PART D - CHAPTER 1

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FUNDAMENTALS OF EXPOSURE AND RISK ASSESSMENT

1.1 INTRODUCTION AND PURPOSE

Series 875, Group B provides guidance for conducting postapplication exposure monitoring studies. The results of these studies are used to characterize risks to humans from reentering areas that have been treated with chemical substances such as pesticide products. This information may be used to evaluate risks associated with specific chemical uses, to determine appropriate regulatory options such as setting restricted-entry intervals for agricultural applications, or to determine whether products can be used in and around the home without appreciable risks to humans.

The risk assessment process estimates the likelihood and magnitude of human health effects that result from environmental exposure. Four steps make up EPA's risk assessment process: hazard identification, dose/response assessment, exposure assessment, and risk characterization. These are briefly defined below:

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

- Dose-Response Assessment. A pesticide's potential for causing adverse health effects is identified through a battery of short-term or acute, intermediate or subchronic, and long-term or "chronic" toxicity testing. In several series of tests, laboratory animals are exposed to different doses of a pesticide, and EPA scientists evaluate the test results to determine the level of exposure in each of those studies that did not cause any noncancer effect. Dose-response assessment is the process of characterizing the relationship between the magnitude of exposure (i.e., doses) and the occurrence of health effects in the foregoing studies.

- Exposure Assessment. Once harmful health effects are identified in the laboratory tests, EPA must estimate the level, duration, frequency, and route of exposure for people.

- Risk Characterization. Risk characterization involves describing the nature and magnitude of the risks by integrating the above factors. By combining estimates of likely or actual pesticide exposure with the toxicity of the pesticide, EPA can characterize the risks that it poses. Simply stated,

$$RISK = Toxicity \times Dose \qquad \text{(Eq. D1-1)}$$

The purpose of Part D, Chapter 1 of these Guidelines is to provide users with basic guidance on the principles of exposure and risk assessment. Part D, Chapter 2 provides users with specific guidance for conducting exposure and risk assessments for postapplication pesticide exposure scenarios. Because the process of identifying hazards, establishing dose response relationships, and determining dietary exposure is beyond the scope of Series 875, Group B, only exposure and risk assessment calculations are included in Part D.

1.2 GENERAL PRINCIPLES OF EXPOSURE ASSESSMENT

Exposure assessment is the process by which: (1) potentially exposed populations are identified; (2) potential pathways of exposure are identified; and (3) chemical intakes/potential doses are quantified. Exposures to pesticides may occur by oral, inhalation, or dermal absorption routes. ***Exposure*** is commonly defined as contact of visible external physical boundaries (i.e., external boundaries such as the mouth, nostrils, and skin) with a chemical agent (U.S. EPA, 1992). As described in the *Guidelines for Exposure Assessment*, exposure is dependent upon the intensity, frequency, and duration of contact. The intensity of contact is typically expressed in terms of the concentration of contaminant per unit mass or volume (i.e., µg/g, µg/L, mg/m^3, ppm, etc.) in the media to which humans are exposed (U.S. EPA, 1992).

Dose refers to the amount of chemical to which individuals are exposed that crosses the external boundary (U.S. EPA, 1992). Dose is dependent upon contaminant concentration and the rate of intake (i.e., inhalation or ingestion) or uptake (i.e., dermal absorption) and may be normalized to body weight as a function of time (i.e., mg/kg/day). ***Potential dose*** is the amount of chemical which could be ingested without cooking or cleaning the food or filtering the water, which could be inhaled without wearing a respirator, or which would be deposited upon the skin without clothing. ***Applied dose*** is the amount of chemical that is actually ingested into the gastrointestinal tract (after food preparation or water treatment), inhaled into the lung (after accounting for the effects of a respirator or particle deposition in the upper airways), or reaches the skin (after penetration through gloves and clothing). Applied dose has sometimes been called ***delivered or deposited dose***. The ***internal dose*** is the amount of chemical absorbed into the body through the

gastrointestinal tract, lung or skin. Internal dose has sometimes been called ***absorbed dose***. The toxicologic basis for risk assessment is typically either the applied dose from animal feeding studies or the internal dose from pharmacokinetic studies followed by intraperitoneal or other injected delivery into the test animal. Field studies using either passive dosimetry (see Part B, Chapter 7) or air monitoring (see Part B, Chapter 8) yield either potential or applied doses which can be related to internal dose through absorption factors. Biological monitoring (see Part B, Chapter 10) yields data which can be related to either applied dose or internal dose through pharmacokinetic models. These latter relationships are discussed in Part D, Chapter 2. Potential dose may be calculated as follows:

$$DR_{pot} = C \times CR \qquad \text{(Eq. D1-2)}$$

where:

DR_{pot} = potential dose rate (mg/day);

C = contaminant concentration in the media of interest (mg/cm^2; mg/m^3, mg/g); and

CR = contact rate with that media (cm^2/day; m^3/day; g/day).

The contaminant concentration is the amount of pesticide in the media to which humans are exposed. The contaminant concentration may be affected by dissipation of chemical over time by evaporation, degradation, or other fate processes. Contact rate may be defined as the rate of ingestion, inhalation, or dermal absorption or as the transfer coefficient (U.S. EPA, 1989a).

Potential doses may also be averaged over body weight and time (mg/kg/day) to calculate an average daily dose. Average daily potential dose rates may be estimated using the standard exposure assessment algorithm shown below (U.S. EPA, 1992).

$$ADD_{pot} = [C \times CR \times ED \times F] \; / \; [BW \times AT] \qquad \text{(Eq. D1-3)}$$

where:

ADD_{pot} = potential average daily dose (mg/kg/day);

C = contaminant concentration (mg/L, mg/m^3; mg/cm^2);

CR = contact rate (L/day; m^3/day; cm^2/day);

ED = exposure duration (years);

F = frequency of exposure events (days/year);

BW = body weight (kg); and

AT = averaging time (days).

Equation D1-3 is structured to facilitate averaging intermittent or seasonal exposure patterns over one or more years. As described above, the contaminant concentration refers to the amount of chemical residue in the media of interest, and contact rate refers to the rate of ingestion, inhalation, or dermal deposition per day. Exposure duration refers to the length of time that contact occurs and is affected by activity patterns; for instance, one year to calculate annual average. Frequency is the number of exposure events over a specified time period. Body weight and averaging time are specific to the population and exposure scenarios being evaluated. The averaging time (AT) is the number of days over which the exposure is averaged. For exposure assessments used to support cancer risk assessments AT is replaced by lifetime (LT) (i.e., 25,550 days = 70 years * 365 days/year). The resulting exposure estimate is referred to as the potential lifetime average daily dose ($LADD_{pot}$). ADD_{pot} and $LADD_{pot}$ are expressed in units of mg/kg/day. Absorbed doses (i.e., ADD_{abs} and $LADD_{abs}$) may be estimated by applying an absorption factor.

Average, high-end, and/or bounding estimates may be made using these algorithms. These exposure descriptors account for individual and population variability and represent points on the distribution of exposures. Average dose rates represent the mean and may be estimated using central tendency values for all the parameters in the ADD or LADD. The high-end potential dose rate (90th or 95th percentile) is a reasonable approximation of dose for individuals at the upper end of the distribution of exposures (U.S. EPA, 1992). High-end values are estimated by setting some, but not all, ADD or LADD parameters to the upper-end values. Finally, bounding potential dose rates are exposures that are estimated to be greater than the highest individual exposure in the population of interest. Bounding estimates are often used in screening-level assessments.

1.3 GENERAL PRINCIPLES OF RISK ASSESSMENT

Risk characterization integrates toxicity and exposure data to provide quantitative estimates of carcinogenic risk and systemic hazards. Carcinogenic risks represent the incremental probability that an individual will develop cancer over a lifetime as a result of exposure to a chemical compound. EPA usually assumes a non-threshold dose-response for carcinogens (i.e., some finite risk no matter how small the dose). For pesticides with carcinogenic endpoints, individual lifetime risk is estimated by multiplying the $LADD_{pot}$ by the cancer potency slope factor as follows:

$$R_i = LADD_{pot} \times SF \qquad \text{(Eq. D1-4)}$$

where:

R_i = excess individual lifetime cancer risk level (unitless);

$LADD_{pot}$ = lifetime average potential daily dose (mg/kg/day); and

SF = cancer potency slope factor $(mg/kg/day)^{-1}$ (also known as Q_1^*).

R_i represents the probability of excess cancer cases over a lifetime. For example, a risk level of 10^{-6} indicates that an excess cancer case is projected to occur in no more than 1 out of a million individuals exposed to this LADD over a lifetime. Annual excess cancer risks may be estimated by dividing the lifetime risk value by the average lifetime (70 years). LADDs are calculated as described previously. Slope factors are conservative estimates of the incremental probability of cancer from a unit dose of chemical over a lifetime. They are chemical-specific values derived from animal toxicity studies and or human epidemiological data and represent the upper 95 percent confidence interval.

Population risks represent conservative estimates of the number of individuals in an exposed population that are likely to be affected by pesticide exposure. Population risks are calculated as follows.

$$POP_{risk} = R_i \times POP_{exposed} \qquad \text{(Eq. D1-5)}$$

where:

POP_{risk} = population risks (number of individuals in an exposed population that are projected to be affected);

R_i = excess individual lifetime cancer risk level (unitless); and

$POP_{exposed}$ = population exposed (number of exposed individuals in the population).

For chemicals with noncancer endpoints (i.e., systemic effects) where a threshold dose-response relationship is assumed, hazard quotients are calculated to characterize the risks associated with exposure.

Hazard quotients are unitless values that are calculated by dividing the average daily dose by a value that represents a toxicity endpoint and are calculated as follows.

$$H = ADD / RfD \qquad \text{(Eq. D1-6)}$$

where:

H = hazard quotient (unitless);

ADD = average daily dose (mg/kg/day); and

RfD = reference dose or other datum indicative of the toxicity endpoint of interest (mg/kg/day).

If the hazard quotient is greater than one, an effect would be expected; but if the ratio is less than one, no effects would be expected. Typically, the reference doses used in these calculations are values below which no adverse health risks would be expected. They are derived by dividing NOAELs by uncertainty and safety factors. RfDs have been developed by EPA for numerous chemical substances based on available animal toxicity data and human epidemiological data.

Noncarcinogenic risks can also be represented as the margin of exposure (MOE). The MOE represents the ratio of a NOAEL to an estimated dose/exposure level. MOEs are calculated as follows:

$$MOE = NOAEL/ADD \qquad \text{(Eq. D1-7)}$$

where:

MOE = margin of exposure (unitless);

NOAEL = no observable adverse effect level (mg/kg/day); and

ADD = average daily dose (or absorbed dose) (mg/kg/day).

High MOE values (i.e., values greater than 100) may imply a low level of concern. In contrast, low MOE values may imply high levels of concern. Further interpretation of the MOE value is dependent on whether the toxicity data are from animals or humans. It should be noted that neither hazard quotients nor MOEs are probabilistic statements of risk. It should also be noted that the use of either potential or absorbed doses is dependent on the nature of the toxicity endpoint. For example, if the toxicity data (e.g, NOEL) are based on

an applied dose, ADD_{pot} or $LADD_{pot}$ values should be used. However, if the toxicity data are based on an internal dose, ADD_{abs} or $LADD_{abs}$ values should be used.

1.4 INPUTS AND STANDARD ASSUMPTIONS USED IN EXPOSURE/RISK ASSESSMENT

Inputs for the standard exposure/risk calculations described above should be representative of the population/scenarios being evaluated. Contaminant concentration values are generated based on residue and dissipation data collected at the site for the media of interest. Factors such as frequency and duration of use can be derived from actual data on the activities/uses associated with site/scenario-specific uses of a chemical, or from general population survey data on activity patterns and product usage. Other inputs to the exposure calculations such as contact rate (ingestion rate, inhalation rate, skin surface area), body weight, and lifetime may be based on standard exposure factors. Mean and upper-percentile exposure factors based on distributions of data collected from the scientific literature are reported in EPA's *Exposure Factors Handbook* (1989a) and EPA's *Risk Assessment Guidance for Superfund* (1989b). Recommended standard exposure factors for use in postapplication exposure assessments are summarized in Part D, Chapter 2. Slope factors and reference doses used in calculating risks and hazards can be obtained from EPA's *Integrated Risk Information System (IRIS)*, EPA's *Health Effects Assessment Summary Tables (HEAST)*, or by contacting EPA's Human Health Assessment Group.

1.5 CHARACTERIZING EXPOSURE/RISK

Risk characterization provides decision makers with a qualitative evaluation of the accuracy of the risk estimates. In characterizing risks from exposure to chemical substances, the variability and uncertainty associated with the exposure/risk estimates should be addressed. The risk characterization should provide information on: (1) potential measurement errors based on the precision and accuracy of the available data, (2) variability of the input data used in the exposure/risk estimates, and (3) uncertainty that results from data gaps or the assumptions used. The risk characterization also assesses the relative importance of these components on the estimates of exposure/dose and risk.

Uncertainty may be introduced into the exposure/risk calculations at various stages of the risk assessment process. Uncertainty may occur as a result of: (1) the techniques used to sample and analyze chemical residues, (2) chemical fate and transport factors, (3) the selection of exposure scenarios and exposure factors, (4) the uncertainties associated with toxicity data that have been extrapolated from high doses in animals to low doses in humans, and that do not account for the interactions of exposures to multiple chemical substances over a lifetime, and (5) the potential size of the exposed populations and subpopulations. Variability can occur as a result of variations in individual day-to-day or event-to-event exposure factors or

variations among the exposed population. Variability can be addressed by estimating exposure for the various descriptors of exposure [i.e., central tendency (mean or median), high-end (90th or 95th percentile), or bounding (100th percentile)] to represent points on the distribution of exposures.

REFERENCES FOR PART D, CHAPTER 1

U.S. EPA. (1989a). Exposure Factors Handbook. Washington, D.C.: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-89/043.

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