Extension Services;
- Academia (e.g., ag schools with expertise concerning a particular crop/target of interest);
- Professional Associations (e.g., builder associations for distribution of home types for indoor air/residential exposure issues);
- Pesticide Manufacturers; and
- U.S.D.A./Agricultural Statistics.

Investigators are required to carefully describe in any submission to the Agency the resources and techniques used to identify a study region. Additionally, any justifications and/or assumptions employed by investigators must also be carefully described.

### 10.4.2 Specific Site Selection Criteria

After a region has been selected in which to conduct a study, the specific study site must be selected. This type of selection is often much more difficult than the process involving regional selection, as described above. It requires an excellent working knowledge of the particular cultural activities, targets/crops, and pesticide use patterns that are of interest. In most instances, the justification of the selection of a specific study site will be easy (i.e., for a majority of crops/targets, practices, may not differ significantly within a region). However, in some instances the nuances between specific study sites within an identified region may significantly impact the resultant exposure levels quantified during the conduct of a study.

Several examples of situations where these nuances may be critical to the selection of a specific study site, include but are not limited to the following:

- Grape Maintenance (e.g., grape trellis patterns are often significantly different between growers in CA, these differences may contribute to the types of exposures quantified at a particular study site);
- Housing Types (e.g., housing types can significantly impact ambient air levels and the mechanisms of residue dissipation and translocation in a domicile over time, major types include plenum, crawl space, basement, and slab construction);
- Orchard Maintenance (e.g., tree spacing and the level of pruning varies between growers in regions for a variety of crops thus effecting foliage contact, foliage contact in turn may impact resultant exposure levels); and
- Harvesting Techniques (e.g., the use of ladders or machinery such as "cherry pickers" may significantly impact exposure levels during the harvesting of tree fruit).

Investigators are required to carefully describe in any submission to the Agency the resources and techniques used to identify a specific study site. Additionally, any justifications and/or assumptions employed by investigators must also be carefully described.

### 10.4.3 Description of Test Subject Activities

Investigators are required to describe the activities of each individual test subject during each replicate. Each description must include, at a minimum, but not necessarily be limited to the following:

- Nature of human activity (e.g., any repetitive or common motions/mechanics to describe the activity -- repeatedly touched left elbow, etc.);
- Source of exposure (i.e., describe in as much detail as possible the location of the treated targets touched during each exposure replicate -- for example, grids on a floor in a residential scenario);
- Level of exertion (i.e., particularly important during biological monitoring as exertion levels may effect the metabolism of the specific pesticide);
- Individual characteristics (e.g., height, weight, age, etc.);
- Unusual conditions contributing to exposure; and
- The efficiency of each test subject (e.g., the number of pounds harvested on a daily basis).
- The experience of each test subject with the task, the product, and any special or personal protective equipment in use.
- Duration and frequency of exposure.

It is also recommended that investigators document, in as complete a fashion as possible, the activities of each test subject throughout a study via photographic and/or videotape records. These records should be retained with the raw data in archives unless specifically required by the Agency.

## 10.5 PRESENTATION OF ACTIVITY PATTERN DATA

| ISSUE: Additional information will be added here. | |
|---|---|

## 10.6 ANALYSIS AND INTERPRETATION OF ACTIVITY PATTERN DATA

**ISSUE: Additional information will be added here.**

ISSUE: How do we address the EMSL ORD Research involving the application of biomechanics to exposure assessment, the use of the NHEXAS questionnaire for developing/refining exposure scenarios, and the implementation of the Therdbase System? Chris Saint will provide language on this.

ISSUE: What level of detail for each type of requirements are necessary to fulfill EPA's needs for this aspect of the guidelines?

ISSUE: How does the Worker Protection Standard requirement for monitoring actual pesticide usage fit into this area in conjunction with the detailed use information section?

ISSUE: Any suggestions for the analysis/validation of the types of data which are required, as described above?

ISSUE: ORD and OPP are very interested in the application of biomechanics to exposure assessment, particularly for residential scenarios at the moment. What utility, if any do you see for this type of information? This could reduce uncertainty in transfer coefficients by providing an alternate method for estimating contact rates. Also, this will provide valuable information to guide the selection of activities to monitor in the residence.

ISSUE: Is it EPA' policy to encourage investigators to conduct exposure studies in ways that can be justified as the "Maximum Exposure Potential" conditions for all pesticides (i.e., worst case scenario). What if there are chronic/subchronic concerns associated with a chemical and the maximum scenario is hardly realistic for a majority of the uses?

ISSUE: As with any exposure/risk assessment, the identification of appropriate exposure factors is critical. The scope of the Human Activity Pattern guidelines requires registrants to include certain types of data pertaining to their specific pesticide products. However, these guidelines do not require registrants to provide/validate all of the required exposure factors for a complete risk assessment. Should EPA, use various sources of data (e.g., ORD research, OPP's Biological and Economic Analysis Division, NHEXAS, etc.) to develop these factors.

# PART B - CHAPTER 11
# GUIDELINE 875.2700 - PRODUCT USE INFORMATION

## 11.1 INTRODUCTION

The availability of product use information allows the Agency to perform better risk assessments as such data will guide the design of a study and will allow EPA to evaluate the representativeness of the study with respect to product use. Registrants should be able to provide the following information:

1) Major crop/use sites by region or country as a whole;
2) Typical application rates;
3) Typical application frequency; and
4) Equipment used for application.

[Additional information TBA.]

## REFERENCES FOR CHAPTER 11

[TBA]

# PART C

# QUALITY ASSURANCE/QUALITY CONTROL

# PART C - QUALITY ASSURANCE/QUALITY CONTROL

## 1.0 INTRODUCTION AND OVERVIEW

***Quality Assurance*** is a "system of activities whose purpose is to provide to the producer or user of a product or service the assurance that it meets defined standards of quality. It consists of two separate but related activities, quality control and quality assessment" (Taylor, 1987).

Quality assurance requirements may be found at part 160.35 of the Good Laboratory Practice (GLP) Standards. These regulations "define the function of the quality assurance unit (QAU) in regulated studies as that of ensuring managers that all aspects of the facility, personnel, performance, record-keeping, and reporting are consistent and in compliance with the regulations. The objective of the regulations is to ensure users...of (the generated) information...of accuracy and to ensure integrity of study conduct and reported results according to specifications in the GLPs. This objective is achieved through the development of quality assurance programs that systematically evaluate and monitor...studies, as well as the activities of the facility and personnel."

**FOR FURTHER READING:**

Garner, W.Y.; Barge, M.S.; and Ussary, J.P. editors. 1992. "Good Laboratory Practice Standards: Applications for Field and Laboratory Studies." American Chemical Society, Washington, DC.

ISSUE: Are there any other good reference books/sources??

***Quality Control*** is the "overall system of activities whose purpose is to control the quality of a product or service so that it meets the need of users. The aim is to provide quality that is satisfactory, adequate, dependable, and economic" (Taylor, 1987).

One of the mechanisms used to measure the "quality" of residue measurements is to quantify analyte loss and characterize positive and negative interferences. This is done by generating recovery data. In general, there are four types of recovery data that may be generated. They serve the following purposes and will be defined in later sections:

(1) ***Laboratory Recovery***: Laboratory recoveries reflect losses that occur during laboratory operations (e.g., extraction, clean-up, analytical measurement, etc.). These studies start during the method validation and method development phase. The purpose of laboratory recovery studies is to assess the general method development and method validation process.

- **Concurrent Laboratory Recovery.** A concurrent laboratory recovery sample is the same as a laboratory recovery sample except that it is run at the same time (i.e., concurrently) as the experimental samples. The purpose of concurrent recoveries is to account for losses under a given set of analytical conditions (e.g., solvents, instrument performance, standards, etc.).

(2) **Storage Stability**: A storage stability study can be conducted prior to or in conjunction with a field study. The purpose of a storage stability study is to determine the stability of analyte(s) in or on appropriate substrates under the same storage conditions that will be used to store field samples.

(3) **Travel Spikes**: Travel spikes account for the stability of the analyte on each sampling matrix during shipment and storage. These DO NOT reflect losses that might occur during sample collection. Travel spikes provide useful information for determining whether the analyte losses occurred during sample collection or during sample shipment and storage.

(4) **Field Recovery**: Field recovery samples account for losses that occur during sample collection, sample handling and storage in the field, transportation from the field to the laboratory, storage in the laboratory, sample extraction, and analysis.

**Quality Assessment** is "The overall system of activities whose purpose is to provide assurance that the quality control activities are done effectively. It involves a continuing evaluation of performance of the production system and the quality of products produced (Taylor, 1987)."

The remainder of Part C is arranged into seven sections: (1) Prefield Considerations; (2) Laboratory Studies Necessary Before Field Studies are Initiated; (3) Field Considerations; (4) Analytical Phase; (5) Sampling/ Handling Procedures; (6) Data Reporting; and (7) other considerations.

The "Prefield Considerations" section provides the investigator with all the background information that needs to be considered before the study is initiated. The section on "Laboratory Studies Necessary Before Field Studies are Initiated" outlines the analytical method development and validation process, and logistical considerations. The "Field Considerations" section describes the QA/QC procedures that should be followed during field operations, and the "Analytical Phase" section describes QA/QC procedures that should be followed during sample analysis. Sample storage, shipment, chain of custody, and other factors are outlined in the "Sample Handling and Procedures" section. Finally, "Data Reporting" describes data analysis, correction, and presentation.

Listed below are some specific definitions for terms used throughout this QA/QC section.

**Activity Period:** [TBA]

**Control samples:** Samples which are free of residues of any analyte(s) of interest that are analyzed concurrently with a set/batch of samples to identify/quantify constant errors which affect a measurement. Results are often used to correct actual data. Sometimes called blank samples.

**Field recovery:** Data from experiments conducted to determine the efficiency of recovery of the analyte from sample collection devices fortified in the field, when subjected to the same environmental conditions and exposure times as field exposure samples. Field recovery samples may also account for losses during shipping, storage, and laboratory operations, as well as field exposure to environmental factors (e.g., temperature, light), depending upon the analysis regimen.

**Handwash Removal Efficiency:** The fraction of pesticide deposited on the hands that can be removed through a specific handwash procedure. The value is generated through laboratory studies and is used to correct field data for incomplete removal.

**Laboratory recovery:** Data from experiments conducted in the laboratory to determine the efficiency of recovery of the analyte from fortified sample collection devices fortified at known levels. This recovery figure refers to laboratory operations (extraction, clean-up, analytical technique, etc.) only, and does not measure losses due to storage conditions or environmental factors.

**Limit of Detection (LOD):** The lowest pesticide level that can be accurately quantitated based on the lowest repeatable analytical standard, for example, residue levels based on the lowest analytical standard which represents 2 times the signal to noise ratio of the detector.

**Limit of Quantification (LOQ):** The lowest known pesticide level added to a blank sample matrix that is extractable and can be accurately quantitated in a repeatable fashion. For example, the lowest reproducible fortification level reported for method validation.

**Method validation:** Process by which it is demonstrated that an analytical method is capable of measuring the nature and the magnitude of an analyte(s) of interest at a desired level of sensitivity and at acceptable levels of accuracy and precision for a specific matrix.

**Replicate:** [TBA]

**Storage stability:** Data from experiments conducted to determine the stability of the analyte on each sampling matrix during storage. Fortified sampling devices must be stored for the maximum amount of time, and under the conditions expected to be encountered for field samples. Storage stability includes losses during storage and laboratory operations.

**Travel spikes:** Data from experiments that are conducted to determine the loss of analyte from fortified sampling matrix during shipping and may also account for losses during storage and laboratory operations, depending upon the analysis regimen, but not for losses due to environmental conditions in the field.

**Work cycle:** One replicate of a single worker involved in a definable sequence of tasks which may be repeated any number of times within one day or less of a given activity.

## 2.0 PREFIELD CONSIDERATIONS

### 2.1 Protocol Development

Registrants are encouraged to submit study designs to the Agency prior to initiation of the study. Several factors must be considered in the overall design of a protocol to conduct any study required under 40 CFR 158.390. Critical factors that must be addressed in any protocol, if appropriate, include the following:

**Environmental Fate and Transport:** The environmental fate/transport characteristics of a pesticide are always at issue. Investigators must rely on historical data, if available, to justify protocol development. Any data utilized must be documented in the following manner: (1) the reliability and applicability of the data must be justified, and (2) the major pathways through which the pesticide will degrade/dissipate must be discussed (i.e., hydrolytic, photolytic, volatilization, etc.).

**Sampler/Dosimeter Durability:** Dosimeters/sample collection devices (i.e., human exposure dosimeters), must be designed to (1) survive the duration of any monitoring effort (2) be the most appropriate device available for monitoring the pesticide(s) for that scenario, (3) do not reach their absorptive capacity (i.e., become saturated), and (4) survive during shipment to and storage at the analytical facility.

**Contingency Planning:** The study protocol should include contingency plans for major weather events, loss of study participants, or other circumstances that may adversely affect successful study completion.

## 2.2 Selecting Study Sites

Study sites must be representative of the exposure scenario of interest. Sufficient documentation must be provided to ensure that the site is representative of the scenario of interest. The site selection process should incorporate the following criteria:

**Climatological Patterns:** The study must be conducted in a climate that is typical for the use pattern of interest. Typically, a study should be conducted in season in the geographic area of concern. Catastrophic or atypical weather events must also be considered in the design of the study as they may preclude the acceptability of the study (e.g., fluke rainstorm in arid California region during an FDR study). The following considerations must be met when submitting climatological data.

**Maximum Exposure Potential:** The site selection process should maximize the potential for exposure under normal cultural conditions unless otherwise directed by the Agency. Researchers should not select sites that will minimize the potential for exposure based on some obvious factor such as the pruning regimen at one orchard vs. another or grape trellising practices). This factor must be considered in conjunction with any toxicological endpoint of concern for each chemical of interest. For example, an upper-end exposure

would be of more interest for a chemical with acute concerns while more typical exposures would be of interest for a chemical with a chronic endpoint associated with it.

**Surrogate Data:** Acceptable surrogate data must be obtained from a source in close proximity to the study site. Surrogate data is often typically used instead of collecting actual samples for defining climatological patterns, soil and water characterizations. Investigators must use their discretion when identifying sources of surrogate data. For example, climatological data from weather station observatories near a study site can serve as an acceptable surrogate for weather information monitored onsite if it can be determined that large variances do not exist between the climatic conditions at the two locations (e.g., spot check similarities at various intervals). On-site monitoring of rainfall is recommended. Surrogate soil and water characterization data must also be justified as above with various types of accompanying data (e.g., Soil Conservation Service or U.S.G.S. maps). [Note: This section applies only to the acceptability of data submitted to the Agency to support concurrent field exposure data. This scope of this section of the guidelines does not include defining parameters for the acceptability of surrogate exposure data to the Agency for any post-application exposure scenario.] Surrogate data may also be used for exposure or transfer coefficients, but not for dislodgable residue data.

## 2.3 Representative Agricultural/Commercial/Industrial Practices

To accurately quantitate residue dissipation rates and concurrent exposure levels during any post-application interval of regulatory concern, representative agricultural practices must be employed. The potential for exposure during reentry can be affected by several factors including, but not limited to, those presented below.

**Geographic Restrictions:** Agricultural practices can affect the potential for exposure to pesticides. Significant variations among agricultural practices can be due to differences in geographic regions (e.g., climate, soil type, cultural practices, etc.). Registrants should consider agricultural practices and label requirements from region to region when developing study protocols (e.g., sugarcane growing practices in the contiguous United States vs. practices in Hawaii or grape growing practices in New York vs. those in the San Joaquin valley of California).

**Reentry Operations:** Protocols must be designed so that reentry exposure is measured during operations that are typical of the major harvesting/maintenance patterns for the

target(s) of interest. Studies would be considered of minimal import by the Agency if the major potential routes of exposure are not addressed.

**Representative Worker Activities:** Acceptable cultural practices (i.e., worker activities during the exposure interval) can vary within regions for particular targets. The Agency is interested in evaluating studies that are based on measuring exposure that can be deemed representative of the typical situation. Registrants should make every possible effort to generate samples under these conditions (e.g., hand harvesting should be evaluated if all but a small number of operations in a particular region of interest are hand harvesting as opposed to mechanical harvesting – grapes in California where a minimal number of growers may opt to periodically use mechanical harvesting).

## 2.4 Representative Residential Patterns

Indoor and outdoor residential activities are of great concern to the agency. In these settings, dermal exposure, non-dietary ingestion, and inhalation exposure are the critical exposure routes of concern. The determination of residential exposure differs significantly from the determination of exposure levels in an agricultural and/or other commercial scenario for several reasons including, but not limited to, the fact that children are exposed to pesticides on a routine basis and that activity patterns within demographic groups are more difficult to determine. Quality control and quality assurance issues specific to exposure assessments in a residential setting, both indoor and outdoor, are discussed below.

**Indoor Sites:** Clearly defining residential activity patterns for any study conducted is critical to the acceptability of the study to the Agency. There is a significant initiative within the Agency to obtain more, higher quality information than is currently available. Residential patterns differ, obviously, from household to household. However, the Agency believes that residential activity patterns can be clustered based on the pesticide of interest and the geographic area of concern (e.g., termiticide use will differ between geographic regions and the residential activity patterns will also differ, consider Florida vs. the Northeast and the fact that older homes typically exist in the Northeast, more open ventilation is common in the south due to the weather patterns and HVAC/construction techniques differ from the North to South thereby having significant impact on air exchange rates). All activity patterns within a test domicile during any study must be thoroughly documented to allow adequate analysis of any parameter which may significantly impact on exposure levels and/or residue dissipation rates. These parameters include, but are not limited to, the following: HVAC system use; ventilation patterns; lighting use (e.g., for photolabile chemicals); detailed descriptions of

surfaces involved in residue dissipation monitoring; and ambient temperature changes during the study.

**Outdoor Sites:** As indicated above, clearly defining residential activity patterns for any study conducted is critical to the acceptability of the study to the Agency. There is a significant initiative within the Agency to obtain more, higher quality information than is currently available. Outdoor residential patterns differ, obviously, from household to household. However, the Agency believes that outdoor residential activity patterns can be clustered based on the pesticide of interest and the geographic area of concern as above with the indoor residential activity patterns (e.g., lawn chemicals, their uses differ between geographic regions and outdoor residential activity patterns will also differ, consider Florida vs. the Northeast).

## 2.5 Use Patterns

To be considered acceptable by the Agency, dissipation and exposure data submitted for registration support must have been generated under conditions that are consistent with the label requirements of the formulated end-use product.

**Application Rates and Techniques:** All pesticide labels prescribe the methods used for the application of the end-use product. The maximum application rate indicated on the product label for the particular target of interest must be used to make all applications throughout a study to estimate the maximum potential for exposure unless otherwise indicated by the Agency. [Note: the Agency reserves the right to alter this requirement, particularly for chemicals with chronic toxicity concerns associated with them.] As numerous pesticide active ingredients are typically labeled for a broad spectrum of uses, the Agency is first interested in those uses where the combination of application rate, application method, and worker activity create the highest potential for exposure.

**Representative End-Use Products:** Representative end-use products (i.e., wettable powders, emulsifiable concentrates, etc.) must be used to make all treatment(s) to the target(s) of interest. Significant differences in residue dissipation rates and exposure levels have been demonstrated to exist between end-use products containing the same active ingredient. Therefore, the end-use product to be applied must be a formulation type known to be most persistent (e.g., a wettable powder) and/or that inherently poses the highest risk in terms of human exposure during reentry operations.

**Seasonal Accuracy:** Studies should be conducted during the season(s) when reentry exposure is of most concern and where conditions pose the greatest risk for human exposure. Data must be collected during the time of the year that the particular reentry operations in question are performed. For example, simulating a harvest operation in the spring when harvest is typically in the fall is not acceptable without prior approval of the Agency (e.g., simulated harvest on tree fruit could entail entering a "cherry picker" and pretending to harvest fruit or performing some other operation such as pruning).

**Application Targets of Interest:** Application targets must represent a typical example for the post-application scenario of concern. Examples include trellising grapes in California and staking tomatoes in Florida. Study results can be skewed if the targets are not representative of those during routine post-application procedures (i.e., reentry to harvest fruit or reentry into a treated facility/domicile). Investigators must provide documentation regarding typical practices associated with a pesticide's use patterns to ensure acceptability to the Agency (i.e., document use practices, see below).

**Geographic Requirements:** Data must be collected in those geographic regions where the targets are typically found and the pesticides of interest are generally used. Several environmental factors, such as soil types and pest populations, may vary among regions thereby warranting various differences in use patterns which may affect the acceptability of an exposure assessment.

## 3.0 LABORATORY STUDIES NECESSARY BEFORE FIELD STUDIES ARE INITIATED

### 3.1 Analytical Method Development/Validation

Analytical methods and sample collection procedures must be validated before field samples are collected. Previously existing analytical methods that are used in the development of new analysis techniques should be referenced by investigators in any submission to the Agency. Researchers must consider the available toxicity data (acute and chronic) during the protocol and analytical method development phase of the study. In other words, analytical methods must be developed that are sensitive enough so that exposures based on LOD/LOQ do not yield unacceptable risks. Defining sample collection procedures prior to initiating the field phase of any study ensures added integrity for the samples. It also lowers the risk to the investigators of study failure due to unforeseen analytical problems.

**Method Development:** To summarize, analytical method development is the process by which scientific principles are applied to define the sample techniques that allow the reliable analysis of specific analytes of interest from a sample matrix. Method development is not covered by any EPA guidelines, nor is it required to be performed under the scope of the Good Laboratory Practices (GLPs). The method should be capable of laboratory recoveries in the range of 70-120 percent during normal operations. A coefficient of variation for duplicates in the same set/batch should be no more than 20 percent. Field recoveries should be no lower than 50 percent within any set/batch. Properly defining a percent recovery value cannot be underestimated. Recovery values are used by the Agency for several purposes, including but not limited to: regulatory acceptability; correcting exposure values; and categorizing data for use as a potential source of surrogate data. Laboratory recovery values (i.e., samples fortified to validate method performance in a laboratory) of less than 50 percent will be judged inadequate by the Agency unless investigators provide justification for their use. Investigators should attempt to develop analytical methods that have quantification limits of 0.01 $\mu g/cm^2$ or lower for any dermal or FDR sample matrix. Inhalation exposure monitoring methods should be capable of, at a minimum, monitoring an average exposure level of 0.01 $\mu g$/liter of air sampled.

ISSUE: Are these detection limits reasonable? Should detection limits be based on the toxicity of the compound? One approach would be to set these limits at one percent of the dermal NOEL (mg/kg). In some definitions, the detection level is 3 x SD while quantitation levels are 10 x SD (ACS Committee on Environmental Improvement, "Principles of Environmental Analysis," Analytical Chemistry, 1983, 55 2210-2216).

ISSUE: Soil methods present a problem. Recoveries for soil may be as low as 50% in which case the coefficient of variation has to be low (less than 15%) to avoid false negatives. If recoveries are low and coefficients of variations are high, a non-detect may actually be a positive and the exposure estimation will be too low. For these cases, replicates of all samples and QC samples will be needed. The number of replicates will need to be determined with a goal that the 99% confidence limits do not include zero. (Statistics for Analytical Chemistry, Miller and Miller, John Wiley and Sons).

**Method Validation:** Establishes performance criteria for a particular method (e.g., the expected accuracy, precision, and specificity of a procedure for specific concentration ranges). Method validation includes the analysis of a range of recovery samples for each matrix. Performance criteria should include a demonstration of the capability to attain reproducible results when measuring analytes at the desired level of sensitivity for all substrates prior to the initiation of field studies. Seven samples per fortification level per matrix are required (U.S. EPA, 1986). The completion of all validation work prior to the initiation of field studies is not mandatory, but it is advisable. Method validation experiments must be conducted under GLP standards. Minimally, the analytical method validation must include the following:

(1) Establishment of the method's working concentration range of expected values from the field studies.

(2) Determination of detector response over a reasonable standard concentration range.

(3) Determination of the accuracy of the method through a recovery experiment which should include fortification of the substrate at the following levels:

- the method limit of quantitation (LOQ),
- an intermatriceste concentration level (e.g., 10x LOQ),
- the maximum concentration of the validation range (e.g., 100 - 1000x LOQ), and
- blank or control substrate.

(4) Determination of the precision of the method by analyzing at least 7 replicates of each fortification level indicated above. However, for those compounds that have been used extensively by the investigator on similar matrices, less than 7 replicates per fortification level may be allowed. Before proceeding with less than 7 replicates, the investigator needs to present the method validation results of other studies and should receive prior approval by the Agency.

**Optional Pre-Trial Field Recovery Study:** Development of an exposure monitoring method may include three phases: (1) the types of monitor(s) to be considered for validation by the investigator should be selected based on: literature review, Agency recommendations, experience, etc.; (2) an analytical method must be developed and sufficiently validated; and (3) the final selection of a sampling protocol may be based on the results of a rangefinder.

Rangefinder studies are intended to provide simulated field recovery results prior to going into the field phase of a study under anticipated ambient field conditions. As this aspect of conducting an exposure study is optional and is intended only to further minimize the risk to investigators the Agency will not require that a specific number of samples be completed. However, it is recommended that any investigator who intends to complete a rangefinder study consult the guidance below for field recovery samples. Laboratory incubators can be used to simulate anticipated field temperature and humidity conditions. If environmental conditions are anticipated to change during sampling intervals, then a worst-case scenario (i.e., most chances for volatilization/degradation) should be simulated. For example, drastic changes in relative humidity in the San Joaquin Valley of California during a typical day indicate that for a photolabile pesticide the study should be conducted in a simulated arid environment (e.g., dry, hot, intense light). Worst-case scenarios should be supported by investigators by providing data pertaining to the physical/chemical characteristics of the pesticide(s) being studied and the anticipated climate where the study is to be conducted.

### 3.2 Logistical Considerations

Logistics pertaining to the preparation and storage of any dosimeter/monitor must be considered by investigators. The design and construction techniques used to prepare the various field dosimeters must be based on the analytical method validation results. To summarize, investigators should thoroughly document any procedure used to prepare a field dosimeter. Such critical issues may include, but are not limited to: solvent extraction procedures for whole-body dosimeters such as a batch-type process; use of dosimeters in a study from the same production lot; and storage conditions for dosimeters prior to the field phase. [Further input TBA -- dosimeter prep., similar lot #s for chemicals & dosimeters, pre-extraction, etc.]

## 4.0 FIELD CONSIDERATIONS

Proper quality control and quality assurance measures during the field phase of a study are critical to the scientific validity of the study and to the regulatory acceptability of the study. There are two aspects to data collection in the field: analytical field operations, and field data collection. Analytical field operations are geared toward quantitatively tracking the residue of concern throughout the field phase of a study (e.g., field recovery samples, optional travel spikes, spiking procedures and the selection of a clean control site). The scope of the second aspect of the field phase of the study pertains to the proper documentation of all activities completed during the field phase of a study. Critical issues include: study site characteristics; application equipment/parameters; climatological data; sampling equipment/techniques; quality control and sample generation; dosimeter/sampler

locations; human activity patterns; and sample storage/shipment. A discussion of each of the issues described above is presented below.

## 4.1 Analytical Field QA/QC Operations

As described above, analytical QA/QC considerations during the field trials of any study pertain to quantitatively tracking the residue of concern. The most effective mechanism for completing this effort is through a properly executed field recovery regimen. Field recovery samples must be included in a study to allow the experimental data to be corrected for losses that occur during all phases of sample collection and analysis. Specifically, field recovery samples account for losses that occur during sample collection. Additionally, field recovery samples may account for residue losses during sample handling and storage in the field, transportation from the field to the laboratory, storage in the laboratory, sample extraction and analysis depending upon the field sampling and analytical regimen. Travel spikes can also be prepared in the field and shipped and stored with the experimental samples. The results of the travel spikes provide a basis for estimating the losses that occur during sample shipment and storage as opposed to those which occur during sample collection. The inclusion of travel spikes is recommended, but not required.

## 4.2 Field Recovery

Field recovery refers to data generated to determine the loss of analyte from sample collection devices fortified in the field, when subjected to the same environmental conditions (e.g., temperature, light, relative humidity, wind) and duration as field exposure samples. As above, dependent upon study design, field recovery samples may also reflect the total of losses that occur during sample collection, shipment, storage, and analysis.

Ideally, a separate set of field recovery samples should be collected for each work cycle at each site. From a logistical standpoint, however, it is often more practical to collect one set of field recovery samples to represent all work cycles at a given site monitored on a given day. This approach is acceptable provided the field recovery samples are collected in a manner that produces the most conservative estimates of recovery (e.g., collected during the highest temperature, wind and/or relative humidity present during any of the work cycles). It may also be acceptable to collect a single set of field recovery samples for all of the worker replicates monitored at a given site over the course of a few days if the environmental conditions are similar each day. This approach is recommended for compounds that are very stable only, and in locations where the climate does not change appreciably from one day to the next during monitoring. The investigator who chooses this approach

to generating field recovery data must demonstrate the stability of the compound as well as the day-to-day consistency of the climate at the study site(s).

A complete set of field recovery samples are used to represent all workers monitored for each sampling matrix during a work cycle irrespective of their particular job function. In addition, the number of field recovery samples collected during a work cycle is not influenced by the number of workers being monitored. A complete set of field recoveries should consist of 3 or more each of blank control samples, low level spikes, and high level spikes. The low and high level spikes should be in the range of the anticipated level of the chemical on the substrate. If the highest expected level is more than 100X the lowest spiking level, it is recommended that a mid-level of fortification be included.

It is advisable to generate sufficient field recovery samples to be analyzed with the actual field samples to serve as concurrent laboratory recovery. At a minimum, a complete set of field recoveries, preferably fortified with formulated product (see Section XXXXX), would consist of the following, when applicable:

**Air sampling matrices**: An appropriate number of controls, low level spikes, and high level spikes should be prepared and analyzed. The analyte should be added to the collection matrices in the field at the time of the study. After fortification and the delivery solvent evaporation, the fortified matrices should be exposed to ambient conditions and attached to air pumps. The pumps should be operated in clean air at a flow rate, and for the length of time, equivalent to the field samples.

**Patches**: An appropriate number of controls, low level spikes, and high level spikes should be prepared and analyzed. The number of patches is irrespective of whether the worker wears one patch or 22 patches. However, if some of the patches are covered by clothing (inside patches versus outside patches), a separate set of fortified patches may be prepared and covered by clothing during the exposure period at the control site. If necessary, fortified outside patches can be substituted for fortified inside patches as they represent the worst case.

**Whole Body Dosimeters (WBDs)**: Preferably, investigators should collect field samples from test subjects in a manner that reflects the exposure to various regions of the body (e.g., field samples should be sectioned into samples of the following: arms, legs, front torso, back torso). A field quality control regimen should reflect this type of study protocol by using pieces of test garments for fortification as field recovery samples. Investigators must use discretion when preparing samples. For example, investigators could split a garment

designated for QC purposes into samples that are reflective of the field samples (e.g., arms or legs) or into smaller fabric swatches (e.g., 100 $cm^2$) and fortify the individual samples. However, several issues exist which must be considered when attempting to prepare such samples. First, fortification levels must reflect the relative size of the QC fabric swatch samples as opposed to a typical sample (i.e., the fortification level should be similar to the anticipated field sample levels on a per area basis as analytical background may be important in the data interpretation). Second, QC sample swatches must be generated from the same production lots of dosimeters and prepared in the same manner (e.g., pre-extraction) as the monitors used to collect the actual field samples. Finally, the quantitation limit for each particular matrix must be considered when specifying fortification levels (e.g., the determination of low fortification levels when prorating based on the surface area of the sample). The use of the patch will conserve considerable storage space and solvent usage. The similarity of recoveries should be established during method development and validation. If it is established that the spiking of patches yields results similar to whole sections of the WBD, it is acceptable to use patches for field recovery samples.

**Gloves, socks, briefs, head bands, etc:** Exposed clothing items, such as gloves (if used as a dosimeter), are to be fortified at both the low level and the high level. Covered items, such as briefs, may only need to be spiked at the low level, covered, and exposed to the elements at the control site.

**Hand rinses, urine:** It is not appropriate to expose hand rinse samples to the environment during the field phase of a study since they are collected, processed, and stored immediately, without significant exposure to the elements. However, all samples should be handled using the same procedures as the actual field samples. Example, spiked hand rinse solutions should be "set out," for as long as it takes to conduct a hand wash (10-15 minutes), prior to storage or packing for shipment. If urine is collected for biological monitoring, it is recommended that 3 samples of control (non-participant or pre-participation) urine be fortified with 2 levels of the urinary analyte (parent or metabolite(s), whichever is appropriate) for each experimental site. These fortifications may be made just prior to going to the field, carried into the field during the course of a work cycle, exposed in a manner similar to participants' urine, and stored and shipped with experimental samples. If stability of the analyte(s) has been rigorously established prior to study initiation, investigators may choose to reduce or eliminate this component from the study design because it is a burdensome task.

**ISSUE: For foliar dislodgable residue dissipation and soil residue dissipation studies, what type of samples should serve as controls and what spiking procedures are preferable?**

## 4.3 Travel Spikes

Travel spikes refer to data from experiments conducted to determine the stability of the analyte on each sampling matrix during shipment and possibly storage. Travel spikes are optional and are left up to the discretion of the investigator. These recovery samples are prepared concurrently with the field portion of the study. They are then shipped and stored with the appropriate experimental samples. Note: There is a significant difference between travel spikes and field recovery samples. The travel spike samples are not exposed to the environmental conditions during the sample collection period. Thus, the results of the travel spike samples reflect losses which may occur during shipment and storage only as opposed to those which occur during sample collection, shipment and storage. It is suggested that one set of travel spike samples be prepared for each experimental site to aid in the interpretation of losses that may occur in field recovery samples. If field recovery samples indicate no significant losses, the travel spikes do not need to be analyzed.

## 4.4 Spiking/Fortification Solutions

If the pesticide is to be applied as a spray, it is preferred that the fortifications of dermal collection devices be made with the formulated pesticide product diluted in the spray matrix (usually water). The concentration may have to be adjusted for spiking at multiple levels. For products applied as a solid (granules, pellets), or for formulations in which it is difficult to get a uniform suspension, and for air collection devices, it is recommended that a solution, usually in an organic solvent of the neat analyte, be used for fortifying all substrates. Such a solution is also recommended for fortifying hand rinse solutions and control urine samples. The organic solvent used to spike the control should not change extraction characteristics as typically an extremely low volume of a highly concentrated solution is used to fortify samples.

## 4.5 Control Site

Blanks and field recoveries are to be located at a "control site" that is upwind and a reasonable distance from the treatment site to avoid contamination of the dosimeters during reentry monitoring. Good planning and adequate resources are required to have the control site established, and all fortified and control collection devices "running" while the field monitoring is in progress.

The exposure time at the control site should approximate the field sampling time as closely as possible.

## 4.6 Field Data Collection

Comprehensive and accurately written field records are critical to obtaining good study results. Electronic records (photographs and videotape) used to supplement a study are helpful. Researchers should consider photographing and/or videotaping the following study phases:

- Study Site Characteristics;
- Application Equipment and Procedures;
- Climatological Data
- Sampling Equipment/Techniques;
- Quality Control and Sample Generation;
- Dosimeter/Sampler Location;
- Human Activity Patterns; and
- Sample Storage and Shipment.

Data collection requirements inherent for any successful study are described below for all phases of a field trial. See Guideline XXXX: Data Reporting Guidelines for additional information as well as for example forms suggested by the Agency for recordkeeping purposes.

## 4.7 Study Site Characteristics

An accurate description of each study site must be included as part of any submission to the Agency. Boundaries, topography, equipment, and the like must be described in detail. Diagrams and/or text must be used when describing the boundaries and topography of a site. Any equipment that is permanently situated onsite that might influence the exposure measurements must be described in the field notes, including such items as:

- Blocking and shade cloth arrangements in greenhouses;
- Ventilation systems; and
- Automated control systems (e.g., greenhouse climate, irrigation, etc.).

Both soil and irrigation water must be characterized where applicable. Soil characterizations must include texture and classification.

## 4.8 Application Equipment and Procedures

Application procedures must be thoroughly documented. Sprayer calibration, tank mix, and formulated pesticide product samples as well as photographic and videotape records are essential in determining whether or not an application is valid. Valid application procedures are essential to any acceptable study.

All application equipment used in a study must be calibrated. If all applications in a multi-application study use the same equipment, then only one calibration is required as long as the application parameters at each site are similar. End-use product samples should be taken and analyzed for validation purposes. In cases where collecting a representative sample is difficult, adequate discussion and background data must be included in any submission to explain why samples were not collected or why the analyses indicate very poor results.

| ISSUE: What if the applications occur over several weeks. Only one calibration? |
|---|

Any equipment that is used during a study such as mechanized harvesting equipment, tractors, hand tools, and stationary packing equipment, must be completely documented. This description should include the following characteristics:

- Equipment capacity (mechanical harvesters, "cherry" pickers, etc.);
- Attainable height (e.g., ladder height, cherry picker height, etc.);
- Equipment model/operating parameters;
- Hand tools (type, size, uses); and
- Picking site logistics/ergonomic factors.

## 4.9 Climatological Data

The following types of data are required, where appropriate, for foliar dislodgable residue and soil residue dissipation studies:

- Air and surface soil temperature extremes (minimum and maximum, soils: 0-6" layer);

- Precipitation (natural and irrigation); and
- Relative humidity.

Study conditions and the physical/chemical properties of the pesticide(s) may require that the following additional information be collected:

- Pan evaporation;
- Average wind patterns;
- Dew point;
- Solar radiation; and
- Ventilation/lighting patterns (e.g., greenhouses).

Measurements must be taken at least once a day, preferably within the same time frame each day (± 2 hours). If available, continuous recording devices should be used, since complete records will provide a more comprehensive view of the relationship between weather patterns and residue dissipation rates, to collect the following:

- Air temperature;
- Wind speed and direction;
- Relative humidity (or "wet bulb" temperature from sling psychrometer); and
- Ventilation/lighting patterns (e.g., greenhouses).

Additional data may be required. The Agency will note these data on a case by case basis.

The use of climate data from offsite sources may be acceptable. Investigators must use their discretion when identifying sources of surrogate data. For example, climatological data from weather station observatories near a study site can serve as an acceptable surrogate for weather information monitored onsite if it can be determined that large variances do not exist between the climatic conditions at the two locations (e.g., spot check similarities at various intervals). On-site monitoring of rainfall is recommended. If surrogate data are used, a general discussion regarding why they were used must be included in any submission. The acceptability of the surrogate data will be judged on a case by case basis (See Section XXXX).

**ISSUE: Is calibration of anemometer required?**

## 4.10 Sampling Equipment/Techniques

A complete description of any sampling techniques utilized by an investigator throughout the course of any study must be provided. The following types of information are required:

- Sampler make and model information;
- SOPs for sampler usage;
- Dosimeter design and attachment mechanisms;

**ISSUE: Further information will be added here.**

## 4.11 Quality Control and Sample Generation

Any sample collection equipment used in a study by an investigator must be validated and/or calibrated. Examples include: personal sampling pumps must be calibrated using a device which is traceable to a primary standard (e.g., bubble meter or, magnahelic or"Buck-Type" Calibrator); thermometers used in any study must be traceable to a NIST primary standard; and weights used to calibrate analytical balances must also be traceable to NIST primary standards (e.g., class P or better ????).

**ISSUE: Further information will be added here.**

## 4.12 Dosimeter/Sample Location

A complete description of any sampling regimens utilized by an investigator throughout the course of any study must be completely described. The following types of information are required:

- Dosimeter location on each test subject;
- FDR Sampling regimen (e.g., Iwata Method for Trees);
- Stationary Air Sampler Placement;

**ISSUE: Further information will be added here.**

## 4.13 Human Activity Patterns

Test subject activities must be thoroughly described. Activities may include the following:

- Scouting;
- Cultural Maintenance (e.g., grape girdling, staking tomatoes);
- Harvesting;
- Preplanting field preparation;
- Packing;
- Indoor residential activities; and
- Outdoor residential activities.

Protocols, for the most part, should be developed to mimic upper-end exposure scenarios unless specified by the Agency. Sufficient information/data must be provided to verify that the activities in a study mimicked these upper-end exposure activities of interest.

The following types of records should be kept as an effective means of relating a test subject's work habits and body mechanics to exposure levels:

- Efficiency (e.g., lb harvested, rows trimmed, etc.);
- Body mechanics (e.g., routinely touches ground, bends or kneels down, etc.);
- Proportions (approximate height and weight);
- Routinely used equipment; and
- Type of clothing worn (protective and/or normal work clothing).

**ISSUE: Further information will be added here based on ORD/EMSL-LV input.**

## 5.0 ANALYTICAL PHASE

A wide variety of techniques can be employed in the development of an instrumental method. For example, gas chromatography (GC) or high performance liquid chromatography (HPLC) method development can employ a wide variety of columns and instrument operating conditions. Complete instrumental methods must be supplied in any submission to the Agency.

The basis for any modern analytical method is the instrumentation. Instrumental methods that are both sensitive and stable should be developed. Peaks of interest should readily be separated from contaminant peaks by intervals (e.g., time, wavelength, etc.) that are large enough to allow for accurate resolution and quantification of the peaks of interest. The lowest level analytical (i.e., calibration) standard should produce a signal that is at least two times greater in magnitude than the noise. In other words, the instrumental signal to noise ratio must be $\geq 2$ for the lowest standard.

### 5.1 Instrument Performance

Instrument performance must be monitored regularly to ensure the reliability of the measurements. Several techniques that can be used to establish instrument performance include, but are not limited to: (1) internal standards, (2) daily comparison of peak areas of analytical standards, or (3) calculation of a correlation coefficient for a particular standard curve. Investigators must establish their own guidelines for determining whether an instrument is functioning properly, as this determination is dependent upon the analytical method, instrument operating parameters, and background levels observed/anticipated in the samples. Investigators should describe in detail any procedures used to monitor instrument performance on a routine basis.

Determining the proper instrument operational quality control procedures is difficult. Investigators must develop operational standards that are pertinent to the pesticide(s) being studied (e.g., detector response patterns affect calibration techniques). Investigators must also develop criteria for scrutinizing daily method performance data. The Agency, however, recognizes that recovery results are proportional to the extraction and instrumental methods as well as the physical/chemical characteristics of the pesticide(s) being studied. Therefore, studies for which the recovery results are marginal will be considered on a case by case basis by the Agency. Investigators should be careful to provide justifications as to why their analytical methods and results appear to be marginal.

## 5.2 Calibration Techniques

As described above, investigators have the option of calculating results in a variety of ways. Interpretation of basic results, however, demands generating a standard (i.e., calibration) curve to which responses from sample extracts can be compared. If calculations are to be done manually, for example, a linear regression analysis can be performed. Investigators should describe all techniques used to calibrate instruments and calculate residue levels. Data integration systems, besides enabling investigators to manipulate/interpret data in a variety of ways (i.e., various peak integration techniques), also typically generate calibration curves as well as calculate and summarize results. Several options for generating calibration curves are usually available in each system (e.g., linear regression for all points, point to point calibration, average values based on multiple analysis, etc.). Investigators must be careful to consider the response patterns of a particular instrumental system (i.e., linear, exponential, threshold, etc.) prior to selecting a means to generate the calibration curve. Technique(s) employed by investigators to calibrate an instrument should be described in any submission to the Agency.

## 5.3 Concurrent Laboratory Recovery

Concurrent laboratory recovery data are data analyzed in the analytical laboratory concurrently with the field samples to determine the recovery efficiency of the analyte from substrates. Laboratory recoveries, typically fortified with technical standards, reflect losses which occur during laboratory operations (extraction, clean-up, analytical measurement, etc.). They do not account for losses which occur during sample collection, shipping or storage. It is recommended that a minimum of 10 percent of the field samples be represented by a laboratory recovery sample for each analytical batch/run, and they should cover the range of concentrations anticipated in field samples.

Concurrent laboratory recovery samples can be either field QA/QC samples analyzed concurrently with the actual field samples or laboratory samples generated (i.e., fortified) in the laboratory. It is recommended that the field QA/QC samples be used as concurrent laboratory samples. When used in this manner, the field QA/QC samples could be used to correct the field samples for both losses in the field and laboratory. However, if the investigator is not confident of the environment fate of the compound in the field and during storage, recovery samples generated in the laboratory should be used to identify where the losses may have occurred (i.e, field or analytical method).

### 5.4 Storage Stability Study

A storage stability study can be conducted prior to or in conjunction with a field study. Its purpose is to determine the stability of analyte(s) in or on appropriate sample matrices under similar storage conditions that will be used to store field samples. Conducting a storage stability study prior to study initiation may eliminate the need for generating storage recovery data during the field conduct of the study.

A storage stability study should include the following parameters:

- preparation and analysis of at least 3 blanks, 3 low-level spikes (2-10X the LOQ), and 3 high level spikes in the expected range of field samples for each storage interval, including the longest interval planned for storage of field samples; and

- storage of stability samples under the same conditions of storage as planned for the field samples (e.g., sample matrices or extracts, ambient temperature and/or frozen, etc ...).

A storage stability study, preliminary, or in conjunction with the field study, is optional if the field QA/QC samples are stored and analyzed with the actual field samples.

## 6.0 SAMPLE HANDLING PROCEDURES

Sample storage and shipment procedures as well as the chain-of-custody system must be documented in full. "The climate in the agrochemical industry has changed over the past two years from limited to total documentation of chain of custody. This change is the result of the Good Laboratory Practice Standards that were enacted in October 1989. Documentation of chain of custody is necessary to provide information concerning the handling of test substances, reference substances, control samples, and treated samples within the analytical laboratory. Chain of custody includes not only the receipt of a substance, but also from whom that substance was received and the condition of the sample upon receipt. Once a substance or sample is in the possession of the analytical laboratory, the storage conditions must be documented. Chain-of-custody documentation provides a 'paper trail' that tracks the removal of these items from storage for any reason: weighing, mixing, spraying, sampling, processing, assay, or shipment" (Garner et al. 1992).

### 6.1 Sample Storage and Shipment

### 6.2 Field Phase

**ISSUE: Further information will be added here.**

### 6.3 Analytical Phase

**ISSUE: Further information will be added here.**

### 6.4 Chain-of-Custody

**ISSUE: Further information will be added here.**

## 7.0 DATA REPORTING

Ideally, all reported values should be greater than or equal to the QL. Any values less than the QL should be reported as nondetectables. An alternative for values less than the QL but greater than or equal to the LOD is to report the value but indicate that the value is less than the QL.

Laboratory results can be calculated and presented using a variety of means. All methods are acceptable to the Agency; however, they must be fully described. Data reduction worksheets should be supplied in any submission to the Agency.

Field exposure samples are corrected based on the field recovery efficiency measured on the day of sampling. This approach involves collection of a set of field recovery samples during each exposure monitoring period on a given day, or a single set of recovery samples collected to represent all exposure monitoring periods for that day (see Section XXXX). These recoveries correct for the day-to-day variations in environmental conditions and produce more specific results for each sample

collection period. The field samples should be corrected for one of the following: field recoveries (if available), travel spikes (if available), storage stability (if available), or laboratory recovery.

In addition to the analytical results, the environmental/site conditions under which the test was conducted should be reported. Such parameters include: air temperature, relative humidity, and air flows for infiltration rates) or wind speed (indoors and outdoors, respectively).

**ISSUE: Further information will be added here.**

## 7.1 Treatment of Non-Quantifiable Residue Levels

**ISSUE: Further information will be added here.**

## 7.2 Presentation of Recovery Data

**ISSUE: Further information will be added here.**

## 7.3 Data Correction Procedures

Illustrated in Figure C-1 are the points in the sampling through sample analysis process that recoveries are used to correct data. [TBA: An explanation of table]

> ISSUE: Further information will be added here. This section will be integrated with Part D.

## 8.0 OTHER CONSIDERATIONS

### 8.1 Protection of Human Subjects

**The Worker Protection Standard:** In conducting any field study, the investigator must insure that the applicable provisions of the Worker Protection Standard regulations are being fulfilled. Generally, hazard information must be available for all workers, appropriate protective clothing must be provided, and decontamination sites and emergency assistance must be available. To determine what you must do to comply with the Worker Protection Standards, refer to:

> U.S. EPA. 1993. "The Worker Protection Standard for Agriculture Pesticides - How to Comply: What Employers Need to Know," EPA 735-B-93-001, July 1993.
>
> Available:
>
> For free by calling: 1-800-381-8473; or
>
> For sale at the Government Printing Office; Superintendent of Documents, Mail Stop SSOP; Washington, DC 10402-9328.

**Informed Consent:** Investigations carried out under these guidelines must be properly designed to provide for maximum protection of the study subject's health. Studies conducted to obtain human exposure data must not violate Section 12(a)2(P) of FIFRA. Specifically, informed consent should be obtained in writing from all subjects who will be exposed as a

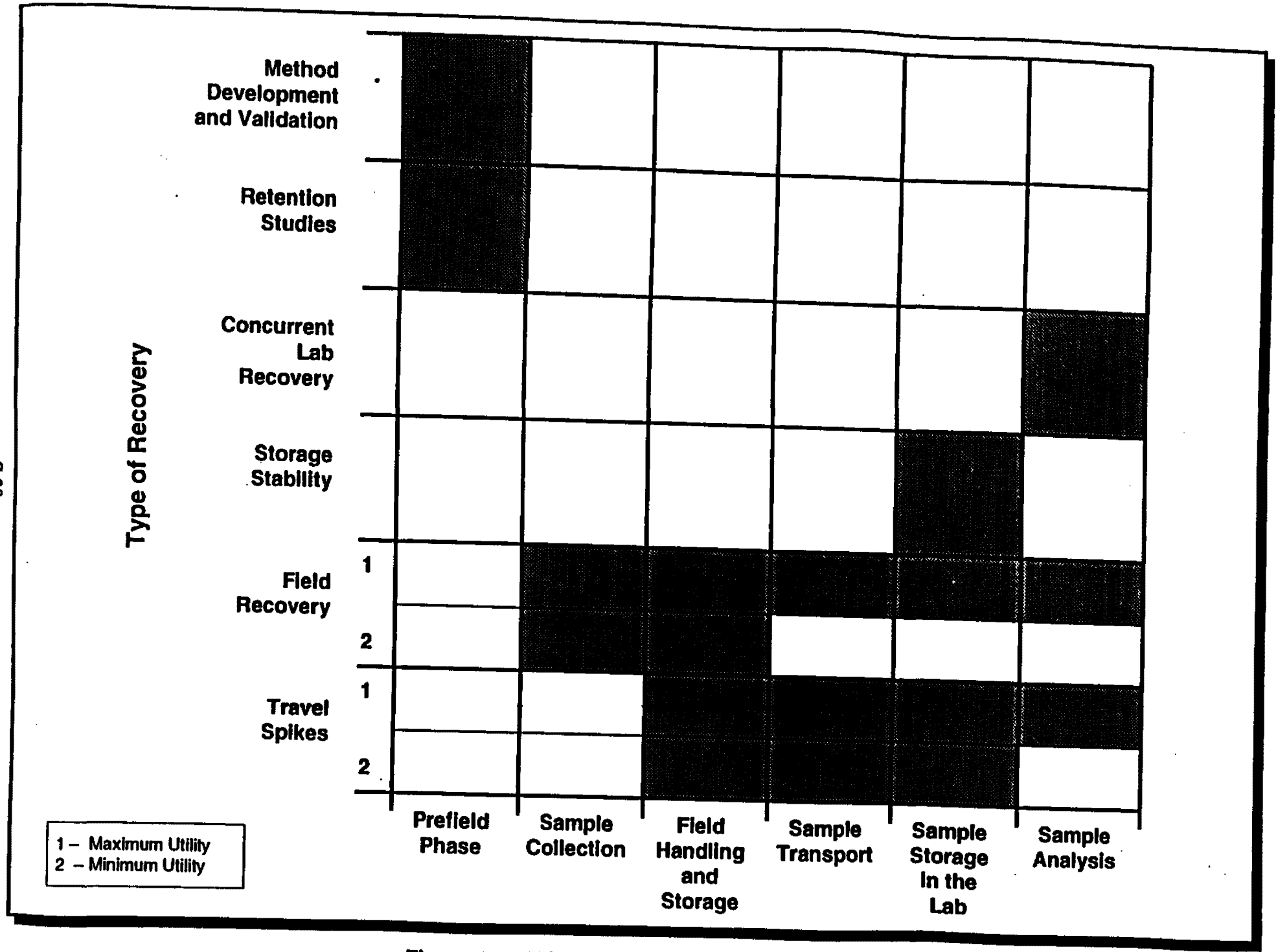


Figure C-1. Utility of Analytical Recovery Data

result of these studies. Also, proposed protocols may need to be approved by the appropriate human studies committee for the state in which the exposure will occur.

## 8.2 Consideration of Good Laboratory Practices

The provisions of the Good Laboratory Practice Standards (see 40 CFR 160) are intended to assure the quality and integrity of data submitted to the Agency. In conducting a study and submitting the data, the investigator must consider the provisions of the GLP standards. Some highlights of the GLP standards that are particularly applicable to post-application exposure studies include:

- Protocol (40 CFR 160.120) [TBA: Description of what's needed in a protocol]

- Test Substance Characterization (40 CFR 160.105). Test substances used in studies must be characterized according to the Good Laboratory Practices (GLPs) presented in 40 CFR 160. Registrants should characterize materials prior to performing field trials. Aliquots of the test substance(s) should be retained during field trials for analysis, if any questions arise regarding the validity of the test substance(s). Test substance(s) include for the purposes of Subdivision K any materials containing the pesticide(s) of interest used in field trials or sample analysis.

- Sample Receipt, Handling, and Tracking (40 CFR 160.XX). Critical to the success of any laboratory operation are the sample receipt, handling, and tracking procedures. Each sample must be identified with an individual code number. Sample receipt and storage inventories must also be maintained in accordance with the GLPs. Storage facilities must be maintained at constant temperatures. Daily records must be collected to verify conditions. Sample shipments must be made using the most expeditious method (e.g., overnight air express services) to ensure the integrity of the field samples. Laboratory operations should maintain Standard Operating Procedures (SOPs) for the operations described above.

- Sample Storage (40 CFR 160.XX). As soon as [the samples reach] the laboratory from the field, all samples held in ice chests must be stored in a freezer pending further treatment. A sample history sheet should be prepared to document laboratory operations. A convenient sheet of this type contains columns labeled: sample number, date sample was collected, date of extraction, date of analysis, and the name(s) of the individual(s) responsible for the task. The lower portion of the sheet

contains spaces for recording the conditions of storage for pads, other matrices, extracts, the extraction procedure employed, and the analytical procedure used. A suggested form of sample history sheet is presented in Guideline XXXX.

| ISSUE: | Should we highlight other provisions of the GLPs? Are there areas of the GLPs where investigators would need additional guidance? |
|---|---|

## REFERENCES FOR PART C

Garner, W.Y.; Barge, M.S.; Ussary, J.P., eds. 1992. Good Laboratory Practice Standards: Applications for Field and Laboratory Studies. American Chemical Society, Washington, DC.

Taylor, John K. 1987. Quality Assurance of Chemical Measurements. Lewis Publishers, Inc. Chelsea, Michigan.

U.S. EPA. 1986. Pesticide assessment guidelines. Subdivision U. Applicator exposure monitoring. Washington, DC: Office of Pesticide Programs. USEPA Publication No. 540/9-87-127. NTIS Publication No. PB87-133286.

U.S. EPA. 1993. The Worker Protection Standard for Agricultural Pesticides - How to Comply What Employers Need to Know. EPA 735-B-93-001. July 1993.

# PART D

# EXPOSURE AND RISK ASSESSMENT

# PART D - CHAPTER 1
# FUNDAMENTALS OF EXPOSURE AND RISK ASSESSMENT

[TBA]

## 1.1 The Basics of Exposure and Risk Assessment

There are four steps in EPA's risk assessment process: hazard identification, dose/response assessment, exposure assessment, and risk characterization.

- Hazard Identification. EPA evaluates a pesticide's inherent toxicity - i.e., the types and degrees of harmful effects a pesticide may cause. This is done principally by evaluating laboratory studies conducted on animals. For example, laboratory studies attempt to determine if a chemical is an eye irritant, causes acute poisoning, causes birth defects, or causes cancer, among other effects. The *Hazard Identification* is generally done by HED's Toxicology Branches.

- Dose/Response Assessment. A pesticide's potential for causing adverse health effects is identified through a battery of short-term or acute, intermediate or subchronic and long-term or "chronic" toxicity testing. In several series of tests, laboratory animals are exposed to different doses of a pesticide, and EPA scientists evaluate the tests to find the level of exposure in each of those studies that did not cause any non-cancer effect. This level is called the "No-Observed-Adverse-Effect-Level," or NOAEL. The *Dose/Response Assessment* is done by HED's Toxicology Branches.

- Exposure Assessment. Once harmful health effects are identified in the laboratory tests, EPA must estimate the level, duration, and frequency, and route of exposure for people. For example: Are people who regularly mix and apply pesticides exposed? Is there a chance of exposure to people through food and drinking water? Can plants and animals other than the targeted pests be harmed or killed by the pesticides? *Exposure Assessment* is done by the Occupational and Residential Exposure Branch (for workers and other exposed populations) and the Chemistry Branches (for dietary).

- Risk Characterization. Finally, the risk from exposure to pesticides is estimated by integrating the above factors. By combining estimates of likely or actual pesticide exposure with the toxicity of the pesticide, EPA can characterize the risks that it poses. Simply stated,

RISK = Hazard x Exposure.

## 1.2 Exposure Descriptors [TBA]

## 1.3 Uncertainties in Exposure/Risk Assessment [TBA]

# PART D - CHAPTER 2
# CALCULATION OF POST-APPLICATION EXPOSURE AND AGRICULTURAL REENTRY INTERVALS

## 2.1 INTRODUCTION

This chapter provides information on the evaluation of both residue dissipation data and human exposure data. Strategies and assumptions for completing exposure and risk calculations based on post-application human exposure and residue monitoring data are included. Basic assumptions and factors are also described, within the context of specific calculations.

## 2.2 PURPOSE

The purpose of this part is to provide users of Series 875 - Group B with a guide for completing exposure and risk assessments for post-application pesticide use scenarios.

## 2.3 PRESENTATION AND BASIC MANIPULATION OF RAW DATA

This section provides guidance pertaining to data reporting and the basic manipulation of any raw data generated under Series 875 - Group B. Definitive Data Reporting Guidelines (DRGs) are included as Appendix I.

The types of data generated under Series 875-Part B include, but may not be limited to, the following:

- Pre-Field Data,
- Field Notes,
- Climatological Data,
- Characterization Data,
- Analytical Methodologies,

- Quality Control Data, and
- Residue Data/Results.

Critical reporting requirements along with requirements for the basic manipulation of the data are discussed below. The Agency encourages investigators to provide their data both electronically (e.g., standard commercially available spreadsheets such as Lotus, Quattro Pro or Excel) and in hardcopy. Data provided in electronic format may ease the Agency's review efforts by eliminating the data entry step and therefore, expedite the reregistration process. Where possible, each specific data point should be entered as an individual piece of information (i.e., individual cell in a spreadsheet).

| | |
|---|---|
| ISSUE: | Are spreadsheet programs, or is a database approach, more appropriate for reporting data of this nature? |
| ISSUE: | Standard formats for each type of data appropriate for electronic reporting need to be developed. |

### 2.3.1 Pre-field Data

Any data that are critical to the design and implementation of a study must be reported in any submission to the Agency. Pre-field data may include the following:

- Detailed Product Use Information,
- Activity Pattern Data,
- Environmental Fate and Transport Data,
- Analytical Methodology,
- Dosimeter Selection Criteria,

- Dosimeter Preparation Data, and
- Site Selection Criteria.

In general, the types of data described above will not typically require significant manipulation prior to use by the Agency. A succinct narrative that summarizes the data should be provided along with the raw data to ease the review process (e.g., Product Use Information, Fate and Transport Data, and Analytical Methodology). Any data used as a reference in this section (e.g., Fate and Transport Data generated under Subdivision N) that have been submitted to the Agency for other reregistration purposes must be clearly identified by the appropriate Agency coding system (e.g., MRID Number).

### 2.3.2 Field Notes

Field notes are a critical component to the successful completion of any study. Field notes should describe, in detail, all activities that occur during the field phase of a study. Field notes may include information pertaining to the following:

- Study Site Description and Map,
- Lot/Batch Numbers for Test Substance,
- Names of Individual Test Subjects,
- Exposure Monitoring Interval,
- Calibration Data for Application Equipment and Monitoring Devices,
- Field Recovery Sample Descriptions,
- Descriptions of Dosimeters, Personal Clothing and Protective Clothing/Equipment,
- Sample Locations in a Treated Area,
- Description of Sampling Equipment,

- Comments not Described in the Fields Above, and
- Any Protocol Deviations.

Typically, several of the types of data included in the list above should be reported electronically as well as in hardcopy. Any map/site description should be as detailed as possible as the Agency may apply Geographic Information System (GIS) technology to the analysis of these types of data. All data collected that are specific to each test subject should also be reported in electronic format for ease of analysis (e.g., exposure interval, personal monitoring pump calibration data, lot/batch number of end-use-product, and clothing/dosimeter scenario).

| ISSUE: | Should electronic format be standardized to include all of the appropriate fields in one spreadsheet/database record? |
|---|---|

### 2.3.3 Climatological Data

Climatological data may be collected using a variety of instruments or the data may be acquired from a variety of off-site sources. Most instruments currently used by investigators are not capable of generating data in an electronic format (e.g., the only way to retrieve the data is to read a meter and record the datapoint in a log book). Also, data retrieved from off-site sources such as NOAA (National Oceanic and Atmospheric Administration), may not be available electronically. However, climatological data should be reported in electronic format, if possible. Such data may include the following:

- Wind speed and direction,
- Solar Radiation,
- Pan Evaporation,
- Temperature (Air and Soil),

- Relative Humidity,
- Description of Weather Events and Irrigation Practices,
- Residential Practices (e.g., HVAC Set Points and Window Use),
- Industrial/Commercial Practices (e.g., Greenhouse Fan/Shade Cloth and Ventilation Practices), and
- Specific Descriptions of Monitoring Equipment.

Means, medians, and ranges for all appropriate data fields should be calculated and submitted (e.g., temperature and relative humidity over specific exposure intervals and/or study days).

| ISSUE: | Should electronic format be standardized to include all of the appropriate fields in one spreadsheet/database record? |
|---|---|

### 2.3.4 Characterization Data

Characterization data may be supplied by investigators for the test substance, study soils and water samples. Characterization of the test substance is a requirement of the Good Laboratory Practices (GLPs). Unless a significant number of lot/batches are used in a specific study there is no requirement for electronic reporting of this data. This is also true for soil and water characterization data unless a significant number of sites are utilized in a study. Typically, test substance characterization data include a description of the analytical procedure, raw data (e.g., chromatograms), and the results. Soil and water characterization data usually contain several categories of results (e.g., soil capacity, texture, pH, etc.).

### 2.3.5 Analytical Methodologies

Analytical methodologies should be developed and validated according to the guidance included in Series 875-Group B. Generally, all methods should be reported in the format required in PR Notice 88-5 (i.e., no independent laboratory method validation required). Only laboratory

validation results are required to be reported in electronic format if these data also have other significance to the study. All results should be reported on the basis of sample matrix. The following summaries of the raw data must be provided for all data:

- Quantification and detection limits for all matrices and how each value was determined,
- Means for all samples,
- Standard deviations ($\sigma$) for all samples,
- Number of replicates per calculation (n) and reason(s) for excluding any datapoints,
- Coefficients of variation (C.V.) for all samples:

$$C.V. = [(100 * (\sigma\ (\%)/Mean\ (\%)))], \text{ and} \qquad \text{Eqn. D2-1}$$

- 95 th percent confidence interval (upper and lower limits) at a minimum over all fortification levels:

$$95\%\ Conf.\ Interval = [Mean\ (\%) \pm ((\sigma\ (\%) * 1.96)/\sqrt{n})]. \qquad \text{Eqn. D2-2}$$

No sample results should be excluded from these calculations unless the exclusion of a datapoint can be justified (i.e., chain-of-custody problem or extraction/analysis problem).

| | |
|---|---|
| ISSUE: | Should any other basic manipulations of the data be completed? |
| ISSUE: | Should a grading criteria be developed in order to provide a systematic mechanism for the evaluation of the method validation data/design? |
| ISSUE: | Should a hierarchy be developed for correcting residue levels with various recovery results (e.g., field recovery values may be the highest priority)? |

### 2.3.6 Quality Control Data

Historically, the most common serious deficiencies in post-application exposure studies has been the lack of adequate quality control data and the lack of a standard reporting format. The various types of quality control data have been previously defined in this document. For example, these data include, but are not limited to, the following: field recovery, laboratory recovery, storage stability, travel spikes (See Part C QA/QC for overview and Figure C-1 for explanations of the various types of data). As above for the method validation results, the following basic summary statistics must be calculated for individual sample matrices/types:

- Means for all samples,
- Standard deviations ($\sigma$) for all samples,
- Number of replicates per calculation (n) and reason(s) for excluding any datapoints,
- Coefficients of variation for all samples (See Eqn. D2-1), and
- 95 th percent confidence interval (upper and lower limits) over all fortification levels (See Eqn. D2-2).

No sample results should be excluded from these calculations unless the exclusion of a datapoint can be justified (i.e., chain-of-custody problem or extraction/analysis problem). Additionally, the basic manipulation of the data should be completed only for individual types of data such as field recovery, laboratory recovery or storage stability. Combining different types of data to complete basic summary calculations is not acceptable and has been identified as a common error in post-application exposure study reports. All quality control data should be reported in electronic format and in hardcopy. Each individual datapoint must be be identified.

### 2.3.7 Residue Data

Data contained in post-application exposure studies can represent one of two types of residues including: (1) environmental matrix levels such as found in soil or foliar samples, and (2) dosimeter levels such as found in a whole-body dosimeters or filters used for inhalation monitoring.

Typically, environmental matrix data are presented as individual replicate sample results collected at specific intervals after application. All such data should be reported as individual

datapoints and not just means at each sampling interval. Residue levels should be presented on a $\mu g/cm^2$ basis where appropriate (e.g., foliar dislodgeable residue levels on a double-sided leaf where a single 1" diameter disc represents $10cm^2$ of surface area). Soil residue levels should be presented on a ppm basis (i.e., $\mu g/g$ of finely sifted soil).

Human exposure monitoring data are complex and may take many forms, depending upon the study design. Most investigators will usually opt to use passive dosimetry techniques for monitoring human exposure levels concurrent to the collection of environmental samples. [Note: For this reason, the discussion here will focus on the use of passive dosimetry. See environmental matrix description above for any discussion of biological monitoring data/results.] Typically, passive dosimetry data are presented as three distinct types of results, identified as the following:

- Dermal exposure (non-hand),
- Dermal exposure (hand), and
- Inhalation exposure.

Dermal (non-hand) exposure levels may be presented in a variety of fashions, depending upon the design of the study (i.e., which types of dosimeter are used). If the Durham and Wolfe patch technique is used, all raw data should be presented on a body sample location basis as $\mu g/cm^2$. If whole body-dosimetry is used in the study, all data should be reported either as: (1) total $\mu g$/sample, or (2) $\mu g/cm^2$, where the surface used to calculate the residue level is based on the unit surface areas for representative body parts presented in Table XXXX of this guideline. Dermal (hand) exposure levels should be presented as total $\mu g$/sample. Hand exposure monitoring samples can represent both hands combined or individual hands. Additionally, hand exposure results should be reported in a way that represents cumulative exposure over the course of an exposure monitoring interval (e.g., if hand samples were collected prior to lunch and at the end of a work day and if the dermal (nonhand) samples were collected only at the end of an exposure interval).

Inhalation data need to be reported in a slightly different format because of the nature of the monitoring techniques. The following types of data are typically required to calculate inhalation exposure levels:

- Residue levels presented as total ($\mu g$/sample),

- Flow rates (Lpm) when personal monitoring pumps are used for sampling (initial, final and mean values), and

- Conversion calculations for passive monitors, if used (e.g., equations for 3M™-type monitors).

## 2.4 EXPOSURE/RISK CALCULATIONS AND PARAMETERS

The purpose of this section is to describe required exposure and risk calculations that pertain to the evaluation of post-application exposure and residue dissipation data. Required types of calculations/parameters include: (1) residue dissipation kinetics, (2) determination of the proper exposure scenario based on detailed product use and activity pattern data, (3) exposure estimates (potential and internal), (4) relationship between activity, ambient residue levels, and exposure (e.g., transfer coefficients), and (5) the regulatory implications of these calculations (e.g., development of Restricted Entry Intervals and product use restrictions and/or cancellations).

All calculations and data manipulations described in this chapter pertain to the assessment of exposures and resultant risks associated with specific uses of a pesticide product. These calculations build upon the basic manipulations of the various types of data described above. Each of the five specific areas of interest are described below on an individual basis. Issues, scenarios and parameters that are pertinent to exposure calculations in specific settings are included as appropriate in each subsection (e.g., ambient concentrations in residential settings and on turf).

The Agency recommends that common, commercially available software packages/equipment be used to complete all calculations (e.g., spreadsheets such as Lotus, Quattro Pro or Excel and statisical packages such as SAS or SPSS). The mention of these products does not constitute official endorsement by the Agency. This recommendation is made to alleviate the need for additional resources to conduct the required quality assurance and review of technical submission.

### 2.4.1 Residue Dissipation Kinetics

Residue dissipation over time may be modelled using pseudo-first order reaction kinetics. Pseudo-first order kinetics are used because determining the actual dissipation mechanism is difficult. Historically, it has been noted that most pesticide residue dissipation occurs exponentially (i.e., in logarithmic fashion) thereby lending credence to the use of pseudo-first order reaction kinetics and other fairly standard treatments of the data.

The first objective for quantitatively describing residue dissipation of pesticide residues over time is to summarize the data as follows:

- Correction of residue levels for recovery values which must be completed for each specific matrix if the recovery correction factor is less than 90%. Recovery correction factors and the correction of residue levels are described in the equations below:

Recovery Correction Factor = ((Field/100) * (Lab/100) * (Storage/100)) (Eqn. D2-3)

Where:

Field = Mean field recovery for matrix (%),
Lab = Mean lab recovery for matrix (%), and
Storage = Mean storage stability recovery for matrix (%).

[Note: As described in the Part C: QA/QC, various combinations of recovery values may be appropriate for correcting residue data. For example, if a field recovery sample is generated concurrently with a field sample and then stored and analyzed concurrently with the field sample then only a correction for that field recovery sample analytical result is appropriate. Investigators must make judgements concerning this issue and clearly explain how residue data were corrected in any submission.]

Corrected Residue Level = Raw Value/Recovery Correction Factor (Eqn. D2-4)

Where:

Corrected Residue Level = Value to be used in all exposure calculations
Raw Value = Uncorrected residue value
Recovery Correction Factor (See Eqn. D2-3 above)

- Means for all replicate samples at a minimum for each sample interval,

- Standard deviations ($\sigma$) for all replicate samples at a minimum for each sample interval,

- Number of replicates per calculation (n) and reason(s) for excluding any replicates at each sample interval,

- Coefficients of variation for all replicate samples (See Eqn. D2-1), and
- 95 th percent confidence interval (upper and lower limits) for all replicate samples (See Eqn. D2-2).

The next objective is to develop an equation which describes the dissipation of residues over time. In most cases, the data will be lognormal. Therefore, the easiest approach is to plot the data (i.e., typically the means for all replicate samples collected at each interval) in a semilog fashion after log transformation of the pesticide residue levels at each sampling interval (i.e., as a convention, natural logs (ln) should be used). The next objective is to complete a linear regression of the data to determine if there is adequate correlation between the residue levels and the duration of the sample collection interval and to develop a linear equation which describes the dissipation of the pesticide residues of interest. The basic recommended equation (i.e., based on the simple $y = mx + b$) is presented below:

$$\text{Residue Level} = e^{([\text{PAI (Days)}] * \text{Slope}) + \text{Constant}} \qquad \text{(Eqn. D2-5)}$$

Where:

| | |
|---|---|
| e | = Inverse natural log (i.e., 2.718281828...), |
| PAI | = Post application interval (Days or Hours as appropriate), |
| Slope | = Slope of semilog plot of ((ln(residue)) vs. time (days or hours)), |
| Constant | = Y intercept of the plot, and |
| Residue Level | = FDR ($\mu g/cm^2$), Soil (ppm), etc. |

Calculation of the half-life for each analyte of concern should be completed using the following equation:

$$t_{1/2}\ (\text{Days}) = (0.693/K_a) \quad \text{where } K_a = \text{X Coefficient} \qquad \text{(Eqn. D2-6)}$$

An example calculation based on the guidance provided above is presented in Figures D-1 and D-2. These calculations and graph were completed using a commercially available spreadsheet program.

| | |
|---|---|
| ISSUE: | What other approaches should be recommended for data which do not easily fit the criteria described above (e.g., nonparametric analysis, 2nd or 3rd order kinetics, and more mechanistic approaches)? |
| ISSUE: | Are the use of commercial software packages acceptable? Should we discount any particular products because of demonstrated poor performance or inapplicability to these type of data? |
| ISSUE: | Should we develop acceptabilty criteria for various approaches to the analysis (e.G., Threshold limits for correlation coefficients calculated using the recommendations described above to indicate the use of the approach described above or to develop a novel approach)? |
| ISSUE: | Should t-tests, analysis-of-variance and other common statistical techniques be required on a routine basis, where appropriate? |
| ISSUE: | Should all datapoints be used in all calculations except for results which can be dismissed due to a collection, transit or laboratory error, or should a systematic approach for dropping data from calculations be agreed upon? Remember that most data of this nature are extremely variable and that differences over several orders of magnitude are not uncommon. |

[TBA]

Figure D-1. Example Kinetics Calculations

[TBA]

Figure D-2. Graph of Example Residue Dissipation Data Set

## 2.4.2 Exposure Calculations for Passive Dosimetry and Biological Monitoring of Human Test Subjects

The exposure calculations described in this section focus on summarizing human exposure monitoring data. Human exposure monitoring data should be reported based on the study design (i.e., passive dosimetry or biological monitoring). Calculations for dermal dosimetry and patch techniques and inhalation monitoring techniques are presented below.

- Correction of residue levels for recovery values using the equations as described in Section 2.4.1,

- Total potential dermal dose for each body part based on patch data and a series of standard surface areas (must complete for each body part)

$$Dose_{Pot}\ Dermal\ (Nonhand)/Body\ Part = Residue * Std.\ Surface\ Areas \qquad Eqn.\ D2\text{-}7$$

Where:

| | | |
|---|---|---|
| $Dose_{Pot}$ Dermal (Nonhand) | = | Potential exposure for specific body parts ($\mu g$), |
| Residue | = | Levels detected in patch ($\mu g/cm^2$), and |
| Std. Surface Areas | = | ($cm^2$) Based on standard surface areas for body parts (e.g., thigh) presented in Table D-1. |

- Total potential inhalation dose for personal monitors,

$$Dose_{Pot}\ Inhalation = ((Residue/Flow\ Rate) * Std.\ Inhalation) \qquad Eqn.\ D2\text{-}8$$

Where:

| | | |
|---|---|---|
| $Dose_{Pot}$ Inhalation | = | Residue inhaled but not abosorbed ($\mu g$), |
| Residue | = | Residue detected on inhalation monitor ($\mu g$), |
| Flow Rate | = | Personal sampling pump flow rate (L/min), and |
| Std. Inhalation | = | Standard inhalation rate for people as they perform various types of tasks/activities as presented in Table D-2 (typically 20 to 29 Lpm). |

- Total potential dermal dose for each test subject,

$$Total\ Dermal\ Dose_{Pot} = Dose_{Pot}\ Dermal\ (Hands) + Dose_{Pot}\ Dermal\ (Nonhand) \quad (Eqn.\ D2\text{-}9)$$

Where:

| | | |
|---|---|---|
| Total Dermal $Dose_{Pot}$ | = | Total potential exposure during a replicate ($\mu$g), |
| $Dose_{Pot}$ Dermal (Hands) | = | Total hand exposure measured during a replicate (All sample results must be added together) ($\mu$g), and |
| $Dose_{Pot}$ Dermal (Nonhand) | = | See Eqn. D2-7, must include all body parts |

For the calculation of the total potential dermal dose for each test subject there is no calculation of total dermal exposure (nonhand) for the whole body dosimetry technique. This is because all results for whole body dosimetry should be reported as ($\mu$g/sample) where a sample may represent a body part (if the dosimeters are cut up), the entire body, or the upper torso (i.e., long-sleeved tee-shirt monitor) and lower body (i.e., long-pant underwear as a monitor). Example calculations are included in Figures D-3 and D-4.

The next step for completing the calculations is to normalize the exposure results to obtain a unit for both inhalation and dermal exposure levels. The use of normalization factors provides a useful way of interpreting post-application exposure data. Normalization factors include:

- ($\mu$g/hour) where the value is calculated by dividing Total $Dose_{Pot}$ (Dermal or Inhalation) by the duration of the exposure replicate (hours), and

- ($\mu$g/activity) where the value is calculated by dividing Total $Dose_{Pot}$ (Dermal or Inhalation) by the efficiency of the test subject in the replicate (e.g., the number of pounds fruit harvested or the number of acres of turf mowed).

The final step for completing exposure calculations for actual exposure data is to summarize the results for each specific job function or activity of concern. The following manipulations of the data should be completed:

- Means for all test subjects for total dermal and inhalation exposure,

- Standard deviations ($\sigma$) for all test subjects for total dermal and inhalation exposure,

- Number of replicates per calculation (n) and reason(s) for excluding any replicates,

- Coefficients of Variation for all test subjects for total dermal and inhalation exposure (See Eqn. D2-1), and

[TBA: Subdivision U values]

Table D-1. Standard Body Surfaces Areas

[TBA]

Table D-2. Standard Inhalation Rate

[TBA]

Figure D-3. Example Dermal Exposure Calculations

[TBA]

Figure D-4. Example Total Exposure Calculations

- 95 th percent confidence interval (upper and lower limits) for all test subjects for total dermal and inhalation exposure (See Eqn. D2-2).

| | |
|---|---|
| ISSUE: | Biological monitoring calculations will be added at a later date. |
| ISSUE: | For atypical inhalation monitoring techniques the calculation of exposure levels may differ significantly from those described above (e.g., 3M type monitors which require a diffusion rate factor be included). Investigators must be very careful to include detailed calculations for any atypical monitoring techniques. |
| ISSUE: | Should more sophisticated statistical techniques be used to calculate parameters such as data distributions as in PHED? |

| | |
|---|---|
| ISSUE: | Coordination with OTS's New Chemical Exposure Limits/Ray Kent 202/260-7974 |

### 2.4.3 Transfer Coefficients

The long-term objective of requiring post-application pesticide exposure and environmental fate (i.e., residue dissipation) data is to establish a series of transfer coefficients (i.e., exposure factors) for various activities that are known to have a risk or hazard associated with them. Transfer factors quantitatively establish the relationship between activity, environmental residue levels and exposure. Until all necessary transfer coefficients are developed and validated, the Agency will continue to require that human exposure monitoring data be developed concurrently with residue dissipation data (e.g., foliar dislodgeable residue or indoor surface residue data). Transfer coefficients are used to calculate exposure levels when no concurrent human exposure monitoring data are available.

***Calculation of Transfer Coefficients***

The calculation of transfer coefficients involves relating exposure levels to ambient environmental residue levels. Transfer coefficients should be representative of particular job functions such as harvesting a crop, packing fruit, or indoor and outdoor residential activities. The basic equation for calculation of a transfer coefficient is presented below:

$$\text{Transfer Coefficient} = (\text{Dose}_{Pot}/\text{Residue Level}) \qquad \text{(Eqn. D2-10)}$$

Where:

| | | |
|---|---|---|
| Transfer Coefficient | = | Residue transfer rate, typically presented as ($cm^2$/hour), |
| $\text{Dose}_{Pot}$ | = | Typically potential human dermal dose, ($\mu g$ or mg/hour), and |
| Residue | = | Environmental residue levels such as FDR ($\mu g$ or $mg/cm^2$) or soil residue (ppm). |

As described above, a transfer coefficient is a simple proportion which compares potential dose to an environmental residue level. More sophisticated techniques, that may account for variability in the relationship between exposure levels and residue levels (i.e., transfer coefficients as calculated above assume that the relationship is linear with no deviation for all residue values may also be utilized). The following are alternate suggestions for the calculation of transfer coefficients:

- Use of a linear equation with a correlation coefficient cut-off value similar to that described above for the residue dissipation calculations presented in Section D.2.4.1, and

- Investigation of calculating transfer coefficients based on other aspects of a test subject's activity such as efficiency (e.g., picking rate).

Investigators must calculate transfer coefficients for every study that contains both residue dissipation and concurrent human exposure monitoring data. Investigators may use whichever techniques that they feel are appropriate for calculating transfer coefficients. However, all calculations must be clearly documented and the use of any statistical tests must be referenced. Example calculations are provided in Figures D-5, D-6, and D-7.

| | |
|---|---|
| ISSUE: | Which approach makes the most sense? Should a selection criteria be developed for selecting one calculation technique over another? |
| ISSUE: | Should transfer coefficients be required for all exposure routes even though dermal exposure accounts for the majority of all exposure based on current thought? |
| ISSUE: | Should the development of extremely specialized transfer coefficients such as for nondietary ingestion for infants/toddlers be within the scope of this section or should these types of issues be dealt with separately? |
| ISSUE: | How refined should transfer coefficients be? For example, is a single grape harvesting coefficient acceptable for the production of grapes across the entire country? |
| ISSUE: | Should transfer coefficients be required on an individual chemical basis or is a cluster analysis for groups of chemicals more appropriate? |

[TBA]

Figure D-5. Transfer Coefficient Calculation Using Simple Proportion

[TBA]

Figure D-6. Transfer Coefficient Calculation Using Linear Regression

[TBA]

Figure D-7. Transfer Coefficient Calculation Using Alternate Normalization Factors

*Use of Transfer Coefficients*

Transfer coefficients are used to calculate exposure levels (i.e., currently the standard transfer coefficient represents total dermal exposure and is presented in units of $cm^2$/hour) using an environmental residue level when no concurrent human exposure monitoring data are available. The basic equation for using transfer coefficients is provided below:

- $Dose_{Pot}$ = Transfer Coefficient * Residue Eqn. D2-11

Where:

| | | |
|---|---|---|
| $Dose_{Pot}$ | = | Usually dermal exposure presented as ($\mu$g or mg/hour), |
| Transfer Coefficient | = | Residue transfer rate to humans usually ($cm^2$/hour), and |
| Residue | = | Environmental residue levels (i.e., FDR ($\mu g/cm^2$) or soil (ppm)) |

The equation described above provides a generic description of the use of transfer coefficients. For all uses of the above equation, the investigator must provide the Agency with thorough documentation concerning the derivation of any calculations completed in a submission to the Agency.

*Currently Used Transfer Coefficients/Approaches*

Default transfer coefficients for dermal exposure were calculated as described above in Eqn. D2-11. Included as Table D-3, are a series of transfer coefficients that have been used historically by the Agency in the absence of study/chemical specific transfer coefficients. These coefficients are based on two-sided leaf areas. If FDR's are expressed as one-sided leaf areas, divide the transfer coefficients by two.

In addition to the dermal exposure transfer coefficients described above, the Agency also has developed a technique for addressing nondietary exposure to infants and toddlers. Due to their unique behavioral patterns, children are believed to have the greatest potential for dermal and non-dietary ingestion exposures from lawn surface residues. In the early 1980's, the exposure of a child to lawn pesticides was evaluated by assuming that the entire skin surface of a child was sprayed with the pesticide at the label rate. In addition, the entire surface of a toy (3 inch diameter ball) was also assumed to be sprayed with the pesticide. The resulting amounts of pesticide on the child's hands and the ball were assumed to be quantitatively ingested while the remaining bodily exposure was assumed to be available for dermal absorption.

To promote consistent turf pesticide exposure assessments within the Agency, "until scientific research is conducted," internal guidance was provided to Agency exposure assessors in July of 1989. In this guidance, it was recommended that lawn surface residues ($mg/m^2$) be combined with contact rate information (transfer coefficients) derived from agricultural studies to estimate exposure. The following relationship had been determined from exposure studies conducted with fruit harvesters:

$$\text{Dermal Exposure (mg/hr)} = \text{antilog}[(\log \text{Dislodgable Residue mg/m}^2) - 0.397] \quad \text{(Eqn. D2-12)}$$

For toddlers (1 to 6 years old) this equation was adjusted by the toddler:adult body surface area ratio of 0.33. For children (7 to 12 years old) it was adjusted by a ratio of 0.43. This resulted in the following relationships:

Toddler

$$\text{Dermal Exposure (mg/hr)} = \text{Dislodgable Residue mg/m}^2 * 0.13\ \text{m}^2/\text{hr} \quad \text{(Eqn. D2-13)}$$

Child

$$\text{Dermal Exposure (mg/hr)} = \text{Dislodgable Residue mg/m}^2 * 0.17\ \text{m}^2/\text{hr} \quad \text{(Eqn. D2-14)}$$

Similar relationships were developed for non-dietary ingestion from the surface of a ball, 3 inches in diameter, and from the surfaces of both hands.

Toddler

$$\text{Total Ingestion (mg/day)} = \text{Dislodgable Residue mg/m}^2 * 0.032\ \text{m}^2/\text{day} \quad \text{(Eqn. D2-15)}$$

Child

$$\text{Total Ingestion (mg/day)} = \text{Dislodgable Residue mg/m}^2 * 0.037\text{m}^2/\text{day} \quad \text{(Eqn. D2-16)}$$

The exposure assessments were completed by assuming that toddlers and children weigh 17 and 31 kg respectively and that they are exposed for 4 hours per day, 5 days per week. Clothing equivalent to diapers and T-shirts for toddlers and shorts and T-shirts for children are accounted for in the above relationships.

As research continues, it is becoming apparent that the above approach to assessing children's exposure to turf pesticides is inadequate. For example, contact rates (transfer coefficients) ranging from 0.25 to 4 $m^2$ for children playing on carpet have been reported. It seems reasonable that contact rates for children playing on turf would be more similar to these than to those derived from fruit harvesters. As concurrent lawn surface residue and human exposure studies are conducted, contact rates for specific activities on turf will be derived and used for future exposure assessments. Further, the Agency will be increasingly utilizing data sources such as the Exposure Factors Handbook (e.g., for body surface areas, weights, and inhalation rates), the Total Human Exposure Relational Database (e.g., for time spent in activities), and the results of ongoing research (e.g., behavioral pattern research on children) in order to better characterize exposures to lawn pesticides. Updated "final" guidance on calculating exposures from lawn surface residues is expected by 1997.

| | |
|---|---|
| ISSUE: | The use of generic transfer coefficients may over or under estimate exposure. |
| ISSUE: | Should the transfer coefficient derived by john ross be used as an interim for indoor exposure calculation? |
| ISSUE: | Coordination with OTS's new chemical exposure limits must be considered/Ray Kent 202-260-7974 |
| ISSUE: | How should nondietary ingestion exposure transfer coefficients be derived and validated? |
| ISSUE: | NACA task force on reentry issues |
| ISSUE: | What about inhalation exposure? |

### 2.4.4 Restricted Entry Interval Determination

The Agency determines Restricted Entry Intervals (REIs) based on the results of chemical/scenario specific hazard/risk assessments. These assessments are structured based on the toxicological endpoints of the specific pesticide. Historically, the Agency has used two distinct techniques for the determination of REIs: (1) the non-detectable residue method, and (2) the Allowable Exposure Level (AEL) method. The non-detectable residue method is no longer considered a primary option for the estimation of REIs. As a result, it will not be discussed in detail

(i.e., REIs are basically set when residues dissipate below the level of detection). The AEL method involves comparison of an exposure level to a toxicological endpoint to determine an AEL. After the AEL is established, a safe residue level (i.e., REI) is then determined by comparison of the exposure level to the environmental residue dissipation data (e.g., FDR dissipation curve).

The first objective for determining an REI is to define the toxicological endpoint of concern. These endpoints may be acute, subchronic or chronic (i.e., cancer) in nature. If the endpoint is acute in nature, the only exposure calculations that need to be completed are to adjust the normalized $Dose_{Pot}$ levels to represent a daily acute $Dose_{Pot}$. This can be completed using the following equation:

$$\text{Daily Dose}_{Pot} = ((\text{Normalized Dose}_{Pot} * \text{Duration})/BW) \qquad \text{(Eqn. D2-17)}$$

Where:

| | | |
|---|---|---|
| Daily $Dose_{Pot}$ | = | Dose resultant from daily activities ($\mu$g or mg/kg/day), |
| Normalized $Dose_{Pot}$ | = | Total $Dose_{Pot}$ in Sections 2.4.3 and 2.4.4, |
| Duration | = | Daily interval (e.g., 8 hours or total picked/day), and |
| BW | = | Body weight, typically 70 kg |

If the endpoint is cancer, a $LADD_{Pot}$ must be calculated (i.e., LADD = Potential Lifetime Average Daily Dose). This value can be calculated using the following equation:

$$LADD_{Pot} = ((\text{Daily Dose}_{Pot} * (\text{Annual Exposure}/365) * (\text{Work Interval}/70\ \text{Yrs}))/BW) \qquad \text{(Eqn. D2-18)}$$

Where:

| | | |
|---|---|---|
| $LADD_{Pot}$ | = | Dose over an individual's lifetime (see Section 4.1) ($\mu$g or mg/kg/day), |
| Daily $Dose_{Pot}$ | = | see Eqn. D2-17, |
| Annual Exposure | = | No. days exposed to chemical per working year, |
| Work Interval | = | No. years worked with specific chemical, and |
| BW | = | Body weight, typically 70 kg. |

After the appropriate $Dose_{Pot}$ or $LADD_{Pot}$ values have been calculated, the next objective is to calculate the risk or hazard level. Risk and hazard levels can be calculated using the following equations:

$$\text{Risk} = LADD_{Pot} * (Q1^*) \qquad \text{(Eqn. D2-19)}$$

Where:

| | | |
|---|---|---|
| Risk | = | Likelihood of developing cancer risk due to exposure to a pesticide over time, |
| $LADD_{Pot}$ | = | Described above in Eqn. D2-18, |
| Q1* | = | Cancer potency factor for pesticide $(mg/kg/day)^{-1}$, |
| Hazard | = | Tox Endpoint/(Daily $Dose_{Pot}$ or $LADD_{Pot}$), |

Where:

| | | |
|---|---|---|
| Hazard | = | Likelihood of deleterious heaalth effect due to chemical exposure, |
| Tox Endpoint | = | Value to quantitatively describe effects due to exposure, and |
| Daily $Dose_{Pot}$ or $LADD_{Pot}$ | = | See above descriptions. |

Example calculations are provided in Figures D-8 through D-.....

[Note: at this point there are several different approaches for determining the REI value based on all of the possible iterations of these calculations. As this is the case a series of example calculations will be prepared and provided at the workshop for discussion and comments.]

| | |
|---|---|
| ISSUE: | $LADD_{Pot}$ parameters need to be addressed. |
| ISSUE: | Approaches for all possible toxicological endpoints need to be addressed. Of specific concern, is the use of subchronic endpoints in assessments. |
| ISSUE: | Should assessments be completed for only actual data points (i.e., study days) where human exposure monitoring data and residue dissipation data were collected concurrently or should values be calculated over an entire interval using a model for $Dose_{Pot}$ such as linear regression or typical transfer coefficient? |
| ISSUE: | Example calculations will be developed for use at the workshop. Please identify any sample calculations which need to be incorporated in the guidelines. |
| ISSUE: | Criteria need to be developed which clearly indicate what types of behaviors/activities are to be considered chronic or acute in nature. |
| ISSUE: | What types of safety factors should be applied for various types/classes of pesticide compounds for these calculations (e.g., organophosphates require more caution on the part of the Agency when considering short-term, high-end exposures)? |

# PART D - CHAPTER 3
# MODELLING

## 3.0 MODELLING [TBA]

Note: The following classes of models will be discussed:

- Source models, based on the physical-chemical characteristics of the chemicals;
- Media concentration models, including multi-compartment mass balance and dispersion-based indoor air models; models for other media may include predicted decay rates and transferability from surfaces to skin as a function of the chemical and environmental conditions;
- Human exposure models, including the linkage of time-location and activity pattern data to predicted contact and transfer rates to estimate exposure and uptake/intake rates; and
- Dose models, to include the matrix effects (e.g., for dust and soil), absorption or penetration coefficients, and pharmacokinetic models.

# APPENDIX I: DATA REPORTING GUIDELINES

[THIS APPENDIX WILL BE COMPLETED AT A LATER DATE]

# APPENDIX II: EVALUATION AND INTERPRETATION OF RESULTS

[THIS APPENDIX WILL BE COMPLETED AT A LATER DATE]