PART B - CHAPTER 1

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PART B - CHAPTER 1
BACKGROUND--GENERAL PROVISIONS
GUIDELINE 875.2000

1.1 PURPOSE AND SCOPE

These guidelines describe the postapplication monitoring data requirements (40 CFR 158.390) that may be required in support of registration.

1.2 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 these guidelines key definitions are provided below:

Absorbed Dose. The amount of pesticide entering systemic circulation after crossing a specific absorption barrier (e.g., the exchange boundary of the skin, lung, or digestive tract); normally expressed as mass per unit body weight per unit time (e.g., mg/kg/day). Internal dose is a more general term denoting the amount absorbed with respect to specific absorption barriers or exchange boundaries (U.S. EPA, 1992).

Activity. A specific action related to a task or behavior that may result in an exposure event (e.g., harvesting pesticide treated crops, crawling on pesticide treated lawn) (also see Task).

Airborne Residue. Residues of a pesticide, including vapors and aerosols and other particulates that remain suspended in the air after pesticide application or that become suspended in the air at a treated site; normally expressed as a concentration, or mass per unit air volume (e.g., mg/m^3).

Ambient Reentry Concentration (ARC). The maximum level of pesticide residues at a treated site that is not likely to pose unreasonable adverse effects on people entering the site.

Analytical Method Development. 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.

Antimicrobial Pesticide. A pesticide that is intended to disinfect, sanitize, reduce, or mitigate growth or development of microbiological organisms; or protect inanimate objects, industrial processes or systems, surfaces, water, or other chemical substances from contamination, fouling, or deterioration caused by bacteria, viruses, fungi, protozoa, algae, or slime (FIFRA, Section 2).

Applied Dose. The amount of a substance presented to an absorption barrier (i.e., skin, lung, or digestive tract) and available for absorption, but not yet having crossed the outer boundary of an organism (U.S. EPA, 1992).

Average Daily Dose (ADD). Dose that is averaged over a specified time period taking into account the frequency, duration, and intensity of exposure during that time period. ADDs are usually expressed in units of mg/kg/day.

Control or Blank Samples. Sample media considered free of residues of any analyte(s) of interest that are handled, stored, shipped, and/or analyzed concurrently with a set or batch of exposure or residue samples. They are typically used to identify and quantify constant errors that affect a measurement. These samples are sometimes called blank samples.

Delivered Dose. The amount of a chemical available for interaction by any particular organ or cell (U.S. EPA, 1992).

Dermal Exposure. This term refers to a quantifiable measure of the amount of residue deposited on skin; normally expressed as a density, or mass per unit time, deposited on a defined skin surface area (e.g., mg/hr hand exposure); equivalent to potential dose for the dermal route.

Dislodgeable Residue. The amount of chemical residues deposited onto the leaf surface that have not been absorbed into the leaf or dissipated from the surface, and that can be dislodged by shaking leaf samples in a detergent solution ($\mu g/cm^2$).

Dissipation Curve. A graphical representation of pesticide residue levels plotted against time of sampling, or the mathematical representation of such a data.

Dose. A term referring generically to the amount of chemical to which an organism is exposed by any of several routes. Specifying the routes within the environmental context and especially the point of measurement is made possible via subcategories of dose (see Potential Dose, Applied Dose, Absorbed Dose, Internal Dose, and Delivered Dose). Dose is normally expressed as a mass per unit body weight per unit time and is frequently expressed in units of mg/kg/day.

Early Entry. The entry of people into a site previously treated with a pesticide prior to the expiration of any established, restricted-entry interval.

End-use Product. A pesticide product whose labeling: (1) includes directions for use of the product (as distributed or sold, or after combination by the user with other substances) for controlling pests or defoliating, desiccating, or regulating the growth of plants, and (2) does not state that the product may be used to manufacture or formulate other pesticide products (40 CFR 152.3).

Exposure. A measure of the environment leading to a dose. Exposure is quantified as the concentration of the agent in the medium in contact, integrated over the duration of the contact (U.S. EPA, 1992).

Exposure Monitoring Period. The length of time that the exposure-related activity of interest is monitored. For the purposes of these Guidelines, the duration over which each replicate is monitored should be representative of a typical activity (e.g., most occupational postapplication activities range from 4 to 8 hours) and be long enough to get quantifiable measurements. (See also Replicate and Work Cycle.)

Field Recovery. The data from experiments conducted to determine the loss of analyte from fortified sample collection devices in the field, when subjected to equivalent environmental conditions and exposure times as field exposure samples. Losses during shipping, storage, and laboratory operations, as well as field exposure to environmental factors (e.g., temperature, light), are included if the samples are handled and analyzed concurrently with the actual field samples.

Fortification. The process by which a known concentration of analyte is added to a sample matrix to assess loss during sample collection, transportation, or analysis.

Hazard Quotient. Unitless value that is calculated by dividing the average daily dose (mg/kg/day) by a value representing a toxicity endpoint (e.g., a reference dose; mg/kg/day).

Internal Dose. The amount of pesticide absorbed through the exchange boundaries of the body (equivalent to the absorbed dose).

Laboratory Recovery. Data from analyses conducted in the laboratory to determine the efficiency of recovery of the analyte from sample collection devices fortified at known levels. Laboratory recoveries reflect losses that occur during laboratory operations (e.g., extraction, cleanup, analytical measurements, etc.); they do not measure losses due to storage conditions or environmental factors. The purpose of laboratory recovery studies is to provide method development and validation data. Concurrent laboratory recovery samples need to be analyzed with the actual field samples to assess daily method performance.

Lifetime Average Daily Dose (LADD). Dose that is averaged over an individual's lifetime taking into account the frequency, duration, and intensity of exposure events. LADDs are usually expressed in units of mg/kg/day.

Limit of Detection (LOD). LOD is the point at which "a measured value becomes...larger than the uncertainty associated with it" (Taylor, 1987). The LOD can be defined in a number of ways, such as the background response plus three times the standard deviation of the lowest measurable concentration, three times the signal-to-noise ratio of baseline noise, three times the standard deviation of the lowest measurable concentration, etc.

Limit of Quantification (LOQ). LOQ is the point at which "measurements become quantitatively meaningful" (Taylor, 1987). It is the lowest pesticide residue that can be accurately quantitated in a reproducible fashion. The LOQ can be defined in a number of ways, such as the background response plus ten times the standard deviation of the lowest measurable concentration, ten times the signal-to-noise ratio of the baseline noise, ten times the standard deviation of the lowest measurable concentration, etc. In practice, the LOQ is the lowest fortification level that shows adequate recovery during the method validation process.

Margin of Exposure. Represents the ratio of a no observable adverse effect level (NOAEL) to an estimated dose/exposure level.

Method Validation. Process by which it is demonstrated that an analytical method is capable of measuring 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.

Percutaneous Absorption. The process by which pesticides pass through the skin barrier and enter systemic circulation; normally expressed as flux (mass per unit skin surface area per unit time), but may also be expressed as a percent (fraction of amount deposited on skin (exposure) reaching systemic circulation times 100) per unit time.

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

Pharmacokinetic Model. A model that can be used to predict the time course of absorption, distribution, metabolism, and excretion of a foreign substance in an organisms body (e.g., pesticide).

Potential Dose. The amount of chemical that could be inhaled without wearing a respirator, or which could be deposited on the skin without wearing clothing. Potential dose is typically expressed as a mass per unit body weight per unit time (i.e., mg/kg/day).

Proposed Restricted-entry Interval. A restricted-entry interval proposed by an applicant as adequate for human protection.

Quality Assurance. 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 Control. 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).

Reentry. The entry of one or more people into a site subsequent to pesticide application.

Reentry Dose Level (RDL). Dose level at which reentry into an area previously treated with a chemical can occur with negligible deleterious effects caused by exposure to the chemical because the biological mode of action threshold for that chemical has not been met (mg/kg/day).

Replicate. An observation or set of observations relating to one exposure monitoring period for one test subject (or volunteer subject). For example, monitoring a reentry crew consisting of ten individual harvesters for one work cycle would involve ten replicates. For the purposes of these Guidelines, the duration over which each replicate is monitored should be representative of a typical activity (e.g., most occupational postapplication activities range from 4 to 8 hours) and be long enough to get quantifiable measurements.

Residue(s), Pesticide Residue(s), and Residue(s) of a Pesticide. Active ingredient(s), toxic impurities of the pesticide, toxic alteration products of the active ingredient, and/or manufacturing impurities of

the pesticide that remain at the site of application or that remain on items that are subsequently removed from the site.

Restricted-entry Interval. The time after the end of a pesticide application during which entry into the treated area is restricted (40 CFR 170.3).

Sampling Interval. The day or hour postapplication which samples for a given study are collected (e.g., 4 hours, 1 day, 2 days, etc.).

Sampling Period. The length of time over which samples are collected at various sampling intervals to characterize dissipation.

Site. A site refers to any plant, animal, object or location to which a pesticide is applied or which is protected by an adjacent application of a pesticide. Examples of sites are: crops, ornamental plants, lawns, stored commodities, domestic animals, households, wood structures, aquatic areas, boats, food processing plants, hospitals, plastic products, humans, and garbage dumps.

Storage Stability Study. A storage stability study determines the stability of analyte(s) in or on appropriate substrates under similar storage conditions that will be used to store field samples. 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. A storage stability study can be conducted prior to or in conjunction with a field study.

Surrogate, Surrogate of a Pesticide, or Pesticide Surrogate. A chemical compound or a mixture of compounds other than the pesticide being investigated that could be used to quantify human exposure to the pesticide being investigated. The surrogate could be an active ingredient of a pesticide registered for that use or a very similar use.

Task. 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 (also see Activity).

Transfer Coefficient. An estimate of the rate of residue transfer to humans that occurs from a pesticide-treated surface during the performance of specific work or other activity, generally expressed in units of cm^2/hour. For example, in agricultural settings, transfer coefficients are calculated as the ratio of worker dose (ug/hr) to dislodgeable residue (ug/cm^2).

Transferable Residues. That portion of applied pesticide residues that area available for nondietary transfer to humans. May be measured by several techniques that do not involve the quantification of total residues in the matrix that is treated.

Travel Recovery Samples. Travel recovery samples account for the stability of the analyte on each sampling matrix during shipment. Travel recovery samples provide useful information for determining whether the analyte losses occurred during sample shipment. Travel recoveries do not account for losses due to environmental conditions during sampling in the field.

Typical End-use Product. A pesticide product that is representative of a major formulation category (e.g., emulsifiable concentrate, granular).

Use Type. A grouping of crops, plants, or situations with similar potential for exposure during postapplication activities.

Watering-in. Irrigation following pesticide application to lawns or turf. For some pesticides, this practice is recommended to move product from blades to thatch and soil.

Work Cycle. A definable sequence of tasks that may be repeated any number of times within one day or less (e.g., for ornamentals, one work cycle could be cutting, bundling, and grading of chrysanthemums). An exposure monitoring period should span at least one, but may include multiple work cycles (see also Exposure Monitoring Period and Replicate).

1.3 REQUIREMENT FOR POSTAPPLICATION EXPOSURE AND SUPPORTING DATA

A restricted-entry interval is required under the provisions at 40 CFR 158.520 (formerly 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. Postapplication data are also needed to determine if a pesticide can be used in a residential or commercial setting without appreciable risk to humans.

1.3.1 Toxicity and Exposure Criteria

As delineated at 40 CFR 158.520, postapplication exposure data may be required when at least one of the toxicity criteria and one of the exposure criteria are met, as follows:

Toxicity Criteria

- 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);
- The acute inhalation LC_{50} of the TGAI is less than 0.5 mg/L (4 hour study);
- The acute oral LD_{50} of the TGAI is less than 50 mg/kg (i.e., toxicity category I);
- 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); developmental toxicity (Guideline 83-3, 83-6); or

- Epidemiological/poisoning incident data indicate that adverse effects result from postapplication exposure.

Exposure Criteria

- Pesticide will be applied to crops or in areas related to agricultural commodity production where human tasks will involve postapplication exposure to pesticide residues; or
- Pesticide will be applied to nonagricultural outdoor sites such as home lawns where human exposure may occur; or
- Pesticide will be applied to indoor sites, either residential, commercial, industrial, or agricultural, where human postapplication exposure may occur.

The toxicity and exposure criteria are currently being developed by the Agency for antimicrobials and will be added to these Guidelines at a later date.

1.3.2 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 Series 875, Group B provided that written evidence is submitted that such data are inapplicable to the specific pesticide or product. 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 restricted-entry 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 Series 875, Group B, if evidence is submitted that specific properties or characteristics of the pesticide or product preclude the requirement for such data. 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.

1.3.3 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 usually rely on data developed by the manufacturing use producer, unless the basic manufacturer no longer supports the registered use. Then, the data burden is on the formulators.

1.4 GENERAL REPORTING REQUIREMENTS

In brief, reporting of study results must follow the provisions described in PR 86-5 and 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.

1.5 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).

1.6 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 a restricted-entry interval or evaluate any risks associated with postapplication exposure scenarios. Those data are described in the following sections of Subdivision F. Detailed information on using those data to determine the restricted entry interval is provided in Part D, Chapter 2 - Calculations.

Sections of Subdivision F

Acute Testing		
Acute oral toxicity - rat	81-1	870.1100
Acute dermal toxicity	81-2	870.1200
Acute inhalation toxicity - rat	81-3	870.1300
Primary eye irritation - rabbit	81-4	870.2400
Primary dermal irritation	81-5	870.2500
Dermal sensitization	81-6	870.2600
Delayed neurotoxicity (acute) - hen	81-7	870.6100
Acute neurotoxicity - rat	81-8	870.6200
Subchronic Testing		
90-Day oral - two species, rodent and nonrodent	82-1	870.3100
		870.3150
21-Day dermal	82-2	870.3200
90-Day dermal	82-3	870.3250
90-Day inhalation - rat	82-4	870.3465
28-Day delayed neurotoxicity - hen	82-6	870.6100
90-Day neurotoxicity - rat	82-7	870.6200
Chronic Testing		
Chronic feeding - two species, rodent and nonrodent	83-1	870.4100
Carcinogenicity - two species, rat and mouse preferred	83-2	870.4200
Developmental Toxicity and Reproduction		
Developmental toxicity - two species, rat and rabbit preferred	83-3	870.3700
Reproduction	83-4	870.3800
Postnatal developmental toxicity	83-6	870.6300
Mutagenicity Testing		
Salmonella typhimurium reverse mutation assay	84-2	870.5265
Mammalian cells in culture	84-2	870.5300
In vivo cytogenetics	84-2	870.5380
		870.5385
		870.5395
Special Testing		
General metabolism	85-1	870.7485
Domestic animal safety	85-2	870.7500
Dermal penetration	85-3	870.7600
Schedule controlled operant behavior	85-5	870.7800
Peripheral nerve function	85-6	870.6850
Immunotoxicity	85-7	870.7800

REFERENCES FOR PART B, CHAPTER 1

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

U.S. EPA. 1992. Guidelines for Exposure Assessment. Washington, D.C.: U.S. Environmental Protection Agency. Federal Register. 57 FR 22888, May 29, 1992.