**PART D - CHAPTER 2**

**CALCULATIONS**

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# GUIDELINE 875.2900

## 2.1 INTRODUCTION AND PURPOSE

The purpose of this chapter is to provide users of Series 875, Group B with guidance for completing exposure and hazard or risk assessments. Quantitative approaches for analyzing nondietary hazards or risks to humans resulting from entry into areas previously treated with a chemical are addressed in this chapter. Both residential and occupational uses of chemicals, as well as any other chemical use scenario of concern regulated by FIFRA, are included. These include uses of, or exposures to, either pesticides or antimicrobials by agricultural workers, industrial workers, homeowners and occupants (lawncare, garden, and indoors), swimmers, and children through nondietary ingestion. The calculations presented in this chapter are based on the generally accepted fundamentals of exposure and risk assessment described in Part D, Chapter 1 that are summarized from U.S. EPA Guidelines for Exposure Assessment (U.S. EPA, 1992). In order to better understand the concepts and principles described in this chapter, a flow chart has been developed that details each major calculation, the logical progression of an analysis, the required analysis inputs, and standard outputs expected (See Figure D2-1.) The specific areas for which calculations are addressed in this chapter include: commonly used formulas; chemical data; exposure/dose calculations; chemical dissipation kinetics; transfer coefficients; risks, hazards, and Restricted-Entry Intervals. The nomenclature used to describe all calculations in this chapter is based on the guidance provided in the U.S. EPA's Exposure Assessment Guidelines (U.S. EPA, 1992).

## 2.2 COMMONLY USED FORMULAS AND APPROACHES

This section describes statistical formulas and approaches that are common to the calculations described in this chapter. These items are described in this section because they have utility in several calculations and are referenced in this chapter frequently.

### 2.2.1 Statistical Formulas

The most common statistical calculations required to manipulate the types of data described in this Guideline include the following: arithmetic mean, geometric mean, standard deviation ($\sigma$), coefficient of variation, 95 percent confidence interval, and linear regression. The arithmetic mean is a simple average. Geometric mean values are calculated by computing the arithmetic mean of log

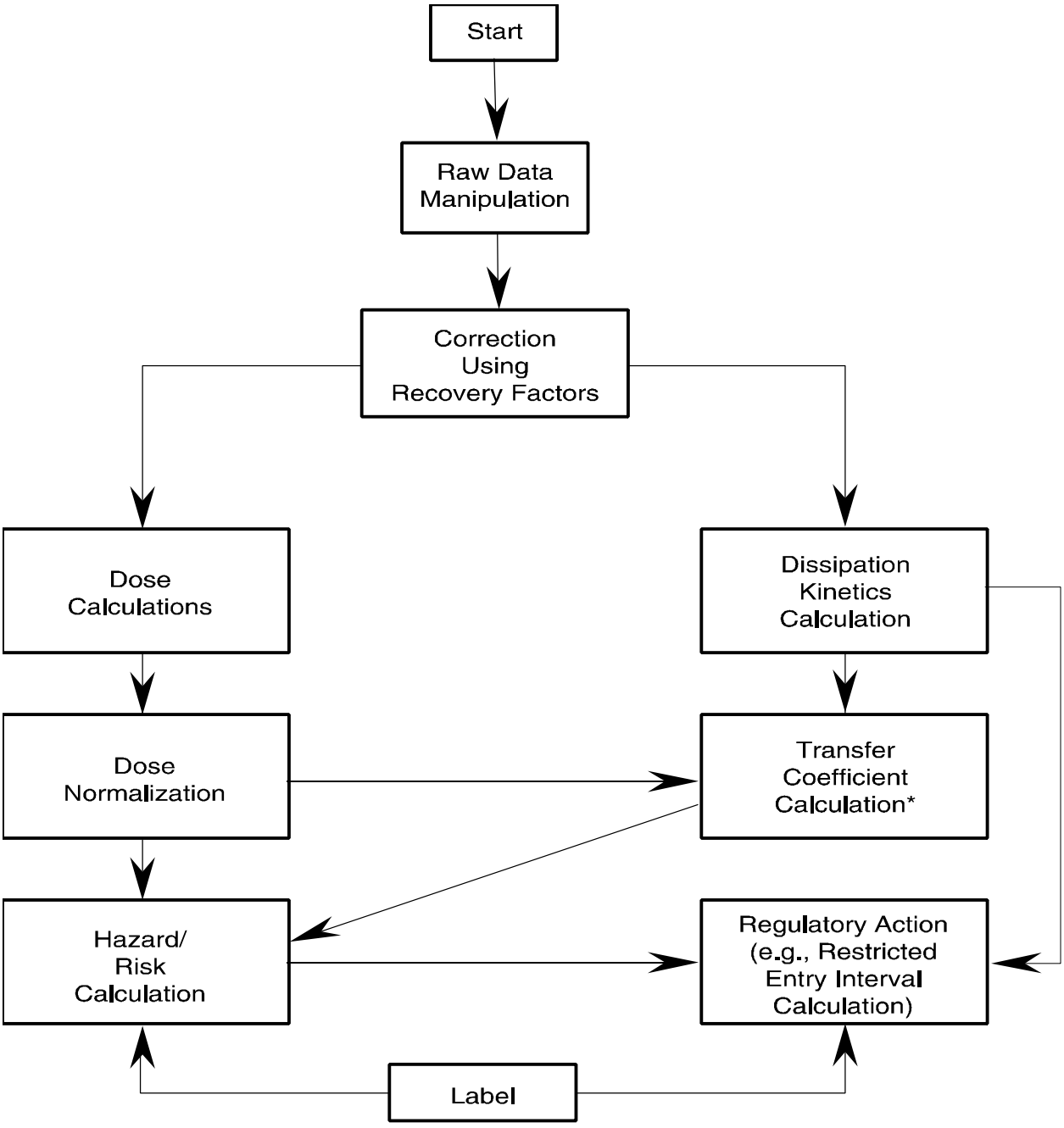


Figure D2-1. Calculation Progression Flowchart

transformed data and then calculating the anti-log of the computed mean. Standard deviation is a measure of the variance of the data and can be computed using standard statistical methods. Calculation of the coefficient of variation and the 95 percent confidence interval can be completed as follows:

$$CV = [100 * (SD / \bar{x})] \quad \text{(Eq. D2-1)}$$

Where:

| | | |
|---|---|---|
| CV | = | coefficient of variation (percent); |
| SD | = | standard deviation; and |
| $\bar{x}$ | = | mean. |

$$95\%\ CI = [\bar{x} \pm ((SD * 1.96)/\sqrt{N})] \quad \text{(Eq. D2-2)}$$

Where:

| | | |
|---|---|---|
| 95% CI = | 95% confidence interval; | |
| $\bar{x}$ | = | mean; |
| SD | = | standard deviation; and |
| N | = | number of datapoints included in calculation. |

Linear regressions can be completed using commonly available software packages. Investigators should specify the software and version used for all calculations.

### 2.2.2 Appropriate Use of Quantification/Detection Limits

Proper definition of the limit of detection (LOD) and limit of quantification (LOQ) for every sample matrix and dosimeter used in a study is critical in all calculations. (See Part B, Chapter 1 and Part C for a detailed explanation.) Historically, the Agency has used one-half of the LOQ to represent chemical concentrations in a matrix when the residue level in that matrix is at or below the assigned LOQ. Using the definitions of LOD and LOQ in Section 1.2 (or quantitatively similar), allows somewhat more qualitative latitude for sample results that are also below the assigned LOD. The following matrix can be used to decide what value should be selected for use in any calculation.

If $X > LOQ$, Use X

If $LOD < X \leq LOQ$, Use 1/2 LOQ

If $X \leq LOD$, Use 1/2 LOD

Where:

X = measured chemical concentration

Investigators should indicate whether calculated values are based on values that are either one-half the LOQ or one-half the LOD. This is necessary for the Agency to adequately interpret study results.

## 2.3 CHEMICAL DATA

Calculations required to manipulate raw residue chemistry data and the techniques required to correct raw data for the appropriate quality control results are addressed in this section.

### 2.3.1 Basic Manipulation of Raw Data

Postapplication exposure and chemical dissipation data are typically generated from one or more of the following types of samples: (1) quality control for all matrices; (2) environmental matrices (e.g., soils); (3) transferable/dislodgeable matrices (e.g., foliar dislodging solutions); (4) filters used for air monitoring; (5) passive dosimeters (e.g., patches, whole-body dosimeters, cotton sample gloves); and (6) biological matrices (e.g., urine or blood). For the purposes of this section, environmental and transferable data will be treated similarly as will any filter and passive dosimeter data.

**Quality Control Data** may include, but are not limited to, the following: formulation characterization, tank mix solution analysis, field recovery, laboratory recovery, storage stability, and travel spikes. (See Part C - Quality Assurance/Quality Control for further information.) Data from blank samples should be manipulated on a case-by-case basis (e.g., a mean and standard deviation might be calculated for blank samples that contain residue levels). The following information and summary statistics must be provided and/or calculated for all other samples:

- Means and standard deviations of the recovery values over each and over all fortification levels on each matrix;
- Coefficients of variation of the recovery values over each and over all fortification levels on each matrix; and
- 95 percent confidence interval of the mean recovery values (upper and lower limits) over each and over all fortification levels on each matrix.

**Environmental Matrix Data** are based on environmental and transferable/dislodgeable sampling methods. These data may include, but are not limited to, the following: dislodgeable foliar residue data, soil

residue data, carpet residue data, ambient air monitoring data, and wipe tests. Unit residue levels should be calculated (e.g., µg/cm$^2$ values for DFR based on the double-sided leaf area of the sample). After this normalization, minimal manipulation of the data is required until corrected for the appropriate quality control results. These data correction procedures are described below.

In cases where a typical Iwata leaf punch is used, the sample surface area is simply calculated by multiplying the number of leaf punches by the surface area of each leaf disc in a sample (double-sided). In cases where the use of a leaf punch is not feasible, the weights of individual samples are recorded and then multiplied by a unit leaf area factor to determine the total area of individual samples. Unit leaf area factors establish a relationship between the weight of a leaf type and the surface area of the leaf type. Investigators may use either a simple proportion or a linear regression to represent the relationship between leaf surface area and sample weight. Using the simple proportion method, sample leaf surface area can be calculated as follows:

$$LA_{sample} = ULAF \times SW_{DFR} \qquad \text{(Eq. D2-3)}$$

Where:

$LA_{sample}$ = leaf area of DFR sample used for all calculations (cm$^2$);

ULAF = unit leaf area factor used for all calculations (cm$^2$/gram); and

$SW_{DFR}$ = weight of sample collected and analyzed in the determination of dislodgeable foliar residues (grams).

$$ULAF = LA_{ulaf}/SW_{ulaf} \qquad \text{(Eq. D2-4)}$$

Where:

ULAF = unit leaf area factor which can be used to calculate the sample surface area from sample weight (cm$^2$/gram);

$LA_{ulaf}$ = surface area of leaf sample collected and analyzed in the determination of the ULAF (cm$^2$); and

$SW_{ulaf}$ = weight of sample collected and analyzed in the determination of the ULAF (grams).

The equation for the linear relationship option is shown below:

$$LA_{sample} = (S * SW) + b \qquad \text{(Eq. D2-5)}$$

Where:

$LA_{sample}$ = leaf area of DFR sample used for all calculations ($cm^2$);

S = slope of line generated during previous linear regression of data ($cm^2$/gram of sample weight of leaves designated for surface area determinations);

SW = weight of DFR sample (grams); and

b = y intercept of the linear equation generated during previous regression ($cm^2$).

**Passive Dosimetry** human exposure monitoring data may include, but are not limited to, the following: patches; whole-body dosimeters; inhalation filters, resins, polyurethane foam, or impinger solutions; cotton gloves; and aqueous handwash solutions.

If the Durham and Wolfe patch technique is used, dermal exposure levels should be calculated based on the surface area of each set of dosimeters in units of µg/$cm^2$. These values should represent the collection patterns described in Part B. If whole-body dosimetry is used, the raw data should be reported in units of µg/sample for each body part sampled. The conversion of patch data to units of µg/sample, for comparison to whole body dosimeters data, are only generated after corrections for recovery efficiency have been made and the data are adjusted for body surface areas.

As with whole body dosimetry data, no manipulation of hand exposure data is required to yield data in units of µg/sample. Hand exposure data can represent both hands combined, or individual hands. Investigators must consider their quality control regimen when designing a sequential sample study. For example, if over the course of an 8-hour monitoring interval more than one set of field recovery samples were generated (e.g., AM and PM), then the raw data should be grouped to enable the appropriate application of recovery correction factors to the raw data within each group.

Generally, raw inhalation exposure data should be divided by the air volume represented by the air sample to yield values in units of µg/$m^3$. Any sequential air concentration data should be grouped in a manner similar to that described above for dermal hand data. Sequential air sampling is common for some

analytes on some sample media (e.g., where exceeding the sample loading capacity would result in breakthrough, or retention characteristics may limit the sample duration).

**Biological Monitoring** data may include, but are not limited to, the following: chemicals excreted in the urine or blood. Results based on these data should be calculated as individual replicate sample results, in the appropriate units, collected at specific sampling intervals and for specific test subjects (e.g., total excreted in urine over a 24-hour interval for each individual test subject). The format for calculating results based on biological monitoring data is dependent upon the pharmacokinetics of the pesticide of interest and must be reflective of the biological processes monitored to determine exposure (e.g., the urine excretion profile).

### 2.3.2 Corrections Based on Quality Control Data

Correcting residue levels based on the quality control data generated in a study is required to accurately account for residue losses and chemical transformations that may occur during the conduct of a study (i.e., after collection of a residue by a dosimeter/sample matrix and prior to quantitation during analysis). Raw residue data must be corrected for recovery if any appropriate recovery correction factor is less than 90 percent. Recovery correction factors and the equations used to calculate them for each sample matrix are described below:

$$RCF = ((FR/100) * (LR/100) * (SS/100)) \quad \text{(Eq. D2-6)}$$

Where:

RCF = recovery correction factor which is applied to raw residue data as shown in Eq. D2-7 (unitless);

FR = arithmetic mean field recovery for matrix (%);

LR = arithmetic mean lab recovery for matrix (%); and

SS = arithmetic mean storage stability recovery for matrix (%).

As described in Part C, various combinations of recovery data may be generated in a study. Therefore, it is the investigators responsibility to determine which quality control data are the appropriate basis for a correction factor. For example, if a field recovery sample is generated concurrently with an actual exposure sample, then stored and analyzed concurrently with the field exposure samples, only a correction for that field recovery sample analytical result is required. Investigators must make judgements concerning this issue and clearly explain/illustrate how residue data were corrected for recovery in any submission to the

Agency. It is not routine to correct residue data based on the results of formulation characterization data or the results of a tank mix analysis. If raw data are corrected, a thorough explanation of the data that initiated such a correction is required (e.g., provide fate data to document hydrolytic instability in a DFR wash solution).

After all correction factors have been calculated, raw residue data must be corrected using the appropriate factors. Investigators must clearly indicate in any submission to the Agency which RCF values are to be used to correct specific sets of raw residue data. The equation that describes this correction process is presented below:

$$C_{cor} = (C_{raw})/(RCF) \qquad \text{(Eq. D2-7)}$$

Where:

$C_{cor}$ = corrected chemical value which serves as the basis for all exposure and chemical dissipation calculations (e.g., µg/sample or µg/cm$^2$);

$C_{raw}$ = raw chemical value which represents data obtained directly from instrument prior to any process that corrects the result based on the quality control regimen of the study (e.g., µg/sample or µg/cm$^2$); and

RCF = recovery correction factor. (See Eq. D2-6 above.)

## 2.4 EXPOSURE/DOSE CALCULATIONS

Algorithms necessary to quantify dose levels for postapplication chemical exposure scenarios are presented in this section. A complete hazard or risk analysis requires the calculation of exposure/dose levels for each route of exposure that is of concern for the specific chemical use scenario (e.g., dermal, inhalation, and/or nondietary ingestion) or a thorough analysis of available biological monitoring data. The basic elements that are required in such calculations are described in this section. These elements include the calculation of exposure, potential dose, or internal dose levels; normalization of exposure/dose levels; and completion of all required statistical manipulations of the normalized values. Please refer to Part D, Chapter 1, Figure D2-2, and the U.S. EPA Guidelines for Exposure Assessment for clarification regarding the nomenclature used in these calculations (U.S. EPA, 1992).

### 2.4.1 Calculation of Exposure and Potential Dose

For the dermal route, potential dose represents the amount of chemical residues that are deposited onto the skin (U.S. EPA, 1992). For the oral and inhalation routes, potential dose represents the concentration available for intake through the mouth or nose while potential dose represents the amount inhaled or taken in through the mouth and nose (U.S. EPA, 1992). The potential dose calculations described in this section may be used to summarize all types of human exposure monitoring data, regardless of the techniques used to generate the data (i.e., passive dosimetry or biological monitoring). Potential dose levels are a required aspect of all calculations based on passive dosimetry. However, for biological monitoring techniques, the calculation of potential dose levels is only an exercise that enables activity/job specific transfer coefficients to be calculated by back calculating to potential dose levels. (See Figure D2-1 above and Section 2.6 below.)

**Dermal Passive Dosimetry** techniques can be categorized based on the nature of the monitoring devices/matrices (e.g., dermal-nonhand and dermal-hand). Algorithms required for calculations specific to each dosimeter type are presented below. Dermal potential dose levels based on patch dosimetry data for nonhand body parts must be calculated using the equation below with standard surface areas for each body part:

$$D_{pot.\ dermal\ (body\ part)} = C_{cor\text{-}patch} * SA \qquad \text{(Eq. D2-8)}$$

Where:

$D_{pot.\ dermal\ (body\ part))}$ = exposure for specific nonhand body parts (µg/body part);

$C_{cor\text{-}patch}$ = corrected patch concentration as described in Eq. D2-7 (µg/cm$^2$); and

SA = human skin surface areas for body parts of interest (cm$^2$/body part).

[Please refer to EPA's Exposure Factors Handbook for appropriate human skin surface areas (U.S. EPA, 1996).] The total, nonhand, potential dermal dose ($D_{pot.\ dermal\ (nonhand)}$) is the sum of all $D_{pot.\ dermal\ (body\ part)}$ across all body parts.

Whole-body dosimeters and glove dosimeters cover each body part of interest during sampling by design (e.g., long-sleeved shirt over the torso and arms). As a result, no further calculation is

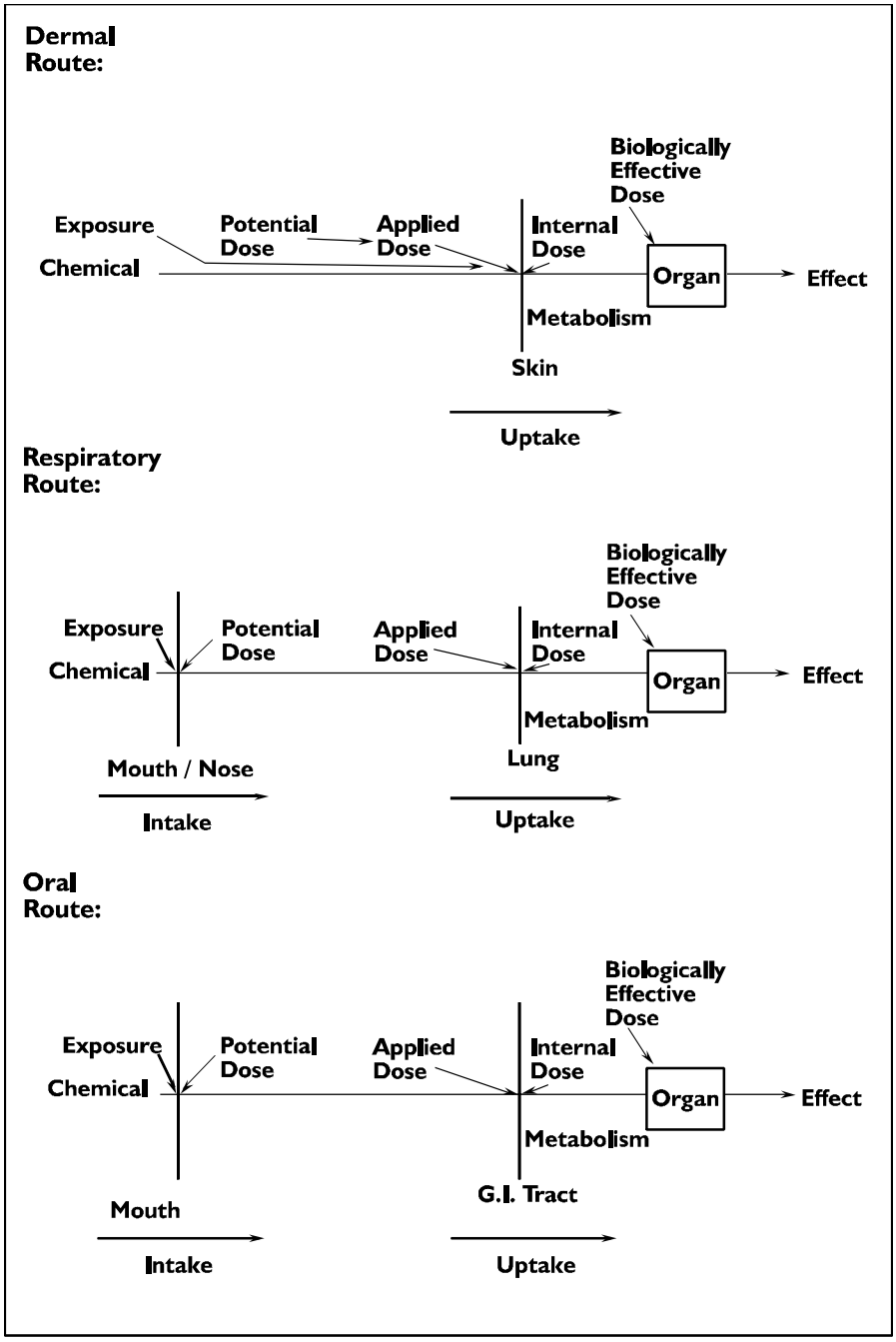


Figure D2-2. Schematic of Dose and Exposure

Source: U.S. EPA, 1992

required other than a summary calculation if the dosimeter garments are sectioned prior to analysis. Dermal hand measures are similar to the whole-body dosimeter data in that they require either no or few calculations. If only one hand monitoring sample was collected, its corrected result is the measured potential dose. If multiple samples were collected during a monitoring period, a cumulative potential dose value must be calculated by adding the values from all intervals. (See Section 2.3.1 for further information.)

The total potential dermal dose for each test replicate can be calculated using the results of the calculations described above and the following equation:

$$D_{dermal\ (tot.\ pot.)} = D_{pot.\ dermal\ (hand)} + D_{pot.\ dermal\ (nonhand)} \qquad \text{(Eq. D2-9)}$$

Where:

$D_{dermal\ (tot.\ pot.)}$ = cumulative potential dermal dose during a replicate, term may represent several dosimeter samples collected from a single exposure replicate (µg or mg/replicate);

$D_{pot.\ dermal\ (hand)}$ = cumulative potential dermal dose to the hands during a replicate (µg or mg/replicate); and

$D_{pot.\ dermal\ (nonhand)}$ = potential dermal dose for nonhand body parts of interest (µg or mg/replicate).

**Inhalation Dosimetry** techniques can be categorized based on the nature of the monitoring devices/matrices (e.g., personal sampling pump or passive badge-type monitor). The algorithm required for calculations specific to the use of filters and sampling pumps (i.e., the most common monitoring approach) is presented below. Investigators should refer to the calculations presented in the User's Manuals for passive, badge-type monitors as these types of calculations are usually specific to the device. Potential inhalation dose for personal monitoring completed using a filter and pump device, excluding passive badge-type monitors, is most often calculated using the equation below:

$$D_{inh(tot.pot.)} = (C_{cor\text{-}inhalation} * IR/FR) \qquad \text{(Eq. D2-10)}$$

Where:

$D_{inh(tot.pot.)}$ = cumulative potential inhalation dose during a replicate; term may include several iterations of this equation that represents several samples collected from a single exposure replicate (µg or mg/replicate);

| | | |
|---|---|---|
| $C_{cor\text{-}inhalation}$ | = | corrected chemical levels measured on inhalation monitor as described in Eq. D2-7 above (µg or mg/sample); |
| FR | = | sampling pump flow rate (L/min); and |
| IR | = | inhalation rate for people as they perform various types of tasks/activities as presented (L/minute). |

[Please refer to EPA's Exposure Factors Handbook for appropriate human inhalation rates (U.S. EPA, 1996).]

Equation D2-10 presented above is a calculation that summarizes the following equations commonly used in industrial hygiene for presenting air monitoring data and calculating inhalation dose. These equations include calculating sample volumes, chemical concentrations, and inhalation dose using a human inhalation rate. Air sample volume can be calculated using the following equation:

$$V = FR \times ED \qquad \text{(Eq. D2-11)}$$

where:

| | | |
|---|---|---|
| V | = | air volume for sample (L); |
| FR | = | sampling pump flow rate (L/min); and |
| ED | = | exposure duration or length of sample collection interval (min). |

The next step in the process is to calculate the exposure concentration (i.e., monitored airborne concentration). In some cases, these exposure concentration values are compared directly with a toxicology endpoint presented as a concentration (e.g., dose concentrations for a 90-day subchronic inhalation study). Exposure concentrations can be calculated using the following equation:

$$C_{air} = C_{cor\text{-}inhalation} / V \qquad \text{(Eq. D2-12)}$$

where:

| | | |
|---|---|---|
| $C_{air}$ | = | corrected chemical airborne exposure concentration measured during a single exposure replicate (µg/L); |
| $C_{cor\text{-}inhalation}$ | = | corrected chemical levels measured on inhalation monitor as described in Eq. D2-7 above (µg); and |

V = air volume for sample (L).

Inhalation dose can then be calculated using the exposure concentration and a human inhalation rate. This calculation of inhalation dose can be used to substitute for the inhalation dose calculation illustrated in Eq. D2-10. Inhalation dose, using Eq. D2-11 and D2-12, can be calculated using the following equation:

$$D_{inh\ (tot.\ pot.)} = C_{air} * IR * ED * CF \qquad \text{(Eq. D2-13)}$$

where:

$D_{inh\ (tot.\ pot.)}$ = cumulative potential inhalation dose during a replicate; term may represent several samples collected from a single replicate (mg/replicate);

$C_{air}$ = corrected chemical airborne exposure concentration measured during a single exposure replicate (µg/L);

IR = inhalation rate for people as they perform various types of tasks/ activities (L/minute);

ED = duration or length collection interval (min.); and

CF = weight conversion factor (1 mg/1,000 µg).

It should be noted that Equations D2-10 through D2-13 apply to monitoring based on the use of sampling pumps and filters. With appropriate modification, the same basic equation can be used for various other types of less common monitoring protocols (e.g., stationary high-volume samples may require altering the units). Investigators must document any modifications of the equation that are used in calculations.

**Biological Monitoring** data may be used to estimate activity-specific transfer factors. A key step in this process is to back calculate potential dose levels. The pharmacokinetic model for each specific analyte of concern must be used to calculate potential dose levels. Investigators must clearly demonstrate the calculations used to define potential dose levels based on biological monitoring data as well as any assumptions pertaining to the relative impact of each exposure route.

### 2.4.2 Calculation of Internal Dose Levels

Internal dose levels can be calculated using either passive dosimetry data in conjunction with the appropriate absorption factors or using biological monitoring data in conjunction with a pharmacokinetic

model. The requirements for calculating internal dose levels depend upon the nature of the toxicological data base. For example, if the toxicological endpoint of concern is based on a dermal application study (e.g., 21 day dermal subchronic), then an internal dose calculation is not required because potential dose levels can be directly compared to the endpoint in any hazard or risk analysis. However, if the toxicological endpoint of concern is based on an oral study, then an internal dose may well be the common denominator by which the oral no effect level from ingestion can be compared to a potential dermal or inhalation dose. For the purpose of this guideline, oral and inhalation potential dose levels will be considered similar to oral and inhalation internal dose levels because data are generally not available to assess the biological pathways that determine internal dose from a potential dose value (i.e., AF in Eq. D2-14 is 100 percent unless chemical/scenario specific data are available). In order to make that comparison, one must be able to calculate an internal dose from the route of exposure that created the toxicologic endpoint of concern.

**Passive Dosimetry** data are used initially to calculate potential dermal and inhalation dose levels as described in Section 2.4.1 above. Using these values, the following equation can be used to calculate internal dose levels:

$$D_{int} = ((D_{dermal\ (tot.\ pot.)} * AF) / 100) + ((D_{inh.(tot.\ pot.)} * AF)/100) \qquad \text{(Eq. D2-14)}$$

Where:

| | | |
|---|---|---|
| $D_{int}$ | = | internal dose based on route of exposure (µg or mg/replicate) (see Eq. D2-9); |
| $D_{dermal\ (tot.\ pot.)}$ | = | potential dermal dose (µg or mg/replicate) (see Eq. D2-9); |
| $D_{inh.(tot.\ pot.)}$ | = | potential inhalation dose (µg or mg/replicate) (see Eq. D2-10); and |
| AF | = | absorption factor through a biological membrane or barrier (%) (e.g., percutaneous absorption). |

**Biological Monitoring** data are typically presented as an internal dose level. Based on the pharmacokinetics of the analyte of interest, investigators must demonstrate a clear calculation of internal dose. Further description of such calculations within these guidelines would not be appropriate as several types of chemical specific, biological processes can be monitored to quantify exposure levels to a chemical.

### 2.4.3 Unit Dose Levels

The calculation of unit levels is a process by which the total dose levels are normalized based on parameters such as duration of each replicate or the productivity of work during the exposure replicate (e.g., pounds harvested, acres mowed, etc.). These normalization factors are typically parameters that are expected to fluctuate with the accompanying dose levels. Dose data presented on a unit basis are easily compared with similar data from other types of activities/job functions to establish a ranking between various scenarios to determine which activities are of highest concern. Unit dose levels can be calculated with data that indicate the duration of the exposure replicate or the activities of the test subject during each replicate (e.g., time during an activity such as harvesting or pounds of crop picked such as tomatoes or grapes). Potential or internal dose levels are used in the calculation depending upon the toxicological properties of the chemical, as defined by available data, the design of the study, and the objective of the assessment. The following algorithm is suggested for the normalization of data:

$$D_{unit} = D_{rep}/NF$$

Where:

| | | |
|---|---|---|
| $D_{unit}$ | = | unit dose level which has been normalized by time, activity, or some other factor; doses are normally reported as µg/hour or µg/activity; |
| $D_{rep}$ | = | total dose incurred by each test subject during an exposure replicate; and |
| NF | = | factor selected by investigators upon which to normalize dose levels for each test subject in a study (e.g., duration of exposure monitoring period, level of activity throughout the exposure replicate, or some other parameter identified by the investigator). |

Investigators may opt to normalize data based on some type of data other than the two options provided above. If this is the case, investigators must provide a detailed justification for the selection.

### 2.4.4 Required Statistical Manipulations

Once all appropriate dose data have been normalized, the final step for completing all required calculations is to summarize the results for each specific job function or activity of concern. These calculations must be completed using the normalized values for each job function or activity monitored in a study and for data pertaining to each toxicologically significant chemical of interest (e.g., parent compound, metabolites, and manufacturing contaminants). The following statistical manipulations of the data should be completed:

- Arithmetic and geometric means for all test replicates based on the exposure route (e.g., dermal, inhalation);
- Standard deviations (σ) for all test replicates based on the exposure route;
- Number of replicates per calculation (N) and rationale for excluding any replicates; and
- Coefficients of variation for all test replicates based on the exposure route (Eq. D2-1).

Because values within many groups of data are distributed lognormally rather than normally, geometric statistical parameters are required along with the arithmetic mean (etc.). As a guide, if the standard deviation approximates or exceeds the mean, data are generally distributed lognormally rather than normally. However, as an alternative, investigators may apply appropriate statistical tests to data to define distributions. Investigators must justify their test selections for distributional analysis (e.g., use of commercial software and test selection).

## 2.5 CHEMICAL DISSIPATION KINETICS

Several standard approaches can be utilized to identify and quantify mechanisms of chemical dissipation and degradation (e.g., 1st order, 2nd order, etc.). Historically, available data have indicated that dislodgeable foliar and soil residue dissipation over time may be modeled using pseudo-first order kinetics. The same observation appears to be true for other residue types (e.g., indoor surfaces and turf). Pseudo-first order kinetics are appropriate because determining the actual dissipation mechanism and defining how individual parameters affect dissipation/degradation are impractical considering the scope of the studies required under these guidelines.

The first objective for completing a kinetics analysis of chemical dissipation data is to ensure that the following calculations have been completed.

- Arithmetic means for all replicate samples for each sampling interval;
- Standard deviations (σ) for all replicate samples for each sampling interval;
- Number of replicates per calculation (N) and rationale for excluding any datapoints for all preliminary statistical calculations; and
- Coefficients of variation for all replicate samples for each sampling interval. (See Eq. D2-1.)

The next objective is to develop an equation that describes the chemical dissipation over time. In most cases, the Agency has observed that chemical dissipation data are lognormally distributed over time. Because values within many groups of data are distributed lognormally rather than normally, geometric parameters are required along with the arithmetic mean (etc.). Testing to determine whether data are normally or lognormally distributed is unreliable for small data sets. Therefore, the decision to assume lognormality is usually adopted, based on experience. The easiest approach for developing a linear equation to describe the data is to plot the data (i.e., typically the means for all replicate samples collected at each sampling interval) in a semi-log fashion after transformation of the chemical residue levels at each sampling interval. As a convention, the Agency prefers that natural logarithms (ln) of the chemical residues be plotted versus dissipation time (postapplication interval). After the plot of the data has been developed, a linear regression must be completed to determine if there is adequate correlation between the residue levels and time (postapplication intervals) to describe the chemical dissipation process using a linear equation. Environmental concentrations can be predicted using semi-log or log-linear regression residue dissipation equations of the form:

$$C_{envir(t)} = C_{envir(0)} e^{(PAI_{(t)} * M)} \qquad \text{(Eq. D2-16)}$$

Where:

$C_{envir(t)}$ = environmental residue concentration (e.g., dislodgeable foliar residue) at time (t), (units are sampling/matrix dependent, typical units are $\mu g/cm^2$ or ppm);

$C_{envir(0)}$ = environmental residue concentration (e.g., dislodgeable foliar residue) at time (0), (units are sampling/matrix dependent, typical units are $\mu g/cm^2$ or ppm) (see Eq. D2-17 below);

e = the base of natural logarithms (i.e., 2.718281828...);

$PAI_t$ = postapplication interval or dissipation time (t, usually hours or days); and

M = slope of line generated during linear regression of data [$\ln(C_{envir})$ versus PAI] (see Eq. D2-17 below).

By taking the natural logarithm of the $C_{envir}$ at each sampling interval and regressing these values against the postapplication interval (PAI) that corresponds to the sample, the regression coefficients M and b can be derived using the linear equation:

$$\ln(C_{envir\ (t)}) = (M * PAI_{(t)}) + b \qquad \text{(Eq. D2-17)}$$

Where:

$C_{envir\ (t)}$ = environmental residue concentration (e.g., dislodgeable foliar residue) at time (t), (units are sampling/matrix dependent, typical units are µg/cm$^2$ or ppm);

M = slope of line generated during linear regression of data [$\ln(C_{envir\ (t)})$ versus PAI];

$PAI_{(t)}$ = postapplication interval or dissipation time (t, usually hours or days); and

b = y intercept of the linear equation generated during regression of the ln ($C_{envir\ (0)}$).

A half-life ($t_{½}$) is a more intuitive expression of the slope (M) calculated above. In addition to the development of an equation that quantifies the chemical dissipation rate, calculation of $t_{½}$ for each analyte of concern should be completed using the following equation:

$$t_{½} = (-0.693/M) \qquad \text{(Eq. D2-18)}$$

Where:

$t_{½}$ = chemical half-life for dissipation data that represents the interval of time it takes for a chemical residue at time 0 to dissipate to 50 percent of the initial level (e.g., days or hours);

0.693 = constant calculated for this kinetics model (i.e., ln(2)); and

M = slope of line generated during linear regression of data [$\ln(C_{envir\ (t)})$ versus PAI].

Natural logarithmic (ln) transformations are required for calculation of the appropriate slope for the pseudo-first order kinetics model described above rather than common base 10 logarithms (log). A model of the form $C_{envir\ (t)} = C_{envir\ (0)}10^{(PAI * M)}$ would be equally valid, but the slope would need to be converted to a half-life via $t_{½} = -0.301/M_{log}$. Additionally, common software packages can be used to complete linear regression calculations. The name and version number must, however, be reported in any submission to the Agency.

The Agency recognizes that completion of a chemical kinetics analysis is often difficult. In a majority of cases, the approach outlined above provides an adequate basis for modeling dissipation of a chemical from treated surfaces and environmental matrices. However, in cases where pseudo-first order

kinetics do not apply, other models may be used, including graphical techniques, if they are adequately explained and justified in any submission to the Agency (e.g., Gustafson and Holden, 1990).

## 2.6 TRANSFER COEFFICIENTS AND EXPOSURE MODELS

The Agency's long-term objective for requiring concurrent postapplication human exposure and chemical dissipation data is to establish a data base of transfer coefficients for specific activities in order to calculate the risk or hazard at other times with other residue levels. Transfer factors quantitatively establish the relationship between activity, chemical concentrations in the environment, and dose. The purpose of transfer coefficients is to calculate dose levels when no appropriate human monitoring data are available (i.e., they provide a mechanism for predicting dose levels when only environmental concentration data are available and they provide a basis for ranking the relative dose levels associated with various activities).

### 2.6.1 Calculation of Transfer Coefficients

The calculation of transfer coefficients involves relating measured doses to concurrently measured chemical concentrations in environmental media. Transfer coefficients should be representative of particular activities including: harvesting and maintaining particular crops; handpacking commodities; or indoor and outdoor residential activities. It should be noted that transfer coefficients typically have only been applied to the dermal exposure route. However, the concept is sound for other exposure routes (e.g., inhalation or nondietary ingestion). When the main source of exposure is via inhalation, dermal transfer coefficients cannot be used to estimate potential bystander exposure and an exposure study should be conducted. The equation below provides an example of the calculation of a transfer coefficient for the dermal exposure route as it is the most commonly used for of the concept:

$$TC = (D_{dermal}/C_{envir}) \qquad \text{(Eq. D2-19)}$$

Where:

TC = residue transfer rate to humans during the completion of specific activities, calculated using concurrently collected environmental data; environmental data may be actual or predicted based on a kinetics analysis of the data--investigators must justify their selection (e.g., $cm^2/hr$);

$D_{dermal}$ = dermal dose (e.g., typically µg or mg/hour); and

$C_{envir}$ = environmental residue concentration (e.g., dislodgeable foliar residue) at the time concurrent to the dermal exposure, (units are sampling/matrix dependent, typical units are $\mu g/cm^2$ or ppm).

[NOTE: The chemical mass in $D_{dermal}$ and $C_{envir}$ must be expressed in the same units for the equation above to be appropriate.]

The transfer coefficient described above is a simple proportion that compares dermal dose to a chemical concentration (i.e., it assumes that the relationship is linear between dose and environmental chemical concentration over time and with fluxuation in the environmental chemical concentration). More sophisticated techniques that may account for variability in the relationship between dose levels and residue levels may also be utilized. For example, as an alternative to point estimates, investigators may wish to consider using the empirical distribution of transfer coefficient data for use in probabilistic assessments. The following are alternative suggestions for quantitatively representing chemical transfer on a job or activity specific basis:

- Develop linear equations that describe the relationship between dose and environmental residue level (e.g., semilog plot of $D_{dermal}$ vs. $C_{envir}$); and
- Investigate calculating transfer coefficients based on other aspects of a test subject's activity such as efficiency (e.g., pounds fruit harvested).

Investigators must calculate transfer coefficients for every study that contains concurrent environmental chemical concentration and dermal dose data. Transfer coefficients must be calculated for every job function that is monitored in a study. Investigators may use whichever technique they feel is appropriate for calculating transfer coefficients. However, all calculations must be clearly documented and the use of any statistical tests must be referenced and justified in submissions to the Agency.

### 2.6.2 Use of Transfer Coefficients

Transfer coefficients (TC) are used to calculate dose levels using an environmental chemical concentration when no concurrent human exposure monitoring data are available (i.e., they provide a surrogate basis for calculating dose levels). Where possible, actual monitoring data as well as dose levels predicted using the TC value should be presented by investigators for comparison by the Agency. The basic premise of the TC approach is generally considered valid for all dermal exposure scenarios including adults engaged in occupational activities and sensitive populations in a residential setting. The Agency is engaged in a research effort that will establish a quantitative basis or predicting exposures to sensitive populations (i.e., defining the extrapolation process from adult test subjects to a sensitive population). In other words, the TC in conjunction with the $C_{envir}$ replace the contaminant concentration (C) and contact rate (CR) terms in the equations that describe dose and average daily or lifetime average daily dose (ADD or LADD). (See Eq. D1-3 for further information.) The basic equation for using transfer coefficients is provided below:

$$D_{dermal} = TC * C_{envir} \quad \text{(Eq. D2-20)}$$

Where:

$D_{dermal}$ = total dermal dose (e.g., µg or mg/hour);

TC = residue transfer rate to humans during the completion of specific activities (e.g., $cm^2$/hour); and

$C_{envir}$ = concentration of residue in an environmental matrix such as dislodgeable foliar residue (µg or mg/$cm^2$), in soil (ppm) or indoor surface residue data (µg or mg/$cm^2$).

For defining a limit of detection/limit of quantification (i.e., until a specific factor for the activities of interest is generated) a transfer coefficient of 10,000 $cm^2$/hr should be used as a surrogate value where no appropriate data exist.

### 2.6.3 Currently Used Assumptions for Assessing Nondietary Ingestion Exposure

As an interim measure, the Agency has developed approaches for addressing nondietary ingestion exposure to toddlers and small children. Nondietary ingestion can occur from hand-to-mouth transfer or direct ingestion of chemicals or chemically treated materials found in the environment. Equations for addressing each scenario are presented below based on the exposure pathways of critical concern to the Agency:

Hand-to-mouth transfer

Nondietary ingestion dose attributable to hand-to-mouth activity includes several scenarios (e.g., smoking with contaminated hands after harvest, exposure to infants after crawling on treated turf). Equation D2-21, presented below, addresses how nondietary ingestion dose due to hand to mouth contact can be calculated.

$$D_{HMI(t)} = C_{envir} \text{ x } HSA \text{ x } F \text{ x } CFI \text{ x } ET \quad \text{(Eq. D2-21)}$$

Where:

$D_{HMI(t)}$ = nondietary ingestion dose attributable to hand to mouth activity at time (t) after chemical application (mg/day);

$C_{envir}$ = environmental residue concentration (e.g., turf dislodgeable foliar residue) at time (t), (units are sampling/matrix dependent, typical units are µg/cm$^2$ or ppm);

HSA = human skin surface areas for body parts of interest (cm$^2$/body part);

F = frequency of hand-to-mouth events (events/min);

CFI = time unit conversion factor (60 min/hr); and

ET = exposure time (hours/day).

[Note: Please refer to the U.S. EPA Exposure Factors Handbook for data pertaining to skin surface areas (U.S. EPA, 1996).]

Foreign object/matter nondietary ingestion exposure

Nondietary exposure attributable to the ingestion of foreign objects or matter laden with chemical residues from a previous application can represent several pathways (e.g., ingestion of soils, turf, and paint chips). Equation D2-22, presented below, addresses how dose attributable to the ingestion of foreign matter/objects laden with chemical residues can be calculated.

$$D_{NDI(t)} = IgR \times WF \times CFI \qquad \text{(Eq. D2-22)}$$

Where:

$D_{NDI(t)}$ = nondietary ingestion dose attributable to ingestion of chemical residue laden materials at time (t) after chemical application (mg/day);

IgR = ingestion rate of foreign objects/materials (g/day);

WF = weight fraction of a chemical residue contained on foreign matter/objects that are ingested (unitless); and

CFI = weight unit conversion factor to convert gram units in the ingestion rate value to mg for the daily exposure (1,000 mg/g).

### 2.6.4 Swimmer Exposure

Swimmer exposure is a unique reentry scenario that is based on the premise of total absorption into the body via seven routes (Dang, 1996). These seven routes are: oral, dermal, inhalation, buccal/sublingual, orbital/nasal, aural, and via male sexual organs. Generally, the oral, dermal, and inhalation exposure routes

contribute predominantly to a swimmer's overall dose resulting from exposure to pool treatment chemicals. Equations D2-23 through D2-29 document the Agency approach for calculating oral (nondietary ingestion), dermal, and inhalation doses to swimmers.

Nondietary ingestion (oral) doses to swimmers can be calculated as follows:

$$D_{int.ing\ (swim)} = C_w * IgR * ET \qquad \text{(Eq. D2-23)}$$

Where:

$D_{int.ing\ (swim)}$ = nondietary ingestion dose attributable to oral intake of pool water while swimming (mg/day);

$C_w$ = chemical concentration in pool water (mg/L);

IgR = ingestion rate of pool water (L/hour); and

ET = exposure time (hours/day).

$C_w$ can either be measured, predicted (i.e, based on the chemical-specific data pertaining to the environmental fate characteristics of the chemical), or approximated as follows:

$$C_w = AR * CF1 * CF2 \qquad \text{(Eq. D2-24)}$$

Where:

AR = application rate of active ingredient (e.g., lbs ai/gal);

CF1 = weight unit conversion factor (4.54E5 mg/lb); and

CF2 = volume unit conversion factor (2.64E-1 gal/L).

Internal dermal doses to swimmers can be calculated as follows:

$$D_{int.derm.\ (swim)} = C_w * HSA * ET * K_p * CF1 \qquad \text{(Eq. D2-25)}$$

Where:

$D_{int.derm.\ (swim)}$ = internal dermal dose attributable to swimming in treated pool water (mg/day);

$C_w$ = chemical concentration in pool water (mg/L) (see Eq. D2-24 above);

HSA = human skin surface areas for body parts of interest ($cm^2$/body part);

ET = exposure time (hours/day);

$K_p$ = dermal permeability coefficient (cm/hr); and

CF1 = volume unit conversion factor (L/1,000 $cm^3$).

[Note: See Exposure Factors Handbook for data pertaining to skin surface areas (U.S. EPA, 1996).]

Inhalation exposures to swimmers can be calculated as follows:

$$D_{int.inh\ (swim)} = C_{vp} * IR * ET \qquad \text{(Eq. D2-26)}$$

Where:

$D_{int.inh\ (swim)}$ = internal inhalation dose attributable to swimming in treated pool water (mg/day);

$C_{vp}$ = vapor concentration of chemical in air ($mg/m^3$);

IR = inhalation rate ($m^3$/hour); and

ET = exposure time (hours/day).

$C_{vp}$ may be calculated as follows (Dang, 1996):

$$C_{vp} = \frac{(C_w * VP * 273\ K * MW * 1{,}000\ L/m^3 * L/1{,}000\ g)}{(760\ mm\ Hg * T * 22.4\ L/mole)} \qquad \text{(Eq. D2-27)}$$

Where:

$C_w$ = concentration of ai in water (mg/L);

VP = vapor pressure (mm Hg or Torr) at the pool water temperature (see Eq. D2-24 above);

T = Kelvin temperature (K); and

MW = molecular weight of water (18 g/mole).

[Note: See Exposure Factors Handbook for data pertaining to human inhalation rates (U.S. EPA, 1996). Dang (1996) also provides information pertaining to the inhalation rates of swimmers.]

## 2.7 AVERAGE DAILY DOSE

Generally, the calculation of an ADD value is required for all hazard or risk assessments. Investigators must determine, based on the route of administration of the toxicological endpoint of concern, whether the $ADD_{pot}$ or $ADD_{int}$ should be calculated. For example, if the endpoint is based on a 21-day dermal subchronic study, the $ADD_{pot}$ should be used. In all cases, as a matter of convention, $ADD_{pot}$ values will be used to represent dose levels that have been adjusted by body weight and the hours spent in each activity. However, if the endpoint is based on an oral administration of test material, $ADD_{int}$ should be calculated (i.e., a dermal absorption factor must be applied to the $ADD_{pot}$; 100 percent is generally assumed if no actual data are available). Additionally, investigators must determine, based on the toxicological endpoint, if any further calculations are required prior to the calculation of the hazard or risk. If the endpoint is acute or subchronic (i.e., less than lifetime), no further calculations are required. If the endpoint is cancer, calculation of the LADD may be also required. (See below.) The equation that can be used to calculate ADD values is presented below:

$$ADD_{pot\ or\ int} = ((D_{unit} * AdF)/BW) \qquad \text{(Eq. D2-28)}$$

Where:

$ADD_{pot\ or\ int}$ = average daily $dose_{pot\ or\ int}$ which is calculated based on the $D_{unit}$ and the appropriate adjustment factors (e.g., µg or mg/kg body weight/8 hour day);

$D_{unit}$ = unit dose (potential or internal) calculated using (e.g., µg/hour) (Eq. D2-15);

AdF = adjustment factor which replaces the quotient [(CR*ED*F)/AT] described in the general equation of ADD included in Chapter 1 of part D. This adjustment factor may be based on, but not limited to, the following: time (e.g., hours at work or in residence), the amount harvested (e.g., pounds picked), or amount maintained (e.g., acres mowed), [Note: this factor must be congruous to the normalization factor used to calculate the $D_{unit}$]; and

BW = body weight value used to normalize the ADD value (kg). Investigators must be careful to determine the appropriate value based on the population at risk (e.g., adults, infants, toddlers, etc.). [Note: See Exposure Factors Handbook (U.S. EPA, 1996) for most recent guidance pertaining to the selection of a proper body weight value.]

As indicated above, the $ADD_{pot}$ or $ADD_{int}$ is typically used for noncarcinogenic chemicals (i.e., the exposures of concern are of an acute or subchronic nature). If the endpoint is cancer, the ADD must be amortized over the duration of a lifetime using the calculation for a LADD. An equation that can be used to calculate LADD values is presented below:

$$LADD_{Pot\ or\ Int} = ADD_{Pot\ or\ Int} * (F/365) * (ED/LT)) \qquad \text{(Eq. D2-29)}$$

Where:

$LADD_{Pot\ or\ Int}$ = $ADD_{Pot\ or\ Int}$ amortized over an individual's lifetime (e.g., mg/kg/day);

$ADD_{Pot\ or\ Int}$ = see (Eq. D2-28) above;

F = frequency of exposure events or the number of days exposed to the pesticide of concern per annum (days/year);

ED = exposure duration throughout a lifetime or the number of years exposed to a specific chemical throughout an individual's lifetime (years); and

LT = anticipated lifetime of an individual in the exposed population of interest (years), investigators must be careful to determine the appropriate value based on the population at risk (e.g., males or females).

The inputs that are selected and used by investigators must be documented for each specific chemical use scenario of concern. Default parameters should be based on standard reference sources such as the Agency's Exposure Factors Handbook (U.S. EPA, 1996) and the Risk Assessment Guide for Superfund (U.S. EPA, 1988). Investigators are encouraged to consult the Agency regarding these types of calculations.

## 2.8 HAZARDS, RISKS, AND RESTRICTED ENTRY INTERVALS

The calculation of hazards or risks resulting from reentry exposure are addressed in this section. Fundamentals and risk assessment are addressed in Part D, Chapter 1. This section addresses specific applications of those principles (i.e., calculation of restricted-entry intervals for commercial, industrial, and

agricultural uses of pesticides and determination of hazard/risk levels in residential settings). With the 1996 passage of the Food Quality Protection Act, investigators are cautioned to consider the new elements of the risk assessment process (e.g., aggregate risk). As such, note that the requirements for residential exposure assessment are much more involved than they have been historically. These requirements are described below as appropriate.

Carcinogenic risks may be calculated as described in Part D, Chapter 1. Calculations are based on LADDs due to the non-threshold nature of carcinogenic risk and are only appropriate when a cancer slope factor is available (i.e., cancer is the endpoint of concern). Risks from postapplication exposures are calculated using the following equation:

$$R = LADD_{Pot\ or\ Int} * (SF) \qquad \text{(Eq. D2-30)}$$

Where:

R = risk which represents the probability of excess cancer cases over a lifetime as described in Part D/Chapter 1 (unitless);

$LADD_{Pot\ or\ Int}$ = described above in (Eq. D2-29); and

SF = cancer slope factor for the chemical of interest $(mg/kg/day)^{-1}$.

Hazard assessment can be based on a variety of toxicological endpoints. As described in Chapter 1 of Part D, a hazard quotient represents the ratio of the calculated dose to the toxicological endpoint expressed as a reference dose or concentration. If the hazard quotient is greater than one, an effect would be expected; however, if the ratio is less than one, no effects would be expected. Hazard quotients are not a probabilistic statement of risk. Based on the common approach utilized by the Agency, noncarcinogenic hazards are also be represented as the Margin of Exposure (MOE). This approach is more common because of the lack of RfD/RfC values for various chemicals. MOE is the ratio of a NOAEL or LOAEL to a dose level. High MOEs (i.e., > 100) imply a low level of concern. As the MOE decreases, the level of concern increases. Neither MOEs nor hazard quotients are a probabilistic statement of risk. MOEs, regardless of the endpoint, can be calculated using the following equation:

$$MOE = TE/(ADD_{Pot\ or\ Int}) \qquad \text{(Eq. D2-31)}$$

Where:

MOE = margin of exposure which reflects the ratio of toxicological endpoint to chemical dose, the level of concern increases as the ratio approaches 0, values approaching 100 or more indicate that concern is negligible for a particular exposure scenario (unitless);

TE = toxicological endpoint which quantitatively represents the biological effect caused by exposure to a chemical (e.g., NOAEL/LOAEL for acute or subchronic data); and

ADD = $ADD_{Pot\ or\ Int}$-based on the descriptions provided above in (Eqn. D2-28).

### 2.8.1 Restricted Entry Interval (REI) Scenarios

Restricted Entry Intervals (REIs) represent the time interval after pesticide application that it takes for resulting residues to dissipate to a level at which human reentry into the treated area would pose a negligible hazard or risk. REIs are used as a tool by the Agency to minimize the risks by altering labels to include the calculated REIs. REIs are generally required only for the completion of assigned tasks in settings where regulation of a chemical via the implementation of an REI is appropriate (e.g., occupational exposure scenarios for agricultural, commercial, and industrial settings). In some cases, the implementation of an REI is inappropriate. For example, for chemicals applied to residential turf, an unacceptable acute hazard is never appropriate (i.e., to allow time for chemical dissipation). Therefore, a different approach must be used for scenarios where the REI is inappropriate. (See Section 2.8.2 below for details.)

Historically, the Agency has used two distinct techniques for the determination of REIs: (1) the nondetectable residue method, and (2) the Reentry Dose Level (RDL) method. The nondetectable residue method entails the identification of the postapplication interval at which residue levels become nondetectable regardless of the quantification or detection limits of the analytical methodologies. This approach is no longer recommended because, for many chemicals, even when one-half of the quantification or detection limits are utilized in the calculations, there is an unacceptable hazard or risk level associated with the exposure scenario.

The RDL method calculates a dose level for reentry that is below a biological threshold. This is accomplished by the application of a safety factor or series of safety factors to the appropriate toxicological endpoint. The generic equation below illustrates the concept:

$$RDL = TE / SF \qquad \text{(Eq. D2-32)}$$

Where:

| | | |
|---|---|---|
| RDL | = | reentry dose level or 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 (e.g., mg/kg/day); |
| TE | = | toxicological endpoint which quantitatively represents the biological effects caused by exposure to a chemical such as the NOAEL/LOAEL for acute or subchronic data (e.g., mg/kg/day); and |
| SF | = | safety factor, based on the nature of the toxicological endpoint, that is used to extrapolate the available toxicological database to the appropriate exposure route of concern in humans (e.g., 10 for interspecies correlation) and to set an appropriate MOE cutoff value (unitless). |

After the RDL is established, an Ambient Reentry Concentration (ARC) is determined by comparing the dose level to the appropriate chemical dissipation data (e.g., plot of DFR levels vs. corresponding dose levels) as illustrated in Figure D2-3. The process can be completed using a graphical procedure or an algorithm that relates residue and dose levels or an algorithm may be developed that relates residue and dose levels (e.g., Eq. D2-19). It should be noted that the ARC which

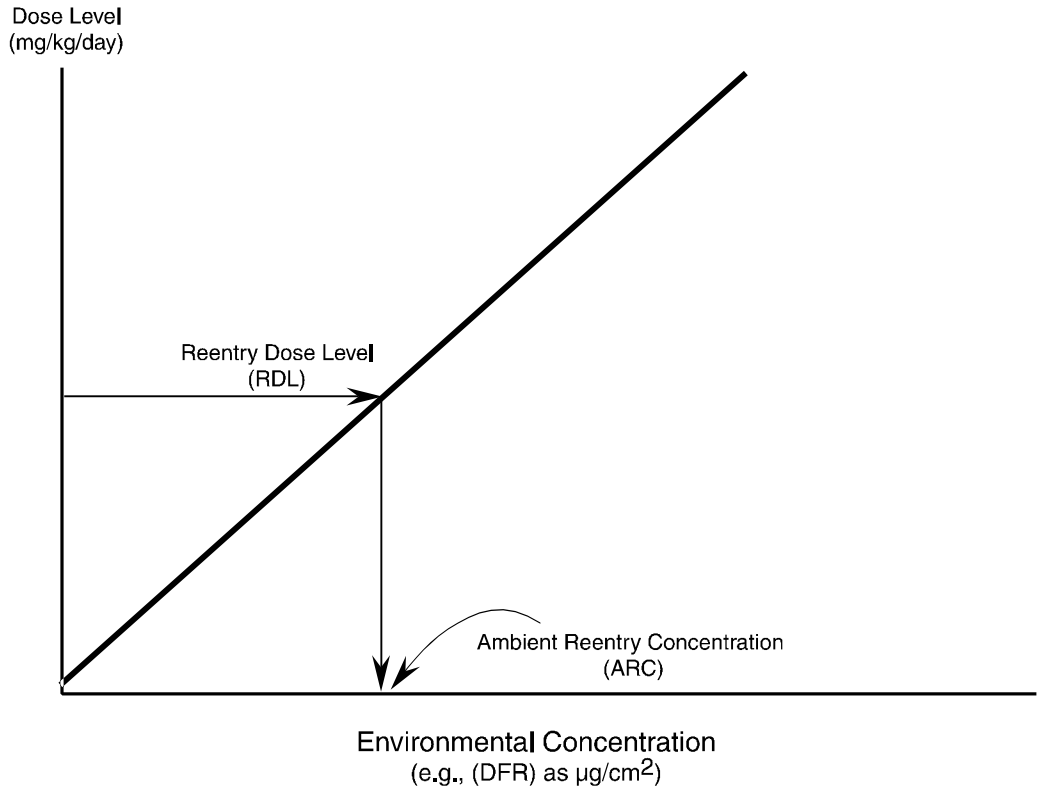


Figure D2-3. Determination of an ARC Using the RDL Method

corresponds to the RDL is dependent on the slope of the line depicted in Figure D2-3. That line is generated from empirical studies in which dislodgeable foliar residues and dermal exposure measurements were collected simultaneously. Essentially, the line represents the transfer coefficient, and is specific to crop activity, and pesticide. The slope of the line will differ depending on differences in one or more of these factors.

Finally, the REI is calculated. The REI represents the interval required for chemical residues to dissipate to the ARC. This determination is made by comparing residue dissipation data to the postapplication interval (e.g., plot of $\ln(C_{envir})$ versus PAI). This process is illustrated in Figure D2-4. The process can be completed using a graphical procedure or an algorithm that relates $C_{envir}$ and the PAI. It should be noted that not all residues are anticipated to decay exponentially. As result, data needs to be modeled appropriately so that an REI can be calculated (e.g., biphasic dissipation).

The application and scope of the calculations described above are similar regardless of the exposure scenario or the sampling protocol (e.g., concurrent residue dissipation and exposure data will be treated in similar fashion regardless of where the data were generated -- agricultural, commercial, or industrial). The Agency recognizes that study and chemical specific adjustments may be required. Investigators must be careful to clearly document any major deviation from the required calculation strategies. It should be noted that several issues exist concerning variability and uncertainty related to the calculation of REIs that eventually must be addressed by the Agency. These issues include the relationship between residue levels and transfer coefficients, selecting appropriate dissipation models, and the calculation of exposure data.

### 2.8.2 Non-REI Scenarios

Calculation of REIs is not appropriate for residential use chemicals as well as a variety of other exposure scenarios where the implementation of an REI may not be feasible (e.g., antimicrobial uses in swimming pools and indoor applications, etc.). Reentry into chemically treated residential areas must be possible on the day of application. The Agency must also consider the only acceptable REI to be the day of application for chemicals with acute endpoints. To determine whether reentry into treated residential areas on the day of chemical application is safe, the procedure for calculating REIs is reversed. First, the ARC on the day of application is determined. Next, the dose level corresponding to that particular ARC is determined based on the equations and guidance presented above in Section 2.8.1. This dose level is then compared to the RDL to determine if humans are adequately protected from adverse effects associated with reentry exposure. (See Figures D2-3 and D2-4 for further information.) The process too can be completed using a simple graphical procedure or an algorithm may be developed that relates residue and dose levels.

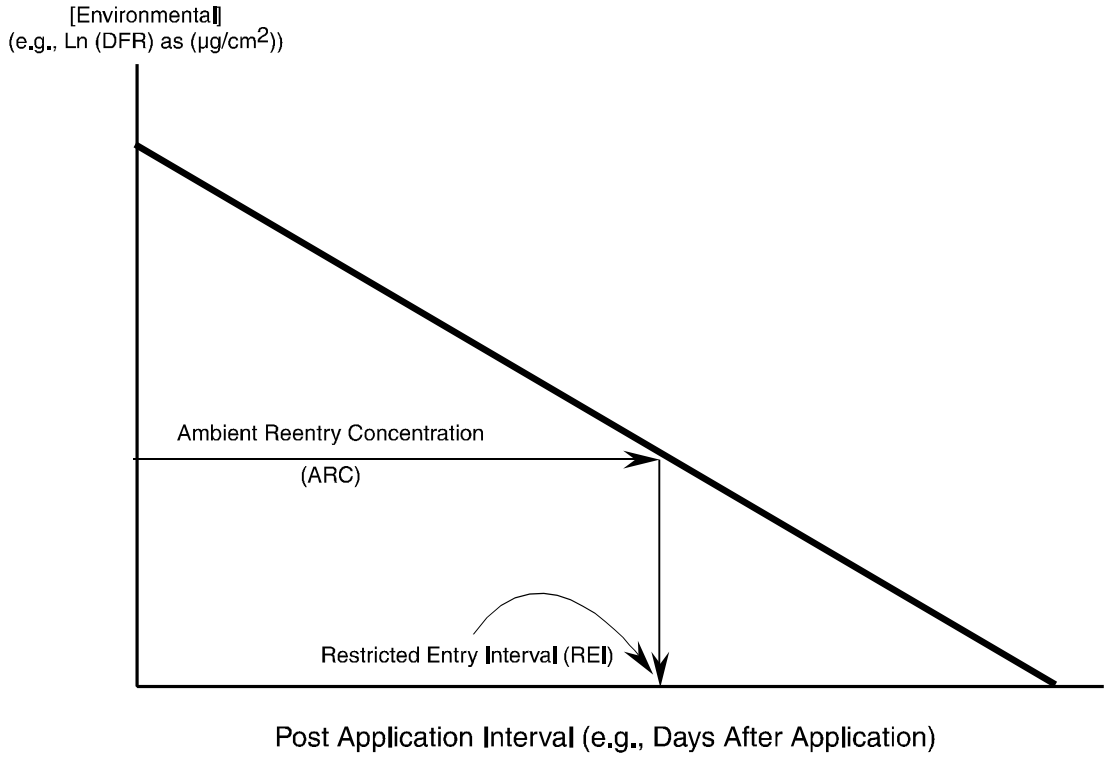


Figure D2-4. Determination of an REI Using the ARC Method

With the enactment of the Food Quality Protection Act (FQPA), the Agency must now also complete aggregate hazard or risk assessments. In particular, this concept applies to residential and nonoccupational exposure scenarios where subchronic and chronic toxicological endpoints have been identified. Historically, the Agency's approach for residential exposure assessment was based on whether or not a single chemical use pattern was "safe" directly after the application. However, in the aggregate risk approach, the Agency must now consider risks associated with multiple use patterns for a chemical even if the use patterns, when considered individually, would be considered acceptable on the day of application. Assessors must calculate risks or hazards from non-REI exposure scenarios until the chemical dissipation reaches the limit of quantification using chemical specific exposure data or surrogate TC values (i.e., calculate exposures for the chemical dissipation curve until the curve reaches the LOQ). The calculated exposures for each scenario must then be summed to calculate aggregate risk.

Several uncertainty and variability issues also exist for non-REI scenarios in addition to those noted above in Section 2.8.1. Dose is a function of exposure, and exposure is a function of environmental concentration and activity pattern. Unless the activity pattern is defined, the dose level associated with an environmental concentration and population of concern cannot be defined. In occupational exposure assessment, transfer coefficients for specific work functions generally define the daily activity pattern. However, the activity patterns for residential scenarios are more difficult to define as they involve different demographic groups (e.g. infants, toddlers, adults) involved in different activities (e.g., walking, crawling, etc.).

## 2.9 EXAMPLE CALCULATIONS

Example calculations are provided in this section that illustrate the general use of the equations presented in sections D2.2 through D2.8 using a hypothetical dataset. This section follows the format of the previous sections. For the purposes of this section, an example has been developed based on an agricultural reentry scenario. However, the same principles can be applied to residential, industrial, and commercial scenarios. Any values or data presented in this section should not be construed as default values or representing Agency policy. They are presented strictly for illustrative purposes. A series of tables are presented that include example data. A parameter is included in these tables that is called "Line Number." This parameter is intended to provide a mechanism for tracking data throughout the example.

### 2.9.1 Example Scenario

The example calculations in this section are based on the following parameters:

- ***Exposure Monitoring Techniques:*** whole body dosimeters (thermal underwear pants and long-sleeved tee-shirts covering the upper and lower body under normal work clothing -- long pants and long sleeves), handwashes collected twice per interval, inhalation monitoring using personal sampling pumps, and head exposure using two 100 $cm^2$ patches;

- ***Exposure Monitoring Regimen:*** 15 replicates of citrus thinning were completed on 3 separate days after application (i.e., days 1, 2, and 4 after application);

- ***Application Scenario:*** an insecticide was applied using an airblast sprayer to citrus 1 day prior to thinning; the example pesticide can also be applied in a residential scenario (a single application scenario is included, multiple application scenarios require assessing accumulation between applications);

- ***Dislodgeable Foliar Residue Monitoring:*** 5 replicate samples were collected at each sampling interval starting prior to application (i.e., baseline), after application (the sprays have dried), and on the following days after application: 1, 2, 4, 7, 10, 14, 21, 28, and 35;

- ***Quality Control:*** Recovery samples were generated in the field for each sampling media as appropriate; all recovery samples were collected, shipped, stored, and analyzed concurrently with field samples -- the recovery data represent field and laboratory recovery as well as storage stability;

- ***Toxicological Endpoints:*** exposure and hazard/risk scenarios are presented for a short-term and a cancer endpoint; the factors used in the example calculations include a percutaneous absorption factor of 15 percent, a 21 day dermal rat study with a NOEL of 10 mg/kg/day, a cancer slope factor of $1x10^{-2}$ $(mg/kg/day)^{-1}$, and a body weight of 70 kg; and

- ***Exposure Calculation Scenarios:*** daily work intervals will be 8 hours and lifetime average daily amortization factors for cancer endpoints will be a 70 year lifetime and a 35 year working lifetime.

### 2.9.2 Commonly Used Formulas and Approaches

This section provides examples of the appropriate use of common formulas/approaches discussed in Section D2.2. The sample raw data to be used for these calculations are presented in Table D2-1. The appropriate use of quantification/detection limits is also presented in this table. For the purposes of this example the quantification limit is the lowest fortification level specified for each matrix and the detection limit is 5x lower for each matrix. "NQ" indicates that the residue level was greater than the LOD but less than the LOQ. "ND" indicates the residue level was less than or equal to the LOD.

### 2.9.3 Chemical Data

Example quality control data are also presented in Table D2-1 and a summary of these data are presented in Table D2-2. The use of basic statistical formulas is also described in Table D2-2. The summary table illustrates how quality control data should be analyzed and presented in any submission to the Agency. The summary table includes the calculation of means, standard deviations ($\sigma$), coefficients of variation, and confidence intervals for each fortification level and over all fortification levels.

After all quality control data are summarized, the next step is to develop unit values (i.e., normalize) for all exposure and environmental data. For example, raw analytical data are generally presented as (µg/sample) values. If the data are Iwata-type dislodgeable foliar residues, the (µg/sample) values have to be normalized based on the double-sided leaf surface area of the sample (i.e., using a 2.5 cm diameter leaf punch for the purposes of this example). Normalization is completed by dividing the residue level by the surface area. In cases where a leaf punch device is not appropriate (e.g., pine needles), the leaf area for each sample must be calculated using a surface area to weight factor. Examples of both of these types of calculations are provided in Table D2-3. Additionally, human exposure monitoring data sometimes require normalization. For dermal patches, this normalization process is analogous to the process for the use of a leaf punch device (i.e., refer to Table D2-3 for guidance). For air monitoring data, the process differs in that the calibration of the air sampling device must be addressed and a volume must be calculated which is used to normalize the measured residue level. An example air calculation is presented in Table D2-4.

After all human exposure and environmental data are normalized, the quality control data should be assessed to determine if correction of the raw residue data are required based on the results of the quality control regimen. Generally, the Agency requires that data be corrected if the recovery correction factor calculated for the dataset is less than 90 percent. In this example, the recovery data presented in Table D2-1 and summarized in Table D2-2 represent the simplest scenario for developing a recovery correction factor. All data presented in the example are assumed to have been generated in the field with

Table D2-1. Raw Data (Day 2) to be Used in Example Calculations

| Line | Field Recovery[a] Whole Body Dosimeters | | Upper Torso Dermal Exposure Using Whole Body Dosimeters[c,d] (not recovery corrected) (µg/sample) | Field Recovery[a] Dislodging Solutions | | Dislodgeable Foliar Residues[b,c] (not recovery corrected) (µg/cm$^2$) |
|---|---|---|---|---|---|---|
| | Fortification Level (µg/sample) | Recovery (%) | | Fortification Level (µg/sample) | Recovery (%) | |
| 1 | 10.0 | 69.5 | 15.0 | 2.0 | 68.0 | 0.8400 |
| 2 | 10.0 | 85.5 | 205 | 2.0 | 65.0 | 0.6500 |
| 3 | 10.0 | 86.0 | NQ | 2.0 | 71.0 | NQ |
| 4 | 10.0 | 65.0 | 1236 | 2.0 | 74.0 | 0.5800 |
| 5 | 10.0 | 71.0 | 115 | 2.0 | 67.0 | 0.6000 |
| 6 | 100.0 | 72.0 | 19.0 | 100.0 | 110 | N/A |
| 7 | 100.0 | 78.0 | 550 | 100.0 | 89.0 | N/A |
| 8 | 100.0 | 89.0 | 89.0 | 100.0 | 75.0 | N/A |
| 9 | 100.0 | 112.0 | ND | 100.0 | 70.0 | N/A |
| 10 | 100.0 | 69.0 | 55.0 | 100.0 | 81.0 | N/A |
| 11 | 1000.0 | 110.0 | 68.0 | 1000.0 | 71.0 | N/A |
| 12 | 1000.0 | 108.0 | 601 | 1000.0 | 112 | N/A |
| 13 | 1000.0 | 89.0 | 428 | 1000.0 | 83.0 | N/A |
| 14 | 1000.0 | 81.0 | 292 | 1000.0 | 69.0 | N/A |
| 15 | 1000.0 | 84.0 | 19.0 | 1000.0 | 73.0 | N/A |

a Field recovery for whole body dosimeter and dislodging solution samples will serve all analytical functions in this example except where noted (i.e., samples are assumed to have been field recovery samples that were shipped, stored and analyzed concurrently with the field samples -- they will also act as laboratory recovery and storage stability data).

b Dislodgeable foliar residue samples represent a double-sided leaf surface area/sample of 400 cm$^2$. The DFR levels presented in this table represent data collected from a site 2 days after application and concurrently with the whole body dosimeter data also presented in this table. Additionally, a total of 5 replicate DFR samples are assumed to have been collected at this sampling interval and that the field recovery data for this study were generated on this sampling day.

c For the purposes of this example, the limit of quantification (LOQ) will be considered the lowest sample fortification level presented above for each matrix (i.e., 10.0 µg/sample for dosimeters and 2.0 µg/sample or 0.005 µg/cm$^2$ for the dislodgeable residue samples). Likewise, for the purposes of this example, the limit of detection (LOD) will be considered 5x lower than the LOQ for calculation purposes. "ND" and "NQ" represent the following: NQ = residue level X if LOD < X < LOQ; ND = residue level X if X ≤ LOD.

d For the purposes of further calculations, the whole-body dosimeter levels presented in this table represent only the upper torso of monitored individuals (i.e., long-sleeved tee-shirts were assumed to have been used as the monitor).

Table D2-2. Summary Statistics for Example Field Recovery[a]

| Fortification Level (µg/sample) | Whole Body Dosimeter Field Recovery | | | | Dislodgeable Foliar Residue Solution Field Recovery | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean[b] (%) | σ[b] (%) | C.V.[c] | 95% CI[d] (%) | Mean[b] (%) | σ[b] (%) | C.V.[c] | 95% CI[d] (%) |
| 10.0 | 75.4 | 9.70 | 12.9 | 66.9/83.9 | 69.0 | 3.54 | 5.1 | 65.9/72.1 |
| 100.0 | 84.0 | 17.42 | 20.7 | 68.7/99.3 | 85.0 | 15.67 | 18.4 | 71.3/98.7 |
| 1000.0 | 94.4 | 13.65 | 14.5 | 82.4/106.4 | 81.6 | 17.83 | 21.9 | 66.0/97.2 |
| All Levels | 84.6 | 15.22 | 18.0 | 76.9/92.3 | 78.5 | 14.67 | 18.7 | 71.1/85.9 |

a Data summaries in this table are based on the raw data presented in Table D2-1. Each fortification level represents 5 recovery samples (i.e., all data assumed to be generated on Day 2 of example as indicated in Table D2-1).

b Mean and σ values calculated using routines provided in a handheld calculator.

c C.V. = coefficient of variation calculated as described in Eq. D2-1 (12.9 = (9.70/75.4)*100)

d 95% CI = 95% confidence interval lower/upper limits calculated as described in Eq. D2-2 (66.9 = 75.4 - ((9.70 * 1.96)/√5))

Table D2-3. Example Day 2 Environmental Data Normalization

| Table D2-1 Data Line | Required Data | | |
|---|---|---|---|
| | **Residue Level[a] (µg/sample)** | **Sample Surface Area[b] ($cm^2$/sample)** | **Residue Level[a] (µg/$cm^2$)** |
| 1 | 336.0 | 400 | 0.8400 |
| 2 | 260.0 | 400 | 0.6500 |
| 3 | ND[c] | 400 | 0.0005 |
| 4 | 232.0 | 400 | 0.5800 |
| 5 | 240.0 | 400 | 0.6000 |

a Residue levels (µg/sample) are not corrected for recovery.

b Surface area (400 $cm^2$) represents a sample that includes forty 1 inch diameter leaf punches where each leaf punch has a double-sided surface area of 10$cm^2$ (( $r^2$) * 2). In the event that, if the leaf punch apparatus could not be used for sampling the particular crop, sample surface areas could be calculated using a pre-dislodging sample weight and a numerical relationship of sample weight to double-sided surface area as illustrated below (see Eqs. D2-3 through D2-5).

$$400\ cm^2 = (20\ cm^2/\text{gram plant material}) * (20\ \text{grams plant material/sample})$$

If a linear regression rather than a unit estimate is used for the calculation a simple linear equation would be developed rather than the above equation using the slope and intercept of the line.

c The assumed value for ND at one-half of the LOD is 0.2 µg/sample based on the detection limit being 5x lower than the LOQ of 2.0 µg/sample (i.e., 20 µg/(5 x 2) - 0.2 µg).

Table D2-4. Example Day 2 Air Data Normalization[a]

| Line Number | Required Data | | | | | | [Air][c] (µg/m$^3$) |
|---|---|---|---|---|---|---|---|
| | Residue Level[a] (µg/sample) | Personal Sampling Pump Operating Parameters[b] | | | | | |
| | | Exposure Interval (minutes) | Initial Flow (Lpm) | Final Flow (Lpm) | Average Flow (Lpm) | Sample Volume (m$^3$) | |
| 1 | 10.0 | 230 | 2.00 | 1.90 | 1.95 | 0.449 | 22.3 |
| 2 | 12.0 | 240 | 2.00 | 2.00 | 2.00 | 0.480 | 25.0 |
| 3 | 5.0 | 250 | 2.00 | 2.10 | 2.05 | 0.513 | 9.7 |
| 4 | 8.0 | 240 | 2.00 | 1.90 | 1.95 | 0.468 | 17.1 |
| 5 | 9.0 | 230 | 2.00 | 2.00 | 2.00 | 0.460 | 19.6 |

a All data included in this table have not been excerpted from the previous tables. Residue levels (µg/sample) are considered corrected for recovery for these example calculations. All data lines are not included in example for clarity.

b Lpm = liters per minute. Sample volume calculated using a conversion factor of (1m$^3$/1000 liters) and the following equation (see Eq. D2-10):

$$\text{Volume (m}^3\text{)} = \text{Interval (min)} * \text{Average Flow (Lpm)} * (1\ \text{m}^3/1000\ \text{liters})$$

c [Air] = Residue Concentration in air. This concentration calculated using the following equation (see Eq. D2-10):

$$[\text{Air}]\ (\mu\text{g/m}^3) = \text{Residue Level (µg/sample)/Sample Volume (m}^3\text{)}$$

the exposure and environmental samples then transported, stored, and analyzed concurrently with the field samples. Therefore, the summarized recovery data are the appropriate correction factors because they represent field and travel recovery, storage stability, and concurrent laboratory recovery. An example correction factor calculation and associated data correction are presented in Table D2-5.

### 2.9.4 Dose Calculations

This section provides examples of human dose level calculations for passive dosimetry-based monitoring as discussed in Section D2.4. Specifically, potential dose, internal dose, unit dose, and required statistical calculations are presented for a scenario that is representative of the calculations required in this guideline. The basis for this example will be the use of passive dosimetry. For the purposes of this example, the monitored test subjects were assumed to be monitored using whole-body dosimeters (long-sleeved shirt and thermal underwear pants), handwashes (both combined for analysis), head patches (one on front and one on back), and personal sampling pumps for inhalation. In this example, two sets of hand wash samples and one set of all other samples were generated over each exposure replicate because each test subject was assumed to have taken a restroom break during the middle of the exposure interval. Examples are not presented for biological monitoring because the use of biological monitoring techniques is less common (due to a lack of adequate chemical-specific pharmacokinetic data), investigators are encouraged to contact the Agency regarding calculations and the appropriate presentation of these types of data.

The first step of the process is to calculate potential dose as described in Section D.2.4.1. In this example, whole body dosimeters and patches are used to illustrate nonhand dermal dose. The surface area of each patch was assumed to be 100 $cm^2$. Patch samples were combined for analysis, therefore, the head sample surface area was 200 $cm^2$. Calculation of total dermal dose is the first requirement as described in Eqs. D2-8 and D2-9. In order to calculate total dermal dose, the head patch value must be adjusted based on the accepted surface area of the head (1300 $cm^2$) and using Eq. D2-8. The next step is to add the hand wash values together to obtain a dose value that is representative of the entire replicate. Finally, the last step is to calculate a cumulative dermal dose value over the entire replicate as described in Eq. D2-9 for each test subject. Table D2-6 illustrates these calculations for a single test subject based on example data from Table D2-1 and additional data developed for the purposes of this example. Along with the calculation of total dermal dose levels, total inhalation doses must be calculated using Eq. D2-10 and a human inhalation rate (e.g., 29 Lpm is used for example purposes).

Table D2-5. Example Residue Recovery Correction Calculation

| Line | Upper Torso Dermal Exposure/ Whole Body Dosimeters (total µg/sample) | | Dislodgeable Foliar Residue (µg/cm$^2$) | |
|---|---|---|---|---|
| | Not Corrected For Recovery[a] | Corrected For Recovery[b] | Not Corrected For Recovery[a] | Corrected For Recovery[b] |
| 1 | 15.0 | 19.9 | 0.8400 | 0.9882 |
| 2 | 205 | 244 | 0.6500 | 0.7647 |
| 3 | NQ | 5.0 | NQ | 0.0025 |
| 4 | 1236 | 1236 | 0.5800 | 0.6824 |
| 5 | 115 | 137 | 0.6000 | 0.7059 |
| 6 | 19.0 | 25.2 | N/A | N/A |
| 7 | 550 | 550 | N/A | N/A |
| 8 | 89.0 | 106 | N/A | N/A |
| 9 | ND | 1.0 | N/A | N/A |
| 10 | 55.0 | 65.5 | N/A | N/A |
| 11 | 68.0 | 81.0 | N/A | N/A |
| 12 | 601 | 601 | N/A | N/A |
| 13 | 428 | 510 | N/A | N/A |
| 14 | 292 | 348 | N/A | N/A |
| 15 | 19.0 | 25.2 | N/A | N/A |

a All data included in this table are excerpted from Table D2-1.

b In this example, the recovery correction factor is the field recovery mean value for fortification level as these data are stipulated to serve as field recovery, concurrent laboratory recovery, and storage stability (i.e., they were stored and analyzed concurrently with the field samples in the example). The factors used to correct sample residue levels were calculated as illustrated in Table D2-2. Values at "ND" or "NQ" are not corrected.

Table D2-6. Example Exposure and Dose Calculations for Day 2 Reentry[a]

| Line Number | Whole Body Dosimeter Residue Levels | | | Handwash Residue Levels | | | Dermal Patch Data (Head Exposure) | | Total Potential Dermal Dose[d] | Internal Dose From Dermal Route[e] | Unit Dose Levels From Dermal Route[f] | | Inhalation Data[g] | | Total Internal Unit Dose[h] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Lower Torso (µg) | Upper Torso (µg) | Total[b] (µg) | Wash #1 (µg) | Wash #2 (µg) | Total[b] (µg) | Patch Residue (µg) | Potential Dose[c] (µg) | (mg) | (mg) | Potential Dose (mg/hr) | Internal Dose (mg/hr) | Monitored [Air] (µg/m$^3$) | Inhalation Unit Dose (mg/hr) | (mg/hr) |
| 1 | 25.0 | 19.9 | 44.9 | 200.0 | 120.0 | 320.0 | 15.0 | 97.5 | 0.462 | 0.069 | 0.116 | 0.017 | 22.3 | 0.039 | 0.056 |
| 2 | 125.0 | 244.0 | 369.0 | 150.0 | 459.0 | 609.0 | 10.0 | 65.0 | 1.043 | 0.156 | 0.261 | 0.039 | 25.0 | 0.044 | 0.083 |
| 3 | 11.0 | 5.0 | 16.0 | 125.0 | 67.0 | 192.0 | 11.0 | 71.5 | 0.280 | 0.042 | 0.070 | 0.011 | 9.7 | 0.017 | 0.028 |
| 4 | 756.0 | 1236.0 | 1992 | 400.0 | 325.0 | 725.0 | 8.0 | 52.0 | 2.769 | 0.415 | 0.692 | 0.104 | 17.1 | 0.030 | 0.134 |
| 5 | 159.0 | 136.9 | 295.9 | 300.0 | 150.0 | 450.0 | 9.0 | 58.5 | 0.804 | 0.121 | 0.201 | 0.030 | 19.6 | 0.034 | 0.064 |
| 6 | 30.0 | 25.2 | 55.2 | 280.0 | 890.0 | 1170.0 | 15.0 | 97.5 | 1.323 | 0.198 | 0.331 | 0.050 | 12.0 | 0.021 | 0.071 |
| 7 | 408.0 | 550.0 | 958.0 | 1200.0 | 230.0 | 1430.0 | 20.0 | 130.0 | 2.518 | 0.378 | 0.630 | 0.095 | 11.0 | 0.019 | 0.114 |
| 8 | 125.0 | 105.9 | 230.9 | 123.0 | 451.0 | 574.0 | 21.0 | 136.5 | 0.941 | 0.141 | 0.235 | 0.035 | 13.0 | 0.023 | 0.058 |
| 9 | 18.0 | 1.0 | 19.0 | 200.0 | 879.0 | 1079.0 | 5.0 | 32.5 | 1.131 | 0.170 | 0.283 | 0.042 | 10.0 | 0.017 | 0.059 |
| 10 | 75.0 | 65.5 | 140.5 | 700.0 | 123.0 | 823.0 | 13.0 | 84.5 | 1.048 | 0.157 | 0.262 | 0.039 | 8.6 | 0.015 | 0.054 |
| 11 | 38.0 | 81.0 | 119.0 | 560.0 | 485.0 | 1045.0 | 14.0 | 91.0 | 1.255 | 0.188 | 0.314 | 0.047 | 9.8 | 0.017 | 0.064 |
| 12 | 789.0 | 601.0 | 1390 | 483.0 | 683.0 | 1166.0 | 20.0 | 130.0 | 2.686 | 0.403 | 0.672 | 0.101 | 15.8 | 0.027 | 0.128 |
| 13 | 423.0 | 509.5 | 932.5 | 1100.0 | 453.0 | 1553.0 | 9.0 | 58.5 | 2.544 | 0.382 | 0.636 | 0.095 | 14.3 | 0.025 | 0.120 |
| 14 | 250.0 | 347.6 | 597.6 | 1050.0 | 234.0 | 1284.0 | 8.0 | 52.0 | 1.934 | 0.290 | 0.484 | 0.073 | 17.7 | 0.031 | 0.104 |
| 15 | 32.0 | 25.2 | 57.2 | 243.0 | 782.0 | 1025.0 | 11.0 | 71.5 | 1.154 | 0.173 | 0.289 | 0.043 | 21.0 | 0.037 | 0.080 |

Footnotes For Table D2-6:

a All data presented in this table are corrected for recovery (see Tables D2-1 and D2-5 for upper torso residue levels). All other dermal data were developed for the purposes of this table. Inhalation data included in lines 1 through 5 are excerpted from Table D2-4. All other inhalation data were developed for the purposes of this table. All handwash data were developed for the purposes of this table.

b Whole body dosimeter and handwash total (µg) values were calculated using the guidance provided in Eq. D2-9 (e.g., lower torso + upper torso = total).

c Potential head dose (µg) value calculated using Eq. D2-8 as follows: Potential Head Dose (µg) = Patch Residue (µg/200 $cm^2$) * 1300 $cm^2$ Dermal Head Surface Area.

d Potential dermal dose (mg) calculated using Eq. D2-9 as follows: (Whole Body (µg) + Hand (µg) + Head (µg))*(1 mg/1000 µg).

e Internal dose from dermal exposure calculated using a dermal penetration factor of 15% and Eq. D2-14 as follows: Internal Dose (mg) = (Potential Dermal Dose (mg) * Penetration Factor (%))/100.

f Unit dose calculated using Eq. D2-15 as follows (replicate duration was 240 minutes or 4 hours): Unit value (mg/hour) = Dose (mg)/Replicate Duration (hours).

g Unit inhalation dose (100% of exposure assumed to be internal dose) calculated using Eq. D2-10 as follows (note first term completed in Table D2-4): Inhalation Unit Dose (mg/hour) = [Air] (µg/$m^3$) * Human Inhalation Rate (29 Liter/minute) * (1 mg/1000 µg) * (60 minutes/hour) * (1 $m^3$/1000 liters).

h Total internal unit dose calculated by adding internal unit doses from dermal and inhalation routes.

After total potential dose levels are calculated, the next step is to calculate internal dose levels if appropriate as determined by the nature of the most sensitive toxicological endpoint (e.g., if the endpoint is an oral or feeding study). The calculation of an internal dose level also requires an absorption factor that is a measure of penetration of a pesticide through a biological membrane or barrier. For the purposes of this example, two dermal toxicological endpoints will be used (i.e., short-term and chronic). The short-term endpoint that will be used for all scenarios is a 21 day dermal rat study while the chronic endpoint will be a cancer slope factor generated using an oral dose. The dermal absorption factor used for the chronic scenario will be 15 percent (i.e., internal dose must be calculated for the cancer endpoint scenario). In a vast majority of the cases, total inhalation potential dose is also treated as the internal inhalation dose due to a lack of adequate data to provide further resolution. Unless data are available to indicate otherwise, or a sampling regimen has been established to measure various particle sizes, further internal inhalation dose calculations are not required. Table D2-6 illustrates the calculation of internal dermal dose levels using Eq. D2-14.

Subsequent to the calculation of dose, the next step is to normalize these values by an appropriate factor to obtain a unit dose level. In most cases, as these are reentry exposure scenarios, the normalization factor will be based on the duration of the exposure monitoring period (e.g., hours spent harvesting or at play on residential turf). Table D2-6 also illustrates the calculation of these unit dose levels.

The final step in the dose calculations is the statistical summary of the dose data via basic manipulations (refer to Sections 2.2 and 2.4.4). Table D2-7 provides a summary of the example dose data.

### 2.9.5 Chemical Dissipation Kinetics

This section provides examples of characterizing chemical dissipation kinetics from environmental media. In this case, the example is based on a typical agricultural reentry scenario (i.e., the use of dislodgeable foliar residues). However, the same approaches can be used to assess chemical dissipation for any environmental media/residue sampling approach (e.g., residues measured from turf, hard indoor surfaces, and carpets). In this example, dislodgeable foliar residues (DFRs) were taken over a 35 day sampling period after a single application to characterize DFR dissipation patterns and to provide data to relate to human reentry exposure levels concurrently measured in order to define transfer coefficients. The approach most commonly used by the Agency is a pseudo-first order kinetics model (i.e., this example will only address this approach -- other approaches used by investigators should be discussed with the Agency).

Table D2-7. Summary Statistics for Example (Day 2) Exposure Data[a]

| Dose Descriptor | Dose Units | Exposure Statistics | | | | | |
|---|---|---|---|---|---|---|---|
| | | Arithmetic Mean[b] | Geometric Mean[b] | σ[b] | C.V.[c] | 95% CI Upper Limit[d] | 95% CI Lower Limit[d] |
| Total Potential Dermal Dose | (mg/hour) | 0.365 | 0.307 | 0.205 | 56.2 | 0.469 | 0.261 |
| Internal Dose From Dermal Exposure | (mg/hour) | 0.055 | 0.046 | 0.031 | 56.4 | 0.070 | 0.039 |
| Inhalation Dose | (mg/hour) | 0.026 | 0.025 | 0.009 | 34.6 | 0.031 | 0.022 |
| Total Internal Dose | (mg/hour) | 0.081 | 0.075 | 0.032 | 39.0 | 0.097 | 0.065 |

a Data summaries in this table are based on the data presented in Table D2-6.

b Mean and σ values calculated using routines provided in a handheld calculator.

c C.V. = coefficient of variation calculated as described in Eq. D2-1 (34.6 = (0.009/0.026)*100)

d 95% CI = 95% confidence interval lower/upper limits calculated as described in Eq. D2-2

$$(0.261 = 0.365 - ((0.205 * 1.96) / \sqrt{15}))$$

To evaluate the kinetics, a log linear regression of measured DFR concentration data versus time is conducted to predict environmental pesticide residue levels over the course of the entire sampling period (i.e., Eq. D2-16). Typically, the Agency uses a semilog regression approach for this effort (see Eq. D2-17). Table D2-8 presents sample data from all sampling intervals corrected for field recovery for use in the example. The Day 2 data are taken from Table D2-1. After the calculation of the linear regression, the Agency also calculates a half-life using the pseudo-first order model (Eq. D2-18). These calculations and a graphical interpretation of the data are presented in Table D2-9 and Figure D2-5.

### 2.9.6 Transfer Coefficients and Exposure Models

This section illustrates the calculation and use of transfer coefficients as presented in Section 2.6 *Transfer Coefficients and Exposure Models.* This section does not provide a discussion concerning the use of the exposure models included in section D.2.6 because the intent of this example is to provide users of Series 875 guidelines with guidance pertaining to the core elements and approaches required for calculations under these guidelines.

Transfer coefficients are used to predict postapplication (i.e., reentry) exposures from environmental chemical concentrations for specific human activities such as tree thinning or children at play on turf. Historically, the agency has used dermal transfer coefficients in conjunction with dislodgeable foliar residue levels to calculate dermal reentry exposures for agricultural workers. This example focuses on this same scenario, agricultural tree thinning. However, the same approaches/techniques can be used for any correct combination of transfer coefficient and environmental concentration (e.g., PUF roller and indoor reentry exposure on carpets).

Several approaches can be used to calculate and present chemical transfer coefficients. These approaches, presented in Section 2.6, include simple proportions and linear regressions. Additionally, that section includes normalization factors other than hours worked that can be used by investigators to present results.

This example will focus on the hours spent thinning orchards during each exposure replicate (i.e., 240 minutes for all dermal exposure replicates). The first step in calculating a transfer coefficient is to summarize the concurrently generated dislodgeable foliar residue and human reentry exposure data. The next step is to calculate the proportional relationship between the datasets. Example calculations of transfer coefficients, based on the example data used throughout this section, are presented in Table D2-10. These transfer coefficients were calculated using Eq. D2-19. All calculations in this table used arithmetic mean values.

Table D2-8. DFR Data To Be Used In Example Kinetics Calculations

| Sampling Interval (Days After Treatment) | DFR Levels (µg/cm²) | | | | | Statistical Summary of DFR Levels[b,c,d] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Replicate 1 | Replicate 2 | Replicate 3 | Replicate 4 | Replicate 5 | Arithmetic Mean (µg/cm²) | Natural Log of Mean (µg/cm²) | Standard Deviation (µg/cm²) | Coefficient of Variation (%) |
| Pre-Application | 0.0025 | 0.0025 | 0.0025 | 0.0025 | 0.0025 | 0.0025 | -5.9915 | 0.0000 | 0.00 |
| 0 | 1.1213 | 1.3201 | 1.2451 | 1.1894 | 1.2015 | 1.2155 | 0.1951 | 0.0734 | 6.04 |
| 1 | 1.0123 | 1.0584 | 1.0432 | 1.0324 | 1.0451 | 1.0383 | 0.0376 | 0.0172 | 1.66 |
| 2[a] | 0.9882 | 0.7647 | 0.0025 | 0.6824 | 0.7059 | 0.6287 | -0.4640 | 0.3704 | 58.91 |
| 4 | 0.5189 | 0.6543 | 0.5646 | 0.5648 | 0.4564 | 0.5518 | -0.5946 | 0.0725 | 13.14 |
| 7 | 0.3712 | 0.3815 | 0.3620 | 0.3700 | 0.3501 | 0.3670 | -1.0025 | 0.0117 | 3.19 |
| 10 | 0.2301 | 0.2295 | 0.2401 | 0.2314 | 0.2416 | 0.2345 | -1.4501 | 0.0058 | 2.48 |
| 14 | 0.1120 | 0.1201 | 0.1098 | 0.1132 | 0.1140 | 0.1138 | -2.1731 | 0.0039 | 3.38 |
| 21 | 0.0584 | 0.0464 | 0.0565 | 0.0496 | 0.0565 | 0.0534 | -2.9296 | 0.0052 | 9.82 |
| 28 | 0.0214 | 0.0195 | 0.0156 | 0.0251 | 0.0165 | 0.0196 | -3.9308 | 0.0038 | 19.58 |
| 35 | 0.0098 | 0.0056 | 0.0097 | 0.0089 | 0.0079 | 0.0084 | -4.7819 | 0.0017 | 20.66 |

a Day 2 data excerpted from Table D2-5. All data in this table are considered corrected for field recovery.

b Mean and standard deviation calculated using all 5 datapoints for each day.

c Coefficient of variation calculated using the following equation: ((Std. Dev./Mean)*100)

d Natural log values calculated using the mean value for each sampling day.

Table D2-9. Summary DFR Kinetics Calculations[a]

| Parameter | Value |
|---|---|
| Constant[b] | -0.003676 |
| Std Err of Y Est | 0.144582 |
| R Squared | 0.993597 |
| No. of Observations | 10 |
| Degrees of Freedom | 8 |
| Correlation Coefficient | -0.996793 |
| Slope (Eq. D2-17 M value) | -0.139813 |
| Std Err of Coefficient | 0.003968 |
| Half Life (Days)[c] | 4.96 |

a Values calculated using a commercial spreadsheet package based on a semilog regression using Eq. D2-17 of Ln[DFR(µg/cm$^2$)] versus sampling interval (days after application).

b Predicted values presented in Figure D2-5 were calculated using Eq. D2-16 or $DFR_{Day\ 21} = DFR_{Day\ 0} * e^{(21\ days * (-0.139813))}$ where $DFR_{Day\ 21} = 0.0529$ µg/cm$^2$ and $DFR_{Day\ 0} = e^{-0.003676} = 0.9963$ µg/cm$^2$

c Half-life value calculated using Eq. D2-18 or ($t_{1/2} = 0.693/0.139813$)

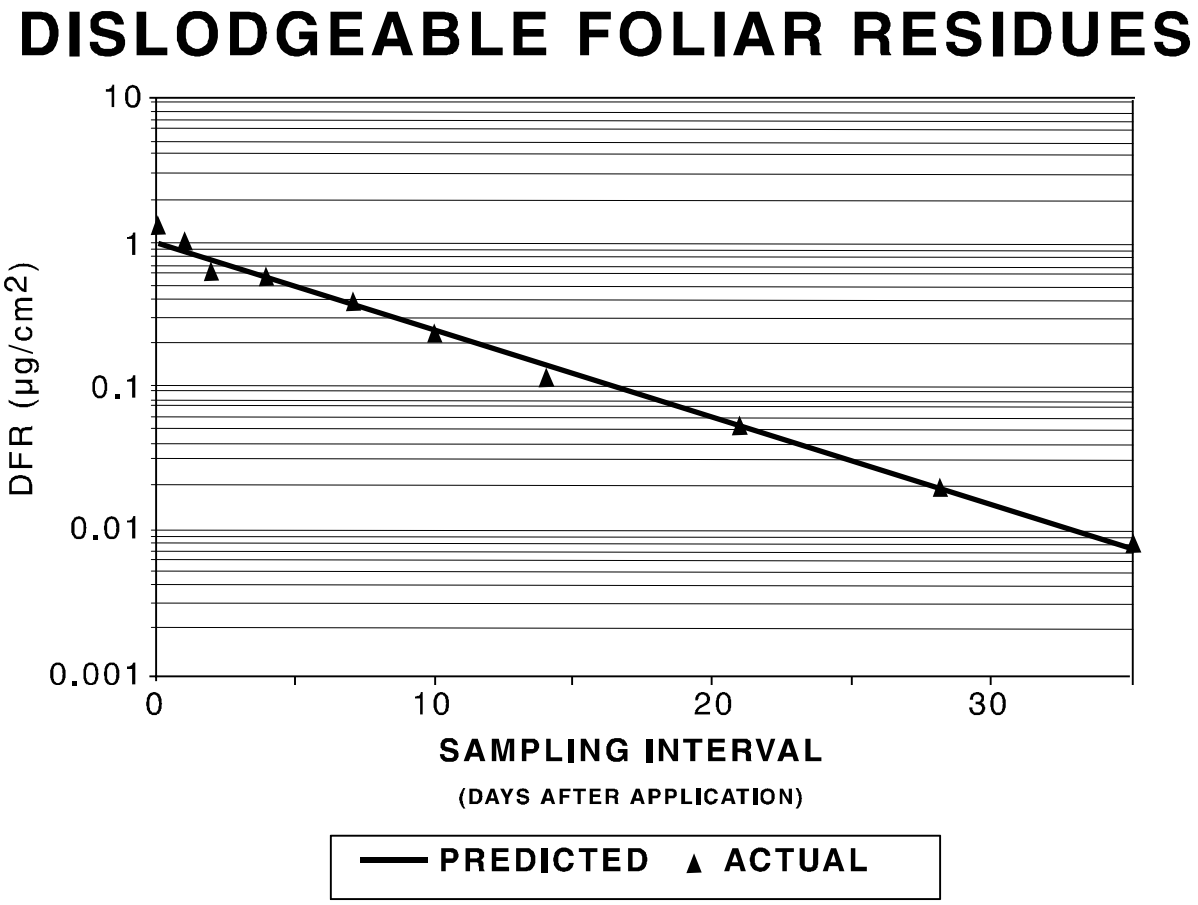


Figure D2-5. Example Chemical Dissipation Data

Table D2-10. Example Transfer Coefficient Calculations

| Study Day | [DFR][a] (µg/cm$^2$) | Unit Dermal Exposure[b] (mg/hour) | Transfer Coefficient[c] (cm$^2$/hour) | N (Exposure/DFR) |
|---|---|---|---|---|
| 1 | 1.0383 | 0.952 | 917 | 15/5 |
| 2 | 0.6287 | 0.365 | 580 | 15/5 |
| 4 | 0.5518 | 0.325 | 589 | 15/5 |
| Mean | 0.9991 | 0.547 | 695[d] | 45/15 |

a Mean DFR levels have been developed throughout the entire example calculation process (e.g., refer to Tables D2-5 and D2-8). This value represents actual measured data corrected for field recovery. Some investigators believe the use of predicted DFR values are appropriate. Any submission to the Agency should clearly indicate which value was selected and a rationale for the selection. DFR levels for Days 1 and 4 have been developed for inclusion into this table.

b Unit dermal exposure levels for Day 2 are have been developed throughout the entire example calculation process (e.g., refer to Tables D2-6 and D2-7). Unit dermal exposure levels for Days 1 and 4 are included in this table with no previous references to them in this example.

c Transfer coefficients calculated using arithmetic mean values for both the DFR and dermal exposure values. Transfer coefficient calculated using Eq. D2-19 as follows (Day 2 provided as example):

580 cm$^2$/hour = ((0.365 mg/hour)/((0.6287 µg/cm$^2$)*(1 mg/1000 µg)))

d There is discussion concerning the use of significant figures when presenting transfer coefficient values. Generally, the Agency believes the use of 1 or 2 significant figures is appropriate based on the uncertainties associated with the data used to calculate them. As a result, a transfer coefficient of 700 will be used in all example REI calculations (e.g., Table D2-12).

In order to calculate dose once activity specific transfer coefficients are known, investigators must use Eq. D2-20 (or some modification thereof if a linear regression as opposed to a proportion is used). Using the same data that are included in Table D2-10, calculation of an exposure on Day 2 can be completed using Day 2 DFR and the mean value transfer coefficient as follows:

0.440 mg/hour (dermal exposure) = 0.6287 µg/cm$^2$ (Day 2 DFR) * 700 cm$^2$/hour (TC) * (1 mg/1000 µg)

Several issues must be considered in the use transfer coefficients. For example, in this instance the transfer coefficients presented in Table D2-10 were similar across each day of reentry (i.e., mean of 564 cm$^2$/hour with a C.V. over all three days of 6.2 percent). As a result, the transfer coefficient used in the example calculation was the mean value generated over all reentry exposure monitoring days (i.e., 1, 2, and 4 days after application in this example). However, in some cases variability in transfer coefficients may occur across time (i.e., the transfer coefficients seem to fluctuate with the DFR data). In those cases, investigators should consider using different transfer coefficients for the same activity depending upon the environmental concentration (e.g., DFR level).

### 2.9.7 Average Daily Dose (ADD) and Lifetime Average Daily Dose (LADD)

The next step in the calculation process is to develop average daily dose estimates for short-term toxicological endpoints and amortized lifetime average daily dose levels for chronic toxicological endpoints (i.e., cancer). In most cases (i.e., except for cancer endpoints), only the calculation of *Average Daily Dose* is required as described in Eq. D2-28. The key element in the application of this equation is to ensure that the adjustment factor (e.g., hours worked per day or hours engaged in a play activity per day) is the same as the factor used to normalize the unit dose value. It should be noted as well that calculation of the average daily dose can also be dependent upon the pattern of reentry days as exposures generally differ over time due to residue dissipation from treated surfaces.

The most common normalization factor used by the agency for postapplication exposure calculations is the duration engaged in the activity. Other factors that have also been used include worker productivity gauged by crops harvested (e.g., pounds per replicate) or acres covered (e.g., acres mowed). For this example, all calculations will be based on the hours worked during citrus tree thinning (8 hours per day is assumed by the agency in all calculations). Unit dermal dose values presented in Table D2-10 were used to calculate Average Daily Dose levels as illustrated in Table D2-11. Additionally, amortized dose levels for cancer endpoints calculated using Eq. D2-29 are illustrated in this table (e.g., a 70 year lifetime and 35 years per activity are assumed for this example).

Table D2-11. Example ADD and LADD Calculations

| Study Day | $ADD_{pot}$ Calculation Parameters (for non-cancer dermal endpoint) | | | $LADD_{int}$ Calculation Parameters (for cancer endpoint) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unit Potential Dermal Dose[a] (mg/hour) | Hours Worked Per Day | $ADD_{pot}$[b,c] (mg/kg/day) | Unit Internal Dose[a] (mg/hour) | Hours Worked Per Day | Average Lifetime (years) | Exposure Duration (days/year) | Exposure Duration (years) | $LADD_{int}$[b,d] (mg/kg/day) |
| 1 | 0.952 | 8 | 0.109 | 0.152 | 8 | 70 | 45 | 35 | 1.01 x 10 |
| 2 | 0.365 | 8 | 0.042 | 0.055 | 8 | 70 | 45 | 35 | 3.87 x 10 |
| 4 | 0.325 | 8 | 0.037 | 0.051 | 8 | 70 | 45 | 35 | 3.59 x 10 |
| Mean | 0.547 | 8 | 0.063 | 0.086 | 8 | 70 | 45 | 35 | 6.06 x 10 |

a Unit dermal dose values excerpted from Table D2-10. Unit internal dose values excerpted from Table D2-7 (Day 2) and developed for example purposes for this table (Days 1 and 4).

b All calculations completed using a body weight of 70 kg.

c $ADD_{pot}$ calculated as follows using Eq. D2-28, 8 hours per day, and a body weight of 70 kg as follows:
0.109 (mg/kg/day) = (0.952 (mg/hour) * 8 (hours/day))/70 kg body weight

d $LADD_{int}$ calculated as follows using Eqs. D2-28 and D2-29, ADD parameters (i.e., 8 hour day and 70 kg body weight) and amortization parameters (i.e., 45 days/year exposure, 35 working years, and 70 year lifetime). The ADD calculation is an interim step not included as a table column. Example calculations for study day 2 are as follows:

$ADD_{int}$ or $6.28 \times 10^{-3}$ (mg/kg/day) = (0.055 (mg/hour) * 8 (hours/day))/70 kg body weight; and
$LADD_{int}$ or $3.87 \times 10^{-4}$ (mg/kg/day) = $6.28 \times 10^{-3}$ (mg/kg/day) * (45 (days/yr)/365 (days/yr)) * (35 years exposure/70 year lifetime)

### 2.9.8 Risks, Hazards, and Restricted Entry Intervals

The Agency typically regulates pesticides by calculating *Margin of Exposure* (MOE) or cancer risks as illustrated in Eqs. D2-30 and D2-31. Example calculations have been developed that illustrate one approach for calculating postapplication risks for a *Restricted Entry Interval (REI)*. It should be noted that there are several different ways to complete these dose/risk calculations (e.g., predicted versus actual dose or predicted versus actual DFR values). The method used here is for illustrative purposes only. An example has been completed for short-term and cancer endpoints for the REI scenario and for the short-term endpoint in the non-REI scenario. These examples are included in Table D2-12. In this example, the mean value transfer coefficient for citrus tree thinning is used in all examples. Using this transfer coefficient value and predicted DFR levels, cancer risks and short-term MOEs were calculated. As indicated in Table D2-12, the REI is 5 days for citrus tree thinning based on the 21 day dermal rat study and the REI is 20 days based on the cancer endpoint.

| EXPOSURE PARAMETERS | |
|---|---|
| DAILY WORK INTERVAL (hrs/day): | 8 |
| BODY WEIGHT (kg): | 70 |
| EXPOSURE FREQUENCY (days worked/year): | 45 |
| EXPOSURE DURATION (years worked): | 35 |
| LIFETIME (anticipated lifetime -- years): | 70 |
| TRANSFER COEFFICIENT (cm2/HOUR): | 700 |

| TOXICOLOGY PARAMETERS | |
|---|---|
| DERMAL PENETRATION FACTOR (%): | 15 |
| 21 DAY DERMAL ENDPOINT (mg/kg/day): | 10 |
| CANCER SLOPE FACTOR (1/(mg/kg/day)): | 0.01 |
| SHORT-TERM MOE SAFETY FACTOR (EQN. D2-29): | 100 |

| DAT | PREDICTED DISLODGEABLE FOLIAR RESIDUES (ug/cm2) | UNIT POTENTIAL DOSE (mg/hour) | UNIT INTERNAL DOSE (mg/hour) | AVERAGE DAILY POTENTIAL DOSE (mg/kg/day) | AVERAGE DAILY INTERNAL DOSE (mg/kg/day) | LIFETIME AVERAGE DAILY INTERNAL DOSE (mg/kg/day) | SHORT TERM REI CALCULATION | | CANCER RISK REI CALCULATION | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | MARGIN OF EXPOSURE | IS REENTRY ACCEPTABLE? | CANCER RISK | IS REENTRY ACCEPTABLE? |
| 0 | 0.9963 | 0.6974 | 0.1046 | 0.0797 | 1.20e-02 | 7.37e-04 | 125 | YES | 7.37e-06 | NO |
| 1 | 0.8663 | 0.6064 | 0.0910 | 0.0693 | 1.04e-02 | 6.41e-04 | 144 | YES | 6.41e-06 | NO |
| 2 | 0.7533 | 0.5273 | 0.0791 | 0.0603 | 9.04e-03 | 5.57e-04 | 166 | YES | 5.57e-06 | NO |
| 3 | 0.6550 | 0.4585 | 0.0688 | 0.0524 | 7.86e-03 | 4.85e-04 | 191 | YES | 4.85e-06 | NO |
| 4 | 0.5695 | 0.3987 | 0.0598 | 0.0456 | 6.83e-03 | 4.21e-04 | 219 | YES | 4.21e-06 | NO |
| 5 | 0.4952 | 0.3467 | 0.0520 | 0.0396 | 5.94e-03 | 3.66e-04 | 252 | YES | 3.66e-06 | NO |
| 6 | 0.4306 | 0.3014 | 0.0452 | 0.0344 | 5.17e-03 | 3.19e-04 | 290 | YES | 3.19e-06 | NO |
| 7 | 0.3744 | 0.2621 | 0.0393 | 0.0300 | 4.49e-03 | 2.77e-04 | 334 | YES | 2.77e-06 | NO |
| 8 | 0.3256 | 0.2279 | 0.0342 | 0.0260 | 3.91e-03 | 2.41e-04 | 384 | YES | 2.41e-06 | NO |
| 9 | 0.2831 | 0.1982 | 0.0297 | 0.0226 | 3.40e-03 | 2.09e-04 | 442 | YES | 2.09e-06 | NO |
| 10 | 0.2462 | 0.1723 | 0.0258 | 0.0197 | 2.95e-03 | 1.82e-04 | 508 | YES | 1.82e-06 | NO |
| 11 | 0.2140 | 0.1498 | 0.0225 | 0.0171 | 2.57e-03 | 1.58e-04 | 584 | YES | 1.58e-06 | NO |
| 12 | 0.1861 | 0.1303 | 0.0195 | 0.0149 | 2.23e-03 | 1.38e-04 | 672 | YES | 1.38e-06 | NO |
| 13 | 0.1618 | 0.1133 | 0.0170 | 0.0129 | 1.94e-03 | 1.20e-04 | 772 | YES | 1.20e-06 | NO |
| 14 | 0.1407 | 0.0985 | 0.0148 | 0.0113 | 1.69e-03 | 1.04e-04 | 888 | YES | 1.04e-06 | NO |
| 15 | 0.1224 | 0.0856 | 0.0128 | 0.0098 | 1.47e-03 | 9.05e-05 | 1022 | YES | 9.05e-07 | YES |
| 16 | 0.1064 | 0.0745 | 0.0112 | 0.0085 | 1.28e-03 | 7.87e-05 | 1175 | YES | 7.87e-07 | YES |
| 17 | 0.0925 | 0.0648 | 0.0097 | 0.0074 | 1.11e-03 | 6.84e-05 | 1351 | YES | 6.84e-07 | YES |
| 18 | 0.0804 | 0.0563 | 0.0084 | 0.0064 | 9.65e-04 | 5.95e-05 | 1554 | YES | 5.95e-07 | YES |
| 19 | 0.0699 | 0.0490 | 0.0073 | 0.0056 | 8.39e-04 | 5.17e-05 | 1787 | YES | 5.17e-07 | YES |
| 20 | 0.0608 | 0.0426 | 0.0064 | 0.0049 | 7.30e-04 | 4.50e-05 | 2055 | YES | 4.50e-07 | YES |
| 21 | 0.0529 | 0.0370 | 0.0056 | 0.0042 | 6.35e-04 | 3.91e-05 | 2364 | YES | 3.91e-07 | YES |

NOTES:

+ PREDICTED DFR VALUES BASED ON KINETICS DATA PRESENTED IN TABLE D2-9 AND FIGURE D2-5.
+ NOMENCLATURE FOR ALL VALUES CONSISTENT WITH TABLES D2-1 THROUGH D2-11.
+ ACCEPTABLE MOE FOR THIS CALCULATION IS 100 (i.e., EQN. D2-29 SAFETY FACTOR).
+ ACCEPTABLE RISK FOR THIS CALCULATION IS 1E-6.

Table D2-12. Example REI Calculations

## REFERENCES FOR PART D, CHAPTER 2

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