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Preparation of Environmental Documentation and Risk Assessments

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WAIVER OF CONFIDENTIALITY

No part of this document is claimed as confidential business information. To the contrary, the purpose of this document is to disclose how SERA, Inc. conducts risk assessments for the USDA/Forest Service and related organizations. The government, general public, and other interested parties should and must have full access to this information.

SERA Inc. will be grateful for any written comments or criticisms of the methods detailed in this report. Well-documented and detailed suggestions for improving these methods are most welcome.

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NOTE: This attachment can be found at the end of this document which itself is being submitted as an attachment to SERA's technical proposal. Typically, this methodology would be a stand alone document with the above referenced GLEAMS attachment included as a separate stand alone

document.

1. INTRODUCTION

1.1. Overview

SERA Inc. has prepared risk assessments for the USDA Forest Service, Office of Forest Health, since 1995 [USDA/FS Contract No. 53-3187-5-12]. In addition, SERA Inc. has prepared various other risk assessments for both the Forest Service and USDA/APHIS since 1990. During this 10-year period, the methods used to conduct these risk assessments evolved and changed substantially. The purpose of this document is to describe in detail the risk assessment methods currently used by SERA, Inc. in the conduct of these risk assessment.

The basic philosophy for preparing the risk assessments is that *each risk assessment must be totally transparent*. If a risk assessment is to be properly reviewed, understood, criticized, and used, the source of all numbers, the calculations used in generating the numbers, and the assumptions used in manipulating the numbers must be specified clearly. In some respects, the transparency of a risk assessment is more important than the specific methods or calculations used to prepare it.. Risk assessment is a form of analysis that relies on scientific method but is not itself a *science*. Reasonable individuals may disagree over which of the numerous methods, tools, and approaches should be used to prepare a risk assessment. Often, available information is not sufficient to support one analytical approach over another. Then, professional judgment must be used to select the method, in which case, the risk assessment must clearly state which assumptions are used and why. As long as the assumptions are made clear, the quality of the risk assessment may be reviewed and the risk assessment may be criticized as appropriate and improved in review.

1.2. Organization

Most risk assessments prepared by SERA have four major chapters, including an introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including the hazard identification, exposure assessment, dose-response assessment, and risk characterization. These are the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments. The subsequent chapters of this document include detailed discussions of each of these steps.

The first chapter of each risk assessment (Introduction) usually consists of chemical-specific and general information. The chemical-specific information focuses on a description of previous Forest Service or other related risk assessments. It also summarizes the sources of information that were consulted and includes a brief discussion of the quantity and quality of the information.

1.3. Information Sources

In most risk assessments, three sources of information are used: the published literature, studies submitted to the U.S. EPA by the registrants of the chemical, and various Internet sites.

There are many commercial databases that can be used to search the published literature. Initially, SERA conducts on-line searches of MEDLINE (including TOXLINE) and AGRICOLA. These two data bases usually identify most of the relevant published literature. Also useful are

TOXLINE65, Excerpta Medica, CAB Abstracts, and CRIS/USDA (Current Research Information System/U.S. Department of Agriculture). Stand-alone versions of FEDRIP and TSCATS are searched for studies that are too recent to be incorporated into the TOXLINE or other online data bases.

For many pesticides, particularly those developed only in the past decade, the most relevant and critical information is found in unpublished studies submitted by the registrant of the pesticide to the U.S. EPA as part of the registration package. These studies are classified as "Confidential Business Information" and cannot be accessed without special clearance from the U.S. EPA. Summaries of these studies in the form of "one-liners" or Date Evaluation Records (DERs) usually are available through a Freedom of Information Act (FOIA) request. Sometimes, summaries of certain CBI studies are published by the U.S. EPA in Federal Register notices, Reregistration Eligibility Decision (RED) documents, or other Agency publications.

Although SERA sometimes obtains DERs and uses U.S. EPA summaries to reflect the views of the U.S. EPA, SERA does not rely on these summaries for an evaluation of the studies. SERA has all appropriate facilities and clearances under the existing USDA contract and orders full-text copies of the CBI studies from the Office of Pesticide Programs (OPP). SERA usually requests about 50-75% of the registration package and personally reviews the studes. Within the limits of the FIFRA statue, SERA summarizes as much of this information as possible in appendices that accompany all full risk assessments. In addition to reviewing the CBI studies, SERA discusses the available information on the chemical with members of OPP/EPA in order to clarify technical issues in the data evaluation.

SERA searches various Internet sites in addition to the published and unpublished literaure. The Internet is a major source of information for many U.S. government agencies (e.g. U.S. EPA, USDA, USGS) . For example, all of the SERA risk assessments are currently on the USDA/Forest Service web site. Furthermore, all of the Agency reviewed RfDs (see section 5.5.2) as well as full-text copies of all completed REDs are on the U.S. EPA web site. In addition to government cites, the web sites of some chemical manufacturers and environmental groups contain information pertinent to the risk assessment. SERA uses discretion in identifying reliable sources of information and clearly identifies those sources in the risk assessment.

1.4. Data Summary

The risk assessments prepared by SERA are technical support documents and address specialized technical methods. These methods used to prepare the risk assessments are described in detail in this document. Moreover, SERA makes no attempt to simplify or abbreviate the description of those methods. In the risk assessment itself, however, an effort is made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. The technical terms used in each risk assessment are defined in a glossary (generally, chapter 6) included in the risk assessment. In addition, some of the more complicated terms and concepts are defined, as necessary, in the text of the risk assessment. Readers wishing to explore and independently assess the methods used in a particular risk assessment are referred to this methods document.

The risk assessments conducted for the Forest Service are not, and are not intended to be, comprehensive summaries of all of the available information. The information presented in the risk assessment document is intended to be detailed enough to support a review of the risk analyses but not as detailed as the information generally presented in Chemical Background documents or other comprehensive reviews.

1.5. Uncertainty and Variability

Given the uncertainties inherent in the data on most pesticides as well as the limitations inherent in the methods used to assess these data, risk assessments are always accompanied by estimates of uncertainty and variability. Within the context of this document, the terms *variability* and *uncertainty* signify different and distinct conditions.

Variability reflects the knowledge of how things may change. Variability may take several forms. For this risk assessment, three types of variability are distinguished: *statistical*, *situational*, and *arbitrary*. *Statistical variability* reflects, at least, apparently random patterns in data. For example, various types of estimates used in this risk assessment involve relationships of certain physical properties to certain biological properties. In such cases, best or maximum likelihood estimates can be calculated as well as upper and lower confidence intervals that reflect the statistical variability in the relationships. *Situational variability* describes variations depending on known circumstances. For example, the application rate or the applied concentration of a herbicide will vary according to local conditions and goals. As discussed in the following section, the limits on this variability are known and there is some information to indicate what the variations are. In other words, *situational variability* is not random. *Arbitrary variability*, as the name implies, represents an attempt to describe changes that cannot be characterized statistically or by a given set of conditions that cannot be well defined. This type of variability dominates some spill scenarios involving either a spill of a chemical on to the surface of the skin or a spill of a chemical into water. In either case, exposure depends on the amount of chemical spilled and the area of skin or volume of water that is contaminated.

Variability reflects a knowledge or at least an explicit assumption about how things may change, while *uncertainty* reflects a lack of knowledge. For example, the focus of the human health dose-response assessment is an estimation of an “acceptable” or “no adverse effect” dose that will not be associated with adverse human health effects. For imazapic and for most other chemicals, however, this estimation regarding human health must be based on data from experimental animal studies, which cover only a limited number of effects. Generally, judgment is the basis for the methods used to make the assessment. Although the judgments may reflect a consensus (i.e., be used by many groups in a reasonably consistent manner), the resulting estimations of risk cannot be proven analytically. In other words, the estimates regarding risk involve uncertainty. The primary functional distinction between variability and uncertainty is that variability is expressed quantitatively, while uncertainty is generally expressed qualitatively.

In considering different forms of variability, almost no numeric risk estimate is presented as a single number. Usually, risk is better expressed as a central estimate and a range, which is sometimes very large.

Because risk assessments are designed to encompass many different types of exposure and must express the uncertainties in the exposure assessments, they involve numerous calculations. Many of the calculations are relatively simple, and the very simple calculations are included in the body of the document. Some of the calculations, however, are cumbersome. For those calculations, a set of worksheets is included as an attachment to each risk assessment. The worksheets provide the detail for the estimates cited in the body of the risk assessment. Samples of these worksheets can be obtained in the SERA risk assessments that are posted at the SERA web site, www.sera-inc.com, of the Forest Service web site, http:/www/fs/fed/us/foresthealth/pesticide/safety_data/risk.html.

2. PROGRAM DESCRIPTION

2.1. Overview

Program descriptions are relatively brief discussions about the pesticide under review and how the Forest Service plans to use the pesticide. The information summarized in the program description includes the identity of the pesticide and its commercial formulations as well as the identity of the inerts, adjuvants, and contaminants in the commercial formulations.. SERA contacts one or more individuals in the Forest Service to obtain information about how pesticide will be used in Forest Service Programs. The program description may include additional information about the use of the pesticide by other organizations, which can be useful in assessing the extent to which the application of the pesticide by the Forest Service contributes to the environmental levels of the compound.

2.2. Chemical Description and Commercial Formulations

In the program description, the identity of the pesticide (i.e., active ingredient) is summarized followed by a brief discussion of the commercial formulations. The discussion of the commercial formulations includes information about the proportion or concentration of the active ingredient in each formulation as well as a general description of the formulation(s) (e.g., physical state—liquid, dispersible granules, etc.—and type of carrier or binding matrix).

Physical and chemical properties that are environmentally significant and probably of greatest relevance to most risk assessments include the vapor pressure, ionization constants (pK_a), water and lipid solubility, and adsorption properties (e.g., K_d, K_{oc}, and K_{ow}). SERA obtains most of the information regarding the physical and chemical characteristics of a compound from the U.S. EPA/CBI files and standard reference sources like the Merck Index (Budavari 1989) or the USDA ARS Pesticide Database (http://ncsr.arsusda.gov/ppdb3/). Data regarding chemical reactivity (e.g., rates of hydrolysis, biodegradation, photodegradation, etc.) and monitored rates of environmental dissipation of the pesticide also are included in this section of the program description. In addition, SERA conducts supplemental literature searches (e.g., the CHEMLINE database available online via the National Library of Medicine) as necessary to obtain information about chemical structures and nomenclature.

The chemical and physical properties of a pesticide are summarized in a table that also includes the name of the compound, synonyms, the CAS number(s), and U.S. EPA registration number. If necessary, the table also indicates the conditions under which certain measurements were made. For example, the solubility of weak acids in water is highly dependent on the pH of the water. Similarly, soil-water partition coefficients vary substantially for different soil types like clay, loam, and sand. Generally, the program description does not include a detailed discussion of the chemical or physical properties of an agent. When necessary, those kinds of discussions may be incorporated into the exposure assessment. If GLEAMS modeling is conducted, an additional table defining the chemical and physical properties used in the model is included in the document (see Appendix 4).

The program description also addresses the issue of inerts in commercial pesticide formulations, which are regulated by the U.S. EPA (Levine 1996). The regulations affect pesticide labeling and testing requirements. As part of its regulatory activity, the U.S. EPA classifies inerts into one of four lists, based on available toxicity data (www.epa.gov/opprd001/inerts/lists.html). Although the lists are useful for setting testing requirements and, perhaps, in encouraging the use of inerts with low inherent toxicity, they do not explicitly consider the potential effects of the inerts on the toxicity of the formulation.

Most chemical manufacturers consider the identity of inert ingredients proprietary information. Inert compounds classified as hazardous by the U.S. EPA must be specified on the MSDS when they are present at a concentration greater than 0.1%. A lack of disclosure means that none of the inert ingredients present at concentrations greater than 0.1% in the formulation are classified as hazardous. As discussed by Levine (1996), the testing requirements for inerts are less rigorous than the testing requirements for active ingredients.

The identity of the inerts is always disclosed to the U.S. EPA as part of the registration process. Although SERA obtains and reviews this information while preparing the risk assessment, SERA does not disclose specific information about the inerts in the risk assessment.

Information about the impurities in technical grade pesticides also must be submitted to the U.S. EPA. SERA obtains and reviews this information while preparing the risk assessment. Since the identities of the impurities also are considered proprietary, SERA does not disclose this information in the risk assessment document; however, the potential impact of impurities on the risk assessment is discussed in the hazard identification section of the document (section 3.2.8).

2.3. Application Methods

The use of herbicides in silviculture and the various methods of herbicide application are described in detail in the general literature (e.g., Cantrell and Hyland 1985) and in environmental impact statements conducted by the Forest Service (e.g., USDA 1989a,b,c). No attempt is made to summarize this information again in the risk assessment. Instead, SERA discusses information relevant to the exposure assessments (section 4) for application methods that the Forest Service uses or may consider using.

Generally, consideration is given to three conventional application methods, including directed foliar applications, broadcast ground applications, and aerial applications. The rationale for selecting these basic application methods is discussed in SERA (1998) and summarized in section 4.2.1 of this document. Sometimes, as with the application of granules (e.g., hexazinone) or the application of a compound directly to water (e.g., 2,4-D), additional application methods are described.

For each application method, this section of the risk assessment focuses on the number of acres that an individual worker might handle in a single work day and any special precautions that may be employed routinely. SERA obtains this information from descriptions of pesticide applications

provided by the Forest Service (e.g., USDA 1989b, p 2-9 to 2-10) and any chemical-specific or site-specific information provided by the Forest Service.

For example, in selective foliar applications, the herbicide sprayer or container is carried by backpack and the herbicide is applied to selected target vegetation. Application crews may treat up to shoulder high brush, which means that chemical contact with the arms, hands, or face is plausible. To reduce the likelihood of significant exposure, application crews are directed not to walk through treated vegetation. Usually, a worker treats approximately 0.5 acre/hour with a plausible range of 0.25-1.0 acre/hour.

Boom spray or broadcast ground applications are used primarily in rights-of-way management. Spray equipment mounted on tractors or trucks is used to apply the herbicide on either side of the roadway. Usually, about 8 acres are treated in a 45-minute period (approximately 11 acres/hour). Some special truck mounted spray systems may be used to treat up to 12 acres in a 35-minute period with approximately 300 gallons of herbicide mixture (approximately 21 acres/hour and 510 gallons/hour)

Aerial applications are made with helicopters or fixed wing aircraft. The compound is applied under pressure through specially designed spray nozzles and booms. The nozzles are designed to minimize turbulence and maintain a large droplet size, both of which contribute to a reduction in spray drift. In aerial applications, approximately 40-100 acres may be treated per hour.

SERA discusses other pertinent details regarding application methods, like restrictions on wind speed during application or targeted droplet sizes in the application of liquid formulations in the exposure assessment (section 4) of the risk assessment..

2.4. Mixing and Application Rates

In this section of the program description, SERA briefly discusses information provided by the Forest Service regarding proposed application rates and pesticide concentrations in field solutions.

The specific application rates used in a ground or aerial applications vary according to local conditions and the nature of the target vegetation. Consequently, application rates are generally expressed as a range with a central or average value. For example, in the recent SERA risk assessment on picloram, application rates used to construct the various exposure scenarios ranged from 0.3 lb a.e./acre to 1.5 lb a.e./acre with a typical rate taken as 0.5 lb a.e./acre. SERA does not derive the application rates, but refers to the product labels to ensure that the proposed application rates do not exceed the labeled rate for a particular use. Moreover, SERA checks all supplemental labels to ensure that special restrictions on use within different geographical areas are clearly stated in the risk assessment. This kind of information is obtained either directly from the manufacturer or from C&P Press at http://www.greenbook.net.

Usually, pesticides are diluted prior to field applications. This detail is referred to in the risk assessment as *field dilution*. For example, the recommended range of mixing volumes for many

liquid pesticide formulations is about 5-25 gallons of water per acre for aerial applications and about 10-100 gallons of water per acre for ground applications.

For the risk assessment, the extent to which a formulation is diluted prior to application primarily influences dermal and direct spray scenarios, both of which depend on the field dilution. The greater the concentration of pesticide in the applied solution, the greater the exposure and the greater the risk. Like application rates, field dilutions are generally expressed as a range with a central or average value.

2.5. Use Statistics

The program description provides two kinds of statistical data regarding pesticide use: past use by the Forest Service for the most recent year where data are available, including information on tank mixtures, when obtainable, and total national or regional use of the pesticide,. The Forest Service provides statistics on the annual use of pesticides. Data regarding total and regional pesticide use data are available from various sources. Agricultural use data is generally available at the U.S. Geological Service web site: wwwdwatcm.wr.usgs.gov/cppt/.

Although neither the statistics pertaining to pesticide use by the Forest Service nor the statistics pertaining to total national or regional pesticide use have a direct impact on the risk assessment, they can be useful in interpreting and better understanding the results of the risk assessment. For example, in a recent Forest Service risk assessment on clopyralid, SERA assessed the potential significance of hexachlorobenzene, a contaminant in clopyralid. By assessing the amount of clopyralid that the Forest Service is likely to use and the total amount of hexachlorobenzene released to the environment each year from all sources, SERA demonstrated that the Forest Service programs would contribute about one part in one-hundred million (100,000,000) parts of the total hexachlorobenzene release.

3. HAZARD IDENTIFICATION

3.1. OVERVIEW

Hazard identification is the process of identifying what, if any, effects a compound is likely to induce in an exposed population. Hazard identification is the first and most critical step in any risk assessment. Unless some plausible biological effect can be demonstrated, the nature of the subsequent dose-response assessment and risk characterization is extremely limited. Both the human health and ecological risk assessments are prepared using *in vivo* and *in vitro* data from experimental animal studies. Additional sources of information like epidemiology studies, case reports, and clinical investigations are used to prepare human health risk assessment. Studies on various model nontarget test species (e.g., ducks, quail, fish, aquatic invertebrates, plants, and terrestrial invertebrates) are commonly available to strengthen the ecological risk assessment. In addition, available field studies on nontarget species are used in ecological risk assessment in much the same way as epidemiology studies are used in human health risk assessments.

The hazard identification is based on a review of the toxicological and pharmacokinetics data and is arranged to focus on the dose-response and dose-severity relationships. Of these two relationships, the dose-severity relationship is generally more relevant for non-carcinogenic effects in humans and nontarget species.

The severity scale used to conduct the risk assessment typically employs four levels of severity. These levels, defined in Table 1, include the no-observed-effect level (NOEL), no-observed-adverse-effect level (NOAEL), adverse-effect level (AEL), and frank-effect level (FEL). An additional term, lowest-observed-adverse-effect level (LOAEL) is sometimes used to designate the lowest AEL. This scale, with minor differences in nomenclature, is used by many government

TABLE 1: Severity definitions used in risk assessment

Acronym	Definition
NOEL	*No-observed-effect level*: No biologically or statistically significant effects attributable to treatment.
NOAEL	*No-observed-adverse-effect level*: Effects that are attributable to treatment but do not appear to impair the organism's ability to function and clearly do not lead to such an impairment.
LOAEL	*Lowest-observed-adverse-effect level*: The lowest exposure level associated with an adverse effect.
AEL	*Adverse-effect level*: Signs of toxicity that must be detected by invasive methods, external monitoring devices, or prolonged systematic observations. Symptoms that are not accompanied by grossly observable signs of toxicity.
FEL	*Frank-effect level*: Gross and immediately observable signs of toxicity.

agencies to classify the toxicological effects observed in experimental or epidemiology studies. In the ecotoxicology literature, the term NOEC—no observed effect concentration—is sometimes used rather than the term NOEL. These terms are synonymous.

The hazard identification process involves making judgments about which effects are most relevant to the assessment of human health or nontarget species. During this process, studies may be eliminated from consideration because they are inherently flawed or because they are grossly inconsistent with the preponderance of other studies.

Although hazard identification results in a qualitative determination, quantitative methods are usually required as in most other assessments of causality. For instance, the process of hazard identification often hinges on a statistical assessment of exposure-response or dose-response relationships. Furthermore, hazard identification must also consider fundamental and qualitative differences among species. Depending on the chemical of concern, hazard identification also may include the use of quantitative or qualitative structure activity relationships or differences in pharmacokinetics.

The hazard identification may cover any number of endpoints, depending on the chemical under assessment. The following topics are generally considered explicitly in each hazard identification:

Acute Toxicity Data
Subchronic or Chronic Systemic Toxic Effects
Epidemiology Studies
Reproductive and Teratogenic Effects
Carcinogenicity
Mutagenicity
Other Toxic Effects
Systemic Toxic Effects from Dermal Exposures
Systemic Toxic Effects from Inhalation Exposures
Kinetic Considerations
Inerts, Impurities, Adjuvants, and Metabolites
Sensitive Subgroups

Additional effects may be discussed, depending on the nature of the available information on the chemical. Most standard texts in toxicology provide overviews of the diverse nature of the effects on different organs (e.g., Klaassen 1996, Haschek and Rousseaux 1991).

3.2. ACUTE TOXICITY

Acute toxicity information is usually expressed as time-specific LD_{50} or LC_{50} values (i.e., doses or concentrations of a toxicant that result in 50% mortality of the test species during a specified exposure or observation period). LD_{50} studies usually involve oral or dermal exposure of mammals, birds, and some invertebrates like the honey bee to a chemical agent. LC_{50} values typically involve inhalation exposure of mammals, aquatic exposure of fish, invertebrates, or plants, and soil exposures with plants and some nontarget fossorial species like earthworms.

Regardless of the test species or exposure media, the methods for analyzing acute toxicity studies are essentially the same.

In data sets used to estimate LD_{50} or LC_{50} values, the responses of organisms to the toxicants are usually presented as levels of mortality (or some other response) that vary according to the measure of exposure to the toxicant. Measures of exposure include dose, concentration, and duration. Simple two-factor relationships can be visually represented by an "x-y" figure with the measure of exposure on the (horizontal) x-axis and mortality on the (vertical) y-axis.

A common model for assessing exposure-response relationships is probit analysis (Finney 1971). Each individual in the population is assumed to have a threshold or tolerance level measured as dose, duration, or some other exposure index. If the exposure is below the threshold, the individual will not respond. If the exposure is at or above the threshold, the individual will respond. The underlying assumption of probit analysis is that the individual tolerances are normally distributed on the exposure metameter.

Exposure metameter is a term used to indicate the units of exposure used in the probit analysis. These units can be either the actual experimental units (e.g., hours or mg/kg) or some transformation of these units. Because the normal distribution is bounded (i.e., probabilities approach but never reach 0 or 1.0), the use of actual experimental exposure units can lead to conceptual inconsistencies like estimates of risk at negative doses. When appropriate scales are used on the x- and y-axes, the relationship between exposure and mortality is a straight line. For most toxicants, the relationship is linear if the appropriate exposure metameter is selected for the x-axis and the y-axis uses a probit scale for mortality.

With the linear transformation, the exposure-probit plot is expressed as an equation for a straight line [y = mx + b]:

$$Y = \beta x + \alpha \qquad \textbf{(1)}$$

where Y is the probit response, β is the slope, x is the measure of exposure (e.g., concentration or duration) and α is the intercept on the exposure axis (i.e., the value of Y when x is zero). If more than one factor is considered in the analysis (e.g., concentration, time, and temperature), Equation 1 can be generalized to:

$$Y = \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n + \alpha \qquad \textbf{(2)}$$

where each x_i is the measure of the i^{th} exposure factor and β_i is the slope of the i^{th} exposure factor. Equation 1 can be rearranged to estimate the exposure associated with a given response rate, Y, (e.g., the dose or time associated with 95% mortality):

$$x = \frac{Y - \alpha}{\beta} \qquad \textbf{(3)}$$

The probit scale is derived from the normal distribution and is essentially the cumulative normal distribution function. With this transformation, 50% mortality corresponds to a value of zero deviates from the population mean. Mortalities >50% correspond to positive deviations and mortalities <50% correspond to negative deviations. This scale is referred to as the normal equivalent deviate (N.E.D.) scale, varying somewhat from the classical literature on probit analysis, in which a 50% response corresponds to a probit value of 5 (Finney 1971). This scaling is a matter of convention and has no effect on the analyses.

Various methods can be used to estimate parameters for the probit model. Eye fit of the probit line can be used to make a rough estimate of the dose associated with a fixed response when experimental data points in the response region are available (Finney 1971). Usually, however, more objective approximations, like simple linear regression analysis (Salsburg 1986) are used. As discussed by Finney (1971), the method of least squares employed in simple linear regression analysis is not the most appropriate statistical method for quantal (responding or not responding) data because the assumption of constant variance is not appropriate. Finney (1971) describes an iterative maximum likelihood method for estimating the model parameters that involves weighting the response rates based on estimates of the variance associated with each response rate. This method progressively weights points near 50% response more than points near the extremes of the response rates (e.g., 1% or 99%).

Acute toxicity studies are relatively inexpensive and often required prior to initiating longer-term studies. Thus, acute toxicity data are the most commonly available type of data on the biological effects of chemicals. Acute toxicity studies are useful for anticipating the potential short-term hazards of chemical exposure. Moreover, within a class of chemicals, acute toxicity data often can be related quantitatively to structural features (e.g., lipophilic, electronic, and stearic parameters). This kind of analysis is applied successfully in mammalian, aquatic, and wildlife toxicology. The structure-activity approach in chemical risk assessment makes it possible to suggest how the addition or deletion of certain structural groups might influence biological activity. Hence, the acute toxicity of a chemical for which there are no experimental data can be estimated.

Acute toxicity data are used also to examine sensitivity patterns among species. The issue of species sensitivity is important in assessing the use of a 10-fold factor for species-to-species extrapolation (Section 5, Dose-Response Assessment). For many chemicals, differences in species sensitivity are apparent and generally indicate that small animals are less sensitive (i.e., have higher LD_{50} values) than large animals. This pattern is the basis for the uncertainty factor of 10 used for animal-to-human extrapolation in the derivation of the RfD (Dourson and Stara 1983) and is often used to extrapolate across species (Davidson et al. 1986) based on the general allometric relationship:

$$LD_{50} = aW^{b} \quad \textbf{(4)}$$

where ***W*** is the body weight and ***a*** and ***b*** are model parameters. When small species are less sensitive than larger species, the slope parameter, ***b***, is negative.

Many environmental assessments are concerned primarily with long-term, low-level exposures. Hence, it would be beneficial if acute toxicity data could be used to estimate chronic NOELs. McNamara (1976) discusses the relationship between acute LD_{50} values and long-term NOELs in mammals. Using experimental data from various sources, this investigator found that the acute LD_{50} divided by l000 resulted in a dose below which no apparent adverse effects were produced during repeated lifetime exposures for 95% of the chemicals on which data were available. A similar approach, which has gained some popularity in aquatic toxicology, is based on the maximum concentration causing no apparent adverse effects in chronic exposures of a given species, divided by the acute LC_{50} for that species. This ratio, called the application factor, is then used to estimate NOAELs for other species by multiplying the acute LC_{50} values for the other species by the application factor. Although both approaches have considerable practical appeal, they are applied with caution. A major problem with these approaches is that the mechanism(s) of acute and chronic toxicity may not be related. Furthermore, the usefulness of application factors is limited by experimental variability and true differences in species susceptibility.

3.3. SUBCHRONIC OR CHRONIC SYSTEMIC TOXIC EFFECTS

More direct measurements of environmentally meaningful NOELs can be made from subchronic and chronic toxicity studies. The studies are usually designed so that the test organism is repeatedly or continuously exposed for a significant portion of its life span to the test chemical.

For both the human and ecological risk assessment, subchronic and chronic toxicity data from animal studies can be used to establish reference doses (RfDs) or other similar criteria. In practice, RfDs are derived by determining a NOEL or NOAEL dose in an experimental mammal and dividing the dose by an uncertainty factor, as discussed in section 5.2.

Because experimental data are often lacking with regard to toxic effects of chemicals on humans or the target species of concern and because such data are usually limited to situations that result from accident, misuse or abuse, it is vital to evaluate the results of controlled animal toxicity studies. In many cases, the findings from animal experiments can be used to confirm and clarify observed effects on humans. In other instances, the results of animal toxicity tests may be the only clear evidence available to indicate the magnitude or probability of an adverse effects. Furthermore, the detailed pathological and physiological analyses that experimental studies allow can significantly increase the understanding of the mechanism of toxic reaction to foreign substances at the molecular and cellular levels.

Whenever the information is available and can be used quantitatively in the risk assessment, complete dose-response and time-response data are discussed and reported in the risk assessment, along with corresponding tabulations. Because such summaries can impair the readability of a document and are not of interest to all readers, these detailed summaries are typically included in appendices. Although extrapolating from such data requires caution, alternative means of

expressing toxicity (e.g., LD_{50}, minimum lethal dose, approximate lethal concentration) often encountered in the literature are of much less use.

The cellular basis of the fate of a compound in animal systems provides the means whereby its ultimate physiological effects are produced. A complete understanding of the mechanisms involved in delivering a chemical substance to specific target sites and in determining the form in which it arrives is of the utmost importance in assessing the severity of a chemical threat. Because signs of toxicity are a result of cytotoxicity and disruption of normal cellular functions, the logical approach to explaining toxic signs begins by narrowing the scope of investigation down to the biochemical level.

A major effort is made to focus on organ level toxicity, relative sensitivities of organs within a species, and the consistency of organ effects and sensitivities among species. In defining dose-response relationships for all routes of exposure, emphasis is placed on equivalencies of effects among different routes of exposure, differentiating apparent route-specific or portal of entry effects from systemic effects common to all routes.

3.4. EPIDEMIOLOGY STUDIES

Strictly defined, epidemiology refers to the study of disease patterns in humans. When good epidemiology data are available, they can serve as the definitive qualitative and/or quantitative estimate of potential human hazard. Occasionally, the unique nature of a chemically-induced effect (e.g., liver angiosarcoma by vinyl chloride) will lead quickly to the recognition of a human risk. More often, however, epidemiology studies in non-occupational situations are not definitive enough to establish chemical cause-and-effect relationships with certainty.

For some compounds, information may be available on toxic effects associated with accidental or normal occupational exposures. This type of information may be used to assess dose-response relationships in humans. Data from human exposure incidents must be carefully analyzed with regard to the nature of the chemical involved, the quantity of chemical present, and the duration of exposure. In addition, the possibility of synergistic and antagonistic effects of other chemicals is quite significant, especially in industrial situations. It is hoped that reports of human surveillance studies, including personal monitoring data as well as retrospective investigations in work populations, can be obtained. Because human living conditions and lifestyles vary greatly, a detailed analysis of particular human situations involving chemical exposures can be extremely valuable in defining public health hazards. Furthermore, toxicological screens and animal model systems cannot substitute for every aspect of human living conditions and cannot duplicate the everyday exposures to which humans are subject.

Information regarding the human health effects of chemical exposure should come from human experience; however, these data are difficult to obtain. Controlled laboratory experiments in which humans are exposed to chemical substances are limited by ethical considerations. When chemicals are administered to humans under controlled conditions, the results may be inconclusive because of inter-individual variability and because of the generally small number of individuals participating in the studies. Case reports of persons with known exposure to a particular chemical

generally provide qualitative evidence of a causal relationship between exposure to that chemical and a particular toxic effect, but exposure levels are seldom known and control data are not available.

3.5. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Teratogenicity studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Another type of reproduction study involves exposing more than one generation of the test animal to the compound. Both types of assays are typically required for the registration of pesticides.

Chemically-induced reproductive impairment is an important response parameter in human and ecological risk assessment. In human risk assessment, teratogenicity, sterility, or decreased reproductive capacity can serve as endpoints in establishing NOELs from chronic exposure. Often, however, the threshold for adverse reproductive effects in mammals is above the threshold for more general toxic effects (e.g., decreased total body weight gain or altered organ weights). Furthermore, many mammalian teratology studies involve single short-term exposures and are, therefore, difficult to apply directly to estimating the risk from environmental exposure.

Teratogenicity and developmental toxicity are terms relating specifically to effects on the conceptus and not to the pregnant female. Although this area of study was traditionally concerned with compounds that resulted in the birth of grossly abnormal offspring, it has been expanded to encompass those dose-related effects resulting in death of the conceptus, functional impairment and altered growth and/or developmental patterns. The physiological processes that produce abnormal development are the same cellular mechanisms associated with chemical toxicity in the adult, including inflammation, degeneration, necrosis, cell differentiation, and proliferation. Nonetheless, the conceptus is viewed as a uniquely susceptible target, due to the occurrence of unusually rapid proliferation and differentiation during fetal development.

3.6. CARCINOGENICITY

Three kinds of data are commonly used to assess potential carcinogenic hazard. These data include epidemiology studies, bioassays on mammals, and tests for genetic toxicity, including mutagenicity. Epidemiology studies involve the comparison of the cancer incidence in two or more populations with varying degrees of exposure to the chemical under study. They are of limited use because many important variables—like quantitative estimates of exposure to the test chemical, differences in diet, and exposure to other potential carcinogens—are not adequately controlled or characterized. Nevertheless, data from well-designed epidemiology studies are the only data accepted as unequivocal proof that a chemical is a human carcinogen. The problems in precisely defining exposure levels and other factors merely inhibit the use of these studies in quantitative risk assessment.

Bioassays on mammals involve the controlled exposure of experimental animals, usually rats or mice, to defined levels of the test substance. In carcinogenicity bioassays, an attempt is made to expose the organism for a significant portion of its life span to the test substances, or at least to observe the organism for a significant portion of its life span. This protocol is necessary because

many tumors appear only late in the life of the organism; thus, premature sacrifice may lead to false negative results. Furthermore, in terms of environmental toxicology, the major concern is the incremental increase in the incidence of cancer attributable to lifetime exposures. Another important element in the design of mammalian bioassays is the proper selection of dose levels. Since for practical and economic reasons, only limited numbers of animals (usually 20-50) are used at each dose level, it is necessary to use elevated dose levels in order to elicit a detectable response. Because excessively high doses that result in overt signs of toxicity may alter the physiology of the animal so that it is no longer a reasonable model for projected human exposures, attempts are made to ensure that doses below the maximum tolerated level are used. In addition, excessively high doses can cause premature mortality, which may mask carcinogenic activity. At the end of the experimental period, all animals are sacrificed and subjected to extensive histopathological analyses. A positive response is usually defined as a significant dose-related increase in the incidence of malignant tumors at a given site in exposed animals.

3.7. MUTAGENICITY

Because carcinogenicity bioassays are time consuming and expensive, it is becoming common to use several mutagenicity screening tests to detect potential carcinogenicity. Mutagenicity studies include tests with microorganisms (e.g., Ames assay), tests for genetic damage in cultured mammalian cells (e.g., unscheduled DNA repair synthesis, sister chromatid exchange, point mutations), and tests for *in vitro* transformation of rodent cell lines. Although the tests are extremely valuable for detecting chemicals requiring further study (i.e., animal bioassay and/or epidemiology), they are not capable of detecting all potential carcinogens or indicating the relative potency of the carcinogens in humans.

Chemically-induced mutation is closely linked to the process of carcinogenesis, for several reasons. Many carcinogens are known to react with DNA in somatic cells and to cause mutations. In addition, individuals with genetic defects in DNA repair capability (e.g., xeroderma pigmentosum) are more sensitive than usual to mutagens and are prone to develop cancer. It is postulated that the interaction of reactive metabolites of chemical carcinogens with DNA may induce tumors either directly by altering genetic material through a somatic mutation or indirectly by altering gene expression.

3.8. OTHER TOXIC EFFECTS

The biological response to a chemical may take numerous forms, depending on the physical/chemical properties of the compound and the conditions of exposure. Most substances are capable of eliciting more than one kind of biological response, which often vary from simple adaptive changes that have little impact on health to severe toxic reactions and death. The nature and degree of toxic response to chemical exposure are often classified in terms of the time scale for the exposure (i.e., acute, subchronic, chronic), the site of response (i.e., local, systemic, mixed), and the persistence of the injury (i.e., reversible, irreversible). For the purpose of environmental hazard assessment, all three methods for classifying toxic effects have important applications.

The various health effects resulting from exposure to environmental chemicals is often described by the tissue pathology, altered biochemical processes, or physiological response. Furthermore, the effects may be general reactions to injury or systemic effects involving a particular organ system.

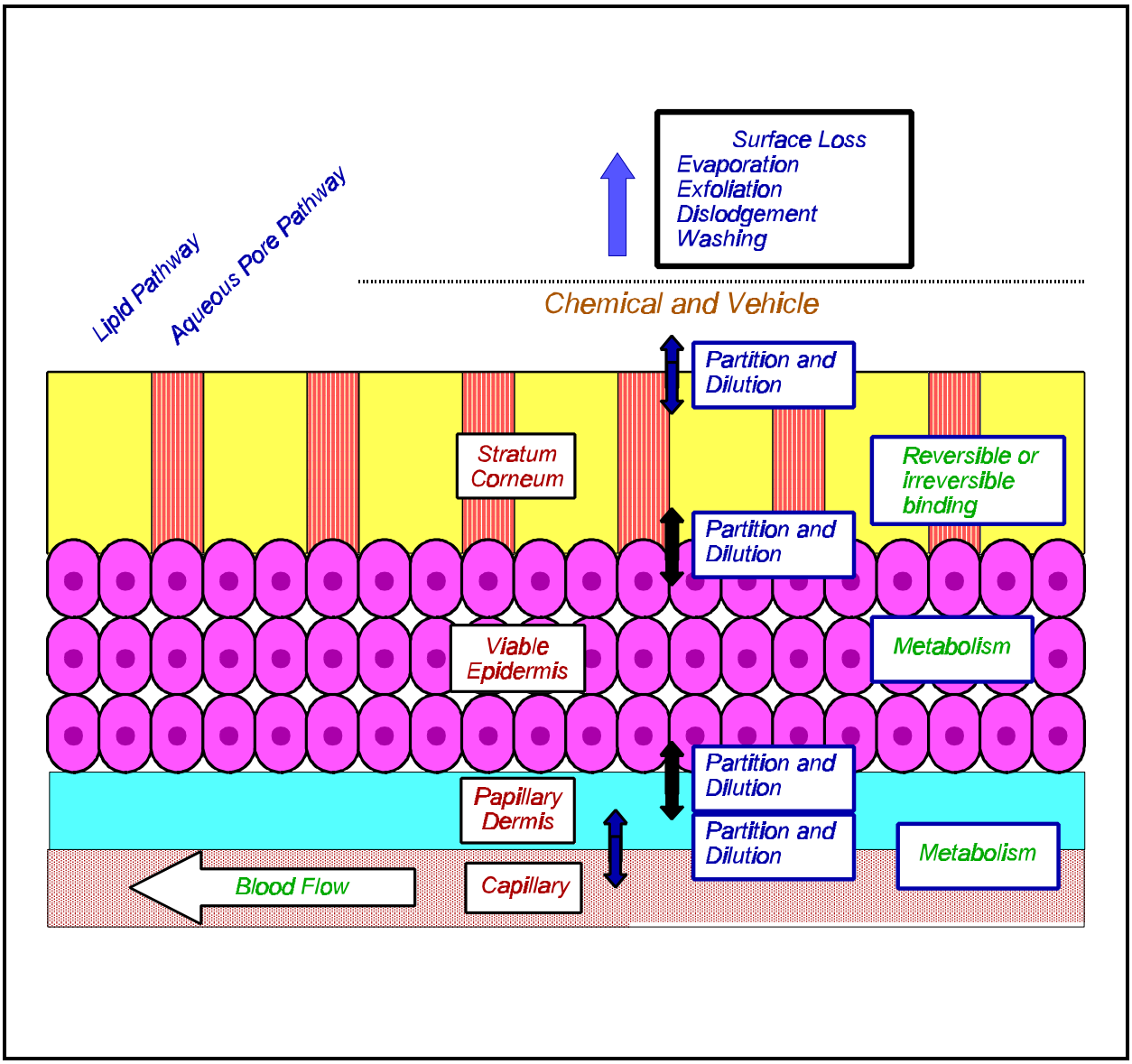

Figure 1: Schematic Overview of Dermal Absorption Processes
(modified from U.S. EPA 1992 and Flynn 1990).

3.9. SYSTEMIC TOXIC EFFECTS FROM DERMAL EXPOSURES

Estimates of dermal absorption rates (k_a, expressed in units of amount/unit time [zero-order] or reciprocal time [first-order]) or dermal penetration rates (K_p expressed in units of cm/hour) are

required for many of the exposure scenarios described in section 4. The biological and chemical processes pertinent to these scenarios are illustrated in Figure 1. The chemical may be deposited on the skin instantaneously (e.g, as in an accidental spill) or gradually (e.g., as uptake from contaminated vegetation). In order for absorption in the systemic circulation to occur, *permeation* across the stratum corneum must occur first—at least in intact skin.

The stratum corneum and dermis are basically lipid-rich barriers that prevent water loss. Thus, compounds with a high lipid solubility are generally more permeable than more water soluble compounds. In addition, transport through the skin is inversely related to molecular size. Thus, for compounds of comparable lipophilicity, smaller compounds tend to be more permeable than larger compounds.

Classical pharmacokinetic dermal absorption rates are used to estimate the absorbed dose associated with dermal deposition scenarios. These rates (k_a) express the amount (zero-order absorption) or proportion (first-order absorption) of a chemical absorbed *into the body* per unit time. In this context, *into the body* means that the chemical will be in the blood stream and subject to metabolism or excretion and capable of interacting in other ways with viable tissue.

As discussed in U.S. EPA (1992), most QSAR relationships for estimating dermal permeability (K_p) take these relationships into account with dermal permeability being positively related to the octanol/water partition coefficient (K_{ow}) and inversely related to molecular weight (MW). U.S. EPA (1992) recommends the following equation:

$$\log K_p = -2.72 + 0.71 \log K_{o/w} - 0.0061 MW \quad \textbf{(5)}$$

where K_p is in units of cm/hour. This equation is based on measured K_p values for 95 organic compounds (Flynn 1990, Table 5-4 in U.S. EPA 1992) with log K_{ow} values ranging from about -2.5 to 5.5 and molecular weights ranging from about 30 to 770. Estimates of K_p from the above equation have an error of about one order of magnitude.

As reviewed by U.S. EPA (1992), some analyses (e.g., Flynn 1990) suggest that the effects of both molecular weight and lipophilicity on permeability may be linear only within certain limits. Based on the analysis by Flynn (1990), relatively lipophobic compounds with log K_{ow} values <0.5 appear to have log K_p values of approximately -3 (MW<150) or -5 (MW>150). At the upper limit, highly lipophilic compounds with log K_{ow} values >3 and molecular weights <150 appear to have log K_p values of about -0.5. Compounds with log K_{ow} values>3.5 and molecular weights >150 appear to have log K_p values of about -1.5 (Flynn 1990).

The series of studies by Feldmann and Maibach (1969, 1970, 1974) represents a unique and highly relevant source of information on *in vivo* dermal absorption in humans. As discussed in U.S. EPA (1992), however, the Feldmann and Maibach publications do not provide sufficient experimental details for the complete derivation of zero-order dermal absorption rates. Nonetheless, as illustrated by Durkin et al. (1995), estimates of dermal absorption rates from the Feldmann and Maibach publications gave much better estimates of absorbed dose than did estimates based on

Fick's first law. Thus, when exposure scenarios are best characterized by deposition on the surface of the skin - as opposed to immersion of the skin in a aqueous solution - first order dermal absorption rates are estimated either from chemical specific data or from structure activity relationships.

SERA (1997) has completed an extensive re-evaluation of these data to improve on the methods proposed by Durkin et al. (1995) in which the Feldmann and Maibach data were fit to the following equation:

$$X_t = \frac{k_a A_0}{k_e - (k_a + k_r)} \left(e^{-(k_a + k_r)t} - e^{-k_e t} \right) \quad \textbf{(6)}$$

where k_a is the first order dermal absorption rate coefficient, k_e is the first order excretion rate coefficient, and k_r is the first order fugitive loss rate coefficient

Feldmann and Maibach (1969, 1970, 1974) did not conduct i.v. elimination studies in humans for all of the compounds. For some of the compounds i.v. studies were conducted in rats and for other compounds judgement was used to estimate k_e. Thus, In the re-analysis, only the 29 chemicals that included i.v. elimination studies in humans are included in the analysis.

For each of these 29 chemicals, a spreadsheet was set up in Excel and the Excel SOLVER function was used to estimate the rate coefficients. Because the results reported in the Feldmann and Maibach publications are expressed as the proportion of applied dose eliminated over a given period, both sides of the above equation were multiplied by k_e. In all cases, the k_e values were derived from the half-times ($t_{½}$) reported in the Feldmann and Maibach publications - i.e., $k_e = \ln(2) \div t_{½}$ - and these k_e values were used as constants rather than as parameters estimated from the models. The only constraint applied to the models was that k_a and k_r both must be greater than or equal to zero.

Unlike the earlier results of Durkin et al.(1995), first-order absorption rate coefficients were best estimated based on both molecular weight and log $K_{o/w}$.:

$$\log_{10} k_{a_{(FirstOrder)}} = 0.233 \log_{10} K_{o/w} - 0.00566 MW - 1.49 \quad \textbf{(7)}$$

All coefficients were significant at $p<0.004$ but the squared correlation coefficients for both models were low, about 0.32. This correlation coefficient is not remarkably lower than the squared correlation coefficient of 0.43 that is obtained for the regression of log K_p on molecular weight and log $K_{o/w}$ using Table 5-7 from U.S. EPA (1992) without censoring. The fugitive loss rates (k_r) were not significantly correlated with either the molecular weight or the $K_{o/w}$. The observed fugitive loss rates fit a log normal distribution [p=0.35 using the Kolmogorov-Smirnov test (Manugistics 1997)] with a mean of 0.032 hour^{-1} and a 95% confidence interval 0.0028 to 0.037 hour^{-1}.

Although there is no information with which to compare the absorption of the esters of weak acids with the acids themselves, Feldmann and Maibach (1969) did assay the absorption of hydrocortisone and testosterone as well as esters of these compounds (Table 2).

TABLE 2: **Comparison of dermal absorption and estimated dermal permeability of hydrocortisone and testosterone with some of their esters**

Chemical	MW[a]	log K_{ow}[a]	K_p[b]	% Absorption[c]
Hydrocortisone	362.47	1.61	0.00016	1.87
Hydrocortisone acetate	404.51	2.30	0.00028	2.55
Testosterone	288.43	3.32	0.0075	13.24
Testosterone acetate	330.47	4.27	0.020 [0.032]	4.62
Testosterone propionate	344.50	4.77	0.037 [0.032]	3.34

[a] Durkin et al. (1995)
[b] Calculated using Equation 1. Limits based on Flynn (1990) in brackets. See text for details.
[c] Feldmann and Maibach (1969). Cumulative percent absorption over a 5-day observation period.

As indicated in Table 2, hydrocortisone and hydrocortisone acetate show a relatively direct relationship between dermal permeability (K_p) and dermal absorption. For testosterone and its esters, however, the correspondence is poor. Although the estimated K_p for testosterone is less than that for either of its esters, testosterone is absorbed to a substantially greater extent than either of its esters. This relationship holds true whether the estimates of K_p for the esters are based on Equation 5 or the upper limit on K_p suggested by Flynn (1990). Thus, while the lipophilicity of the esters is greater than that of the parent compound for both testosterone and hydrocortisone and the esters of both of these compounds are estimated to have a greater permeability (K_p) than the corresponding parent compound, the relationship of ester formation to dermal absorption is inconsistent.

Many factors can influence the dermal penetration and dermal absorption of chemicals, and some of these factors may be useful in understanding the lack of a consistent relationship between dermal permeability and dermal absorption. U.S. EPA (1992) provides an overview of these factors, and additional information and analyses are presented in other reviews and books on dermal absorption (e.g., Klein-Szanto et al. 1991, Rice and Cohen 1996, Scott et al. 1989, Wang et al. 1993).

As illustrated in Figure 1, dermal absorption involves both permeation of the epidermis as well as partitioning from the dermis into capillary blood. At least to some extent, this process will be affected by the relative differences in the fat and water content of the skin and blood. As illustrated in Figure 2, whole skin tissue contains about 10% fat [260 g/2600 g] and 61% water [1600 g/2600 g] (ICRP 1992, Table 105, p. 284). The outer layer of the skin, the stratum corneum, contains almost 20% fat and 40% water (Klein-Szanto et al. 1991). Whole blood contains only about 0.65% fat [36 g/5500 g] and about 80% water [4400 g/5500 g] (ICRP 1992, Table 105, p. 280). Blood plasma contains about the same amount of fat as whole blood [23 g/3100 g or 0.74% fat] but a greater proportion of water [2900 g/3100 g or 93% water].

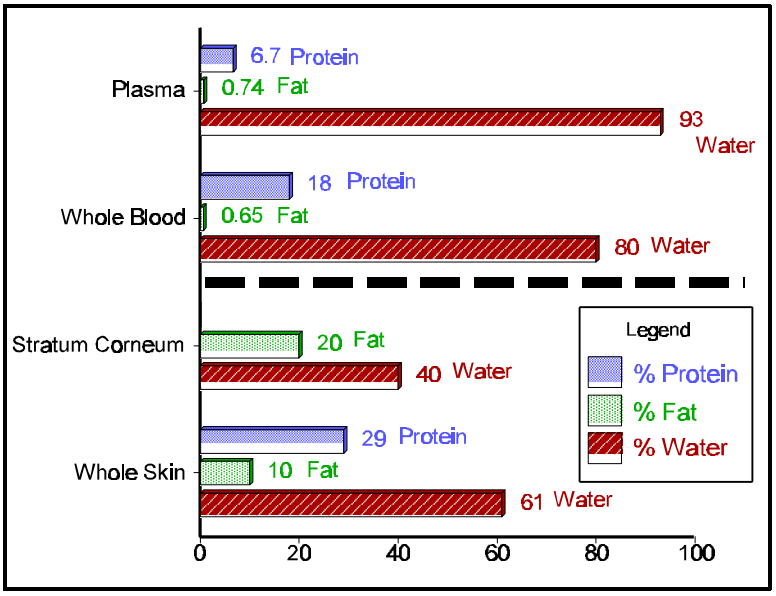

Figure 2: Composition (%) of the blood and skin (data from ICRP 1992 and Klein-Szanto et al. 1991).

Because the skin, and especially the epidermis, is comprised of more lipids and less water than blood or plasma, increasing lipophilicity, which tends to increase dermal permeability or penetration, will tend to decrease partitioning from skin into blood. Thus, it does not follow that apparent dermal absorption rates (k_a) will directly parallel dermal permeability (K_p).

The binding of the chemical to endogenous protein may also complicate the relationship between estimates of dermal permeability and dermal absorption. Skin is relatively rich in protein [750 g/2600 g or about 29%] (ICRP 1992, Table 105, p. 280). Plasma contains less but still significant levels of protein [210 g/3100 g or 6.7%], as does whole blood [990 g/5500 g or 18%]. Different chemicals may bind to different proteins with varying degrees of affinity. Moreover, skin and blood consist of different and multiple kinds of proteins. Compounds that bind tightly to some skin proteins may penetrate quickly into the dermis (high K_p) but partition rather slowly into blood plasma (low k_a). Conversely, if a chemical has a high affinity for plasma proteins, the concentration in the aqueous phase of the plasma will tend to diminish, favoring the partitioning from the dermis to the blood. Thus, the net affect of protein binding on dermal penetration or dermal absorption cannot be determined in the absence of specific data on the chemical of concern. Hence, protein binding is another factor that may account for apparent discrepancies between dermal absorption rates (k_a) dermal permeability (K_p).

Another factor affecting the rate of dermal absorption involves penetration of the chemical through the epidermis to the dermis where absorption into the blood may occur. The epidermis is relatively thin, generally about 35 to 100 μm for men and 20 to 65 μm for women. In some parts of the body, like the fingers and soles of the feet, the epidermis is much thicker, ranging from 400 to 1400 μm for men and from 400 to 1000 μm for women (ICRP 1992, Table 6, p. 49). The consequences of different skin thicknesses are variability in permeation/absorption and a lag period in apparent absorption.

Furthermore, different parts of the body may have different rates of dermal absorption. Similarly, skin thickness and/or composition in the same part of the body may differ among individuals. The variability among individuals is likely to contribute to the observed inter-individual differences in dermal absorption rates. Differences in skin composition may also influence the permeability rate (K_p) of a compound either at different anatomic sites of an individual or at the same anatomic site among individuals (Klein-Szanto et al. 1991).

The other consequence of different skin thicknesses or differences in skin composition involves the apparent lag period between dermal exposure and dermal absorption. U.S. EPA (1992, p. 4-28) indicates that the apparent lag time for penetration of the stratum corneum is proportional to the square of the thickness of the stratum corneum and inversely proportional to the diffusiveness of a chemical within the stratum corneum. Although this relationship may adequately describe permeation (K_p), the rate of absorption is not likely to change in a quantal manner (i.e., remaining zero at times less than the 'lag time' and changing to a constant value at times greater than the lag time). In other words, penetration of the stratum corneum and functional saturation of the underlying skin tissue is not instantaneous. Initially, the functional absorption rate (k_a), which is assumed to be a constant under the assumption of zero- or first-order kinetics, may actually be negligible but approach a constant value, either in terms of zero- or first-order coefficients, as permeation of the skin approaches a steady-state or psuedo-steady state.

The vehicle in which a compound is applied also may affect permeability and absorption. Moreover, these effects may be competing. There is ample evidence that some vehicles enhance dermal absorption and dermal permeability of various compounds, while other vehicles retard the processes (e.g., Walters 1989, Guy et al. 1989, Williams and Barry 1989). In general, vehicles that hydrate the skin or alter the physical state of the stratum corneum (e.g., some solvents) may enhance permeability. On the other hand, highly lipophilic vehicles may retard both permeability and the subsequent absorption of lipophilic compounds by impeding the partitioning of the chemical from the vehicle into the skin. The converse is true for highly lipophobic compounds in a lipophobic vehicle. Thus, the influence of a specific vehicle on *absorption* may not be related to its effect on *permeation*. These confounding factors may need to be addressed when data regarding the effects of various vehicles on dermal absorption are not consistent.

3.10. KINETICS CONSIDERATIONS

The kinetics used in the hazard identification generally concern dermal absorption rates, although other applications of simple kinetic models are found in the exposure assessment (section 4).

Two types of rate processes are generally used in the discussion of the dermal absorption as well as other processes relating to exposure assessments: zero-order and first-order.

Zero-order and first-order processes are detailed in standard texts on pharmacology and kinetics (O'Flaherty 1981, Goldstein et al. 1974, and Benet et al. 1996). The abbreviations used in this discussion are summarized below:

A_0	amount applied at t=0 - i.e., applied dermal dose
A	amount of dose remaining at the administration site at time t
x_t	an amount or concentration in the body or at the site of administration at time t
X	amount in the circulation at time t
k	any first-order rate coefficient
k_a	first-order rate coefficient for absorption [units of reciprocal time]
k_{az}	zero-order rate coefficient for absorption [units of amount or proportion per unit time]
k_e	first-order rate coefficient for elimination [units of reciprocal time]
d	general abbreviation for *change in* or *delta*

The term *zero-order* is used to describe processes in which the rate of absorption, elimination, or metabolism involves a constant amount per unit time. Thus, zero-order rate coefficients are usually expressed in units such as mg/hour and are described by the general differential equation:

$$\frac{dx_t}{dt} = k_{az} \qquad \textbf{(8)}$$

which states that the rate of change in the amount (x_t) per unit time (dx_t/dt) is constant (k). In some cases, zero-order rate coefficients may be expressed in units of fractional amount (relative to some initial state) per unit time and expressed in units of reciprocal time, identical to those of first-order rate coefficients.

The term *first-order* is used to describe processes that occur in a fixed proportion relative to an instantaneous amount or concentration per unit time. Thus, first-order rate coefficients are usually expressed in units of reciprocal time (e.g. hour^{-1}) and described by the general differential equation:

$$\frac{dx_t}{dt} = k \cdot x_t \qquad \textbf{(9)}$$

which states that, at time t, the rate of change in the amount or concentration per unit time (dx_t/dt) is equal to some constant (k) multiplied by the concentration or amount (x_t) at time t.

In a zero-order process, the amount of absorption, elimination, or some other process at time *t* is the integral of Equation 8, which is the product of time and the zero-order rate coefficient (k_{az}):

$$x_t = k_{az} \cdot t \quad \textbf{(10)}$$

Similarly, in a first-order process, the corresponding amount at time *t* is the integral of Equation 9:

$$x_t = x_0 \cdot e^{-kt} \quad \textbf{(11)}$$

where x_0 is the amount at time zero.

Note that the left hand side of Equations 10 and 11 are in units of concentration or amount. In general, the two units are interchangeable. The amount of a substance in a particular media is the concentration in the media times the volume of the media. The proportionality constant, V_d, is the apparent volume of distribution,

$$V_d = x_0 / c_0 \quad \textbf{(12)}$$

where c_0 is the concentration at time zero and x_0 is the administered dose.

One of the most common expressions of first-order rate kinetics is the half-time ($t_{½}$), which is defined as the interval (Δt or t_2-t_1) required for a *x* to be reduced by a factor of 2 (i.e., x_1/x_2 = 0.5). The relationship between the first-order rate coefficient (*k*) and $t_{½}$ follows from a rearrangement of Equation 11 in which x_2/x_1 is set to 0.5:

$$\begin{aligned} x_1 &= x_0 \cdot e^{-kt} \\ \therefore x_2 &= x_1 \cdot e^{-kt} \\ x_2/x_1 &= 0.5 = e^{-kt_{1/2}} \\ \ln(0.5) &= -k t_{1/2} \\ t_{1/2} &= \frac{\ln(0.5)}{-k} \simeq \frac{0.693}{k} \\ k &= \frac{\ln(0.5)}{-t_{1/2}} \simeq \frac{0.639}{t_{1/2}} \end{aligned} \quad \textbf{(13)}$$

Zero-order absorption with first-order elimination describes a process in which the chemical is absorbed at a *constant amount* in any unit of time and the chemical in the circulatory system is eliminated at a *constant proportion* for any unit of time. Under these conditions, the amount in the circulation at time *t* is:

$$X = \frac{k_{az}(1-e^{-k_e t})}{k_e} \quad \textbf{(14)}$$

and at infinite time (steady state), the elimination rate will be equal to the absorption rate,

$$k_e x = k_{az}. \quad \textbf{(15)}$$

In first-order absorption with first-order elimination both the absorption rate and the elimination rates are assumed to be proportional to the concentration of the chemical at the absorption site and within the body, respectively. Thus, the rate of change in the amount of chemical on the surface of the skin at time *t* (*dA/dt*) is governed solely by the amount (*A*) remaining on the skin at time *t* and the absorption rate coefficient (k_a):

$$dA/dt = -k_a A. \quad \textbf{(16)}$$

In other words, absorption is assumed to be the only process that removes the dose from the site of administration. The amount of unabsorbed dose at time *t* is thus the integral of Equation 16:

$$A = A_0 e^{-k_a t} \quad \textbf{(17)}$$

Analogous to zero-order absorption with first-order elimination (see Equation 14), the rate of change of the chemical in the circulation (*dX/dt*) at time *t* is the difference between the absorption rate (k_aA) and the elimination rate ($k_e X$):

$$\frac{dX}{dt} = k_a A - k_e X. \quad \textbf{(18)}$$

The solution to the simultaneous differential equations for first-order absorption with first-order elimination is:

$$X = \left(\frac{k_a A_0}{k_e - k_a} \right) (e^{-k_a t} - e^{-k_e t}). \quad \textbf{(19)}$$

Although first-order absorption with first-order elimination involves first-order rate coefficients (k_a and k_e) that can be converted into corresponding half-times (see Equation 13), half-time is not a meaningful concept in first-order absorption with first-order elimination because the times to either 50% absorption or 50% elimination are not constant.

In first-order absorption with first-order elimination, the shape of the concentration-time patterns differ as the relationship between k_a and k_e changes. For the special and unusual case of k_a=k_e,

Equation 19 does not apply, and alternate derivations have been developed (Goldstein et al. 1974, O'Flaherty 1981). In the case of instantaneous absorption ($k_a \approx \infty$), the kinetics are identical to simple first-order elimination.

For the less extreme case in which the rate of absorption is greater than the rate of elimination ($k_a > k_e$), the slope of the terminal phase of the concentration/time curve (i.e., ln or log concentration of some biological media such as blood or urine versus time) is linear with a slope of $-k_e$. When the rate of absorption is less but not remarkably less than the rate of elimination ($k_a < k_e$), the elimination curve will be non-linear. When, however, the rate of absorption is much less than the rate of elimination ($k_a \ll k_e$), the terminal slope of the concentration-time curve is $-k_a$ rather than $-k_e$ (Wurster 1965). This finding is referred to as the 'flip-flop' phenomenon by O'Flaherty (1981, p. 134). Thus, if the terminal phase of the concentration-time curve is linear and if first-order absorption with first-order elimination is a plausible model, the only way to determine if the apparent terminal phase represents k_a or k_e is to conduct an independent experiment in which k_e is measured after an intravenous injection [i.e., as in the experiments by Feldmann and Maibach (1969, 1970, 1974)].

The principal reason for using dermal absorption coefficients is that dermal exposure is usually compared with dose/response assessments (e.g., cancer potency estimates or RfDs) for oral routes of exposure. In general, oral first-order absorption coefficients are likely to be much higher than dermal absorption coefficients. Consequently, (i.e., Equation 19), oral exposure usually leads to peak body burdens that are higher than equal doses given by the dermal route. This general pattern is illustrated in Figure 3 for a compound with a k_e of 0.05 $hour^{-1}$, and a k_a of 0.005 $hour^{-1}$ dermal absorption and 0.5 $hour^{-1}$ oral absorption.

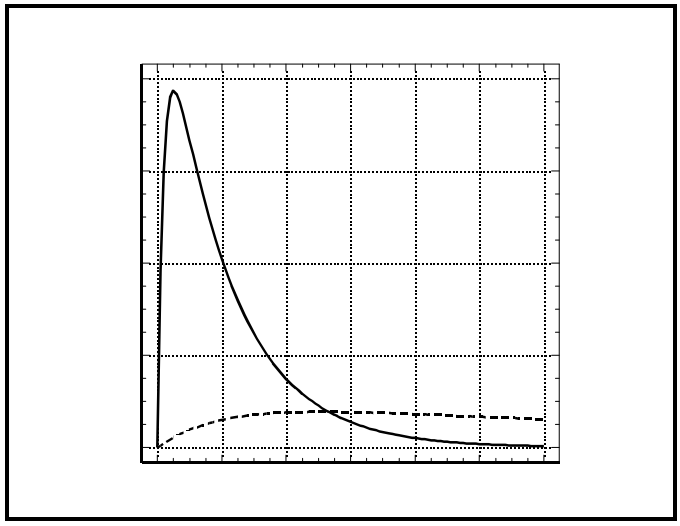

Figure 3: Comparison of tissue levels after oral (solid line) and dermal (dashed line) exposures (see text for details).

For toxic effects that occur primarily when some threshold concentration in the body is exceeded, oral doses are usually more toxic than dermal doses (e.g., Gaines 1969). In that case, risk characterizations based on dermal exposure assessments and oral dose-response assessments will be inherently and perhaps grossly conservative. In cases when the area under the curve is the primary determinant of toxicity, risk characterizations based on dermal exposure assessments and oral dose- response assessments should be reasonably unbiased so long as the exposure assessment correctly and appropriately estimates the absorbed dose.

3.11. INERTS, ADJUVANTS, AND IMPURITIES

Workers and members of the general public may also be exposed to various inerts, adjuvants, and impurities contained in commercial formulations of pesticides.

Impurities are inadvertent contaminants in the pesticide. Inerts are compounds intentionally added to the formulation, which have no inherent pesticidal activity and do not affect the pesticidal activity of the active ingredient. Generally, inerts are added to the formulation to facilitate its handling, mixing, or stability. Adjuvants are compounds that are not in themselves pesticidal but that enhance the pesticidal activity of the active ingredient. Inerts, adjuvants, and impurities are considered together because, from the perspective of risk to human health, the distinction between these compounds is not important.

The U.S. EPA is responsible for the regulation of inerts and adjuvants in pesticide formulations. As implemented, these regulations affect only pesticide labeling and testing requirements. As part of this regulatory activity, U.S. EPA classifies inerts into four lists based on the available toxicity information: toxic, potentially toxic, unclassifiable, and non-toxic. Any compound classified by U.S. EPA as toxic or potentially toxic must be identified on the product label if the compound is present are a level of 1% or greater in the formulation. All such compounds are considered explicitly in the risk assessment. If the compounds are not classified toxic, all information on the inert ingredients in pesticide formulations is considered proprietary under Section 10(a) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). In that case, the formulators of the pesticide need not and typically do not disclose the identity of the inert or adjuvant.

Joint exposure to the active ingredients, adjuvants, and inerts is, by definition, exposure to chemical mixtures. If the information regarding the toxicity of the mixture is adequate, this information should be used for the risk assessment. Hence, the mixture is treated as if it were an individual chemical (i.e., individual chemical risk assessment methodologies are applied to the mixture data). For pesticides, there will typically be information on the acute toxicity of formulations - i.e., the active ingredients and adjuvants - but very little if any information on subchronic or chronic toxicity.

If data on the mixture of concern are not available or are inadequate, one of the additivity models, similar joint action (dose addition) or independent joint action (response addition). These models, if defensible, can be used to assess the toxicity of a mixture using a simple algebraic process that derives the *hazard index*. The general equation for the hazard index is:

$$HI = \frac{E_1}{DL_1} + \frac{E_2}{DL_2} + \ldots + \frac{E_n}{DL_n} \qquad \textbf{(20)}$$

In Equation 20, E_1 is the level of exposure to the first chemical in the mixture and DL_1 is some "defined level" for exposure to the first chemical, such as an RfD. Similarly, E_2 and DL_2 are the corresponding levels for the second chemical. This approach can be continued for any number of

chemicals, signified by *n* in Equation 20. Each of the individual ratios (e.g., E_1/DL_1) is called the *hazard quotient*. The *hazard index* is the sum of the hazard quotients:

$$HI = \sum_{i=1}^{n} HQ_i = \sum_{i=1}^{n} \frac{E_i}{DL_i} \quad \textbf{(21)}$$

When this approach is used, concerns about interaction and other uncertainties should be expressed as clearly as possible.

3.12. SENSITIVE SUBGROUPS

The hazard identification will also include the identification of *biologically sensitive* subpopulations. Biological sensitivity here refers to a group of individuals or a subpopulation who for reasons of developmental stage or some other biological condition are significantly more susceptible than the general population to a compound. Issues regarding individuals at greater risk because of increased exposure are addressed in the exposure assessment (Section 4).

Biologically sensitive subpopulations do not include individuals at the extreme lower end of a uni-modal distribution of tolerances. Conceptually, the welfare of those individuals should be incorporated into a uni-modal model in the dose-response assessment. Failure to differentiate among *biologically sensitive* subpopulations, sensitive individuals in a uni-modal population, and individuals at increased risk due to high levels of exposure may add a substantial amount of confusion to the risk assessment.

Some individuals may be atypically sensitive to chemical exposure because of their age (e.g., Calabrese1986). Frequently, the very young or the very old are especially susceptible to the toxic effects of chemicals. Thus, everyone will belong to a high risk group at one or more times during their life span. Genetic factors, in contrast to developmental and aging factors, affect smaller subsections of the population. Some genetic conditions thought to predispose or enhance susceptibility to toxicants and the associated type of toxicant include cholinesterase variants (insecticides, cystic fibrosis), ozone and respiratory irritants, cystinosis and cystinuria (metals), glucose-6-phosphatase dehydrogenase deficiency (carbon monoxide), glutathione, glutathione peroxidase, and glutathione reductase deficiencies (lead and ozone), immunoglobulin A deficiency (respiratory irritants), immunological hypersensitivity (isocyanates), porphyrias (hexachlorobenzene, lead, barbiturates), sickle cell trait (aromatic amino and nitro compounds), and sickle cell anemia (carbon monoxide, cyanide). Furthermore, any genetic deficiency that results in altered xenobiotic metabolism may enhance susceptibility to chemicals.

Pre-existing disease states make individuals more susceptible to toxic chemicals. People with liver disease are less able than others to metabolize and detoxify foreign chemicals, and people with kidney disease are less able than others to excrete toxic chemicals. Carbon tetrachloride, PCBs, DDT and other pesticides are among the chemicals that many people with liver disease may find more difficult to tolerate. People with kidney disease are especially sensitive to the effects of lead and other heavy metals. Asthma, chronic respiratory disease and heart disease predispose

individuals to respiratory irritants, such as, nitrogen dioxide, ozone, sulfates, sulfur dioxide and carbon monoxide.

Behavioral and life style factors, such as smoking and alcohol and drug use not only increase an individual's exposure to toxic chemicals, but also increase the individual's susceptibility to other chemicals. Cigarette smoke itself contains a variety of carcinogens and other toxic chemicals. The chemicals in cigarette smoke may potentiate the toxicity of other pollutants. Alcohol and drug use enhance susceptibility to PCBs and pesticides by altering metabolizing enzyme systems in the liver. Dietary habits also may influence the toxicity of chemicals by producing changes in physiological and biochemical functions and nutritional status. Obese individuals may be more susceptible than others to toxic chemicals.

4. EXPOSURE ASSESSMENT

4.1. Overview.

The exposure scenarios considered in a risk assessment involving pesticide exposure are determined by the application method and the chemical and toxicological properties of the compound. Depending on the properties of the chemical and the application method, the risk assessment may consider acute, subchronic, or chronic durations of oral, dermal, inhalation or combined exposure to the pesticide.

Exposure scenarios are developed for workers, members of the general public, and various groups of nontarget species. For workers and the general public, two types of exposure scenarios are generally taken into consideration. They are *general exposure* and *accidental/incidental exposure*.

The term *general exposure* refers to human exposure resulting from the normal use of the chemical. For workers, general exposures involves the handling and application of the compound. These general exposure scenarios can be interpreted relatively easily and objectively. The exposure estimates are calculated from the amount of the chemical handled/day and the exposure rates for the worker group. Although each of the specific exposure assessments for workers involves degrees of uncertainty, the exposure estimates are objective in that they are based on empirical relationships of absorbed dose to pesticide use. For the general public, the general exposure scenarios are somewhat more arbitrary and may be less plausible. For each pesticide, at least three general exposures scenarios are considered, including walking through a contaminated area shortly after treatment, the consumption of ambient water from a contaminated watershed, and the consumption of contaminated vegetation. These three scenarios are consistently used because one of these three scenarios generally leads to the highest estimates of exposure. Additional scenarios discussed below may be considered for each of the individual compounds as warranted by the available data and the nature of the program activities.

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Some if not all of these general exposure scenarios for the general public may seem implausible or at least extremely conservative. For example, in many cases, compounds are applied in relatively remote areas. Thus, it is not likely that members of the general public would be exposed to plants shortly after treatment. Similarly, the estimates of longer-term consumption of contaminated water are based on estimated application rates (lbs a.i./acre) and monitoring studies that can be used to relate levels in ambient water to treatment rates in a watershed. In most pesticide

applications, however, substantial proportions of a watershed are not likely to be treated. Finally, the exposure scenarios based on longer-term consumption of contaminated vegetation assume that an area of edible plants is inadvertently sprayed and that these plants are consumed by an individual over a 90-day period. While such inadvertent contamination might occur, it is extremely unlikely to happen as a result of directed applications (e.g., backpack applications). Even in the case of boom spray operations, the spray is directed at target vegetation and the possibility of inadvertent contamination of cultivated or edible vegetation would be low. In addition, for herbicides and other phytotoxic compounds, it is likely that the contaminated plants would show obvious signs of damage over a relatively short period of time.

All of the factors discussed above concerning general exposure scenarios for the general public have merit and must be considered in the interpretation of the risk characterization (Section 6). Thus, the *typical* hazard to the general public may often be negligible because significant levels of exposure are not likely. For the general public, the general exposures may be regarded as *extreme* in that they are based on very conservative exposure assessments and/or very implausible events. Nonetheless, these general exposure assessments are included because the risk assessment is intended to be extremely conservative with respect to potential effects on the general public and to provide estimates regarding the likelihood and nature of effects after human exposure to pesticides.

Accidental/incidental exposure scenarios describe specific examples of gross over-exposure associated with mischance or mishandling of a chemical. All of these exposure scenarios are arbitrary in that the nature and duration of the exposure is fixed. For example, the worker exposure scenario involving immersion of the hands is based on a 1-minute period of exposure but could just as easily be based on an exposure period of 5 seconds or 5 minutes. Similarly, the consequences of wearing contaminated gloves could be evaluated at 4 hours rather than at 1 hour. These scenarios, however, are intended to provide an indication of relative hazard among different pesticides and different events in a manner that facilitates conversion or extrapolation to other exposure conditions.

Like the general exposure scenarios, the accidental exposures for the general public may be regarded as more extreme than those for workers. Three scenarios are included in each exposure assessment. They include direct spray, the consumption of contaminated water shortly after a spill, and the consumption of contaminated vegetation shortly after treatment. The direct spray scenario is clearly extreme. It assumes that a naked child is sprayed directly with a pesticide as it is being applied and that no steps are taken to remove the pesticide from the child for 1 hour. There are no reports of such incidents in the literature, and the likelihood of such an incident occurring appears to be remote. Nonetheless, this scenario and others like it are useful not only as a uniform comparison among pesticides but also as a simplifying step in the risk assessment. If the *'naked child'* scenario indicates no basis for concern, other dermal spray scenarios will not suggest a potential hazard and need not be explored. If there is a potential hazard, other more plausible exposure scenarios may need to be considered. The other two accidental scenarios are similarly motivated as uniform comparisons among chemicals as well as a means of evaluating the need to explore additional exposure scenarios.

In all cases, the level of exposure is directly proportional to the exposure parameters. The exposure associated with wearing gloves for 4 hours is 4 times the exposure associated with wearing contaminated gloves for 1 hour. Similarly, the general exposure scenarios for workers are based on an 8-hour work day. If a 4-hour application period were used, the hazard indices would be reduced by a factor of two. As another example, general exposure scenarios for both workers and the general public are linearly related to the application rate. Consequently, if the application rate were to double or vary by some other factor, the estimated exposure would double or vary by the same factor. Thus, the specific exposure parameters used in the risk assessment are selected to allow for relatively simple extrapolation to greater or lesser degrees of exposure.

Additional variability is taken into consideration by estimating exposure doses or absorbed doses for individuals of different age groups (i.e., adults, young children, toddlers, and infants). Children may behave in ways that increase the exposure to applied pesticides (e.g., long periods of outdoor play, pica, or imprudent consumption of contaminated media or materials). In addition, anatomical and physiological factors, such as body surface area, breathing rates, and consumption rates for food and water, are not linearly related to body weight and age. Consequently, the models used to estimate the exposure dose (e.g., mg/kg body weight/day) based on chemical concentrations in environmental media (e.g., ppm in air, water, or food) indicate that children, compared with individuals of different age groups, are generally exposed to the highest doses of chemicals for a given environmental concentration.

4.2. Workers

4.2.1. General Exposures.

The potential exposures of and health effects in pesticide applicators is a major focus in such USDA risk assessments. The concern for worker exposure is motivated by obvious ethical considerations as well as the understanding that pesticide applicators are likely to be the individuals who are most exposed to the pesticide during the application process.

Two general types of methods can be considered for worker exposure modeling, deposition-based and absorption-based. The U.S. EPA's Office of Pesticide Programs employs a deposition-based approach using data from the Pesticide Handler's Exposure Database (Leighton and Nielsen 1995). In this type of model, the exposure dose is estimated from air concentrations and skin deposition monitoring data. Using these estimates, the absorbed dose can be calculated if estimates are available on absorption rates for inhalation and dermal exposure.

The USDA Forest Service has generally used absorption-based models in which the amount of chemical absorbed is estimated from the amount of chemical handled. Absorption based models rather than a deposition based model have been used by the Forest Service because of two common observations from field studies. First, as discussed in the review by van Hemmen (1992) most studies that attempt to differentiate occupational exposure by route of exposure indicate that dermal exposure is much greater than inhalation exposure for pesticide workers. Second, most studies of pesticide exposure that monitored both dermal deposition and chemical absorption or some other method of biomonitoring noted a very poor correlation between the two values (e.g.,

Cowell et al. 1991, Franklin et al. 1981, Lavy et al. 1982). In USDA Forest Service exposure assessments for workers, the primary goal is to estimate absorbed dose so that the absorbed dose estimate can be compared with available information on the dose-response relationships for the chemical of concern. Thus, if dermal deposition does not correlate well with absorbed dose and if the inhalation route is not a substantial factor in worker exposure, the absorption-based approach may have some advantages when compared to the deposition-based approach.

Initially, SERA's risk assessment for the Forest Service adjusted the exposure rate by the estimated dermal absorption rate, typically using 2,4-D as a surrogate chemical when compound specific data were not available. Subsequently, SERA (1998) conducted a detailed review and re-evaluation of the available worker exposure studies that can be used to relate absorbed dose to the amount of chemical handled per day. This review noted that there was no empirical support for a dermal absorption rate correction. Two factors appear to be involved in this unexpected lack of association:

> algorithms for estimating dermal absorption rates have large margins of error
>
> and
>
> actual levels of worker exposure are likely to be far more dependent on individual work practices or other unidentified factors than on differences in dermal absorption rates.

Thus, in the absence of data to suggest an alternative approach, no corrections for differences in dermal absorption rate coefficients or other indices of dermal absorption seem to be appropriate for adjusting occupational exposure rates. Although pesticide application involves many different job activities, exposure rates can be defined for three categories: directed foliar applications including cut surface, streamline, and direct sprays involving the use of backpacks or similar devices, broadcast hydraulic spray applications, and broadcast aerial applications. While these may be viewed as crude groupings, the variability in the available data do not seem to justify further segmenting the job classifications - e.g., hack-and-squirt, injection bar. All of the details of the worker exposure calculations are summarized in standard worksheets C01a (directed ground), C01b (broadcast ground), and C01c (aerial). These and other standard worksheets discussed in this section can be obtained from any of SERA's risk assessments at http:/www/fs/fed/us/ foresthealth/pesticide/safety_data/risk.html. The following subsections give the rationale for the approach detailed in these worksheets.

4.2.1.1. Directed Foliar Applications. Based on the data reviewed by SERA (1998b), the mean (95% confidence interval) of the exposure rates for all ground workers involved in directed foliar backpack applications is about 5.3×10^{-3} (2.4×10^{-4} to 9.7×10^{-3}) mg/kg/lb a.i. handled. The mean and the confidence interval are based on a log normal distribution (mean=0.005297, SD=0.00232, p=0.46 using Kolmogorov-Smirnov test). These estimates are based on the mean data on glyphosate (Jauhiainen et al. 1991), triclopyr BEE (Middendorf 1992), picloram (Libich et al.

1984), and 2,4-D (Libich et al. 1984) but the estimates exclude the backpack applicators from Lavy et al. (1987) because of the atypical and very heavy dermal contact.

An alternate analysis for backpack workers can be based on individual data points rather than means for each of the four chemicals. However, as detailed in the appendix, the estimate for glyphosate from the Jauhiainen et al. (1991) study involved making several assumptions concerning urinary levels that are not as well supported as the measured values from the studies reported by Libich et al. (1984) and Middendorf (1992) - although the resulting estimates of absorbed dose rate from the Jauhiainen study are very consistent with those from the other two studies. For this reason, no data from Jauhiainen et al. (1991) were included in the analysis based on individual data. Two other points were censored from the analysis, workers G and H from the study by Middendorf (1992). As detailed by Middendorf (1992), neither of these two workers wore gloves and both had levels of exposure that were atypically high. Thus, data on a total of 16 workers can be used in the analysis of the individual worker exposure rates, 14 from the Middendorf (1992) study and two from the Libich et al. (1984) study. These individual data also fit a log normal distribution (p=0.78 using Kolmogorov-Smirnov test). The mean (95% confidence interval) of the absorbed rate for these 16 workers is about 3.2×10^{-3} (3.4×10^{-4} to 1.0×10^{-2}) mg/kg/lb a.i. handled and the standard deviation of the estimate is 0.00457.

Although the estimates based on the averages for four chemicals are not substantially different from the analyses based on the individual data points for three chemicals, the analysis based on individual workers is used for estimated exposures from directed foliar application. The available data on other application methods (i.e., hack-and-squirt and injection bar) suggest exposure rates that may be less than those of backpack workers by about a factor of 2. This difference is not substantial or statistically significant. Since the estimate of the magnitude of the difference is based on only two studies and two chemicals, the better documented rate for backpack applicators is recommended for these other types of manual ground applications.

4.2.1.2. Broadcast Ground Applications. Estimates of worker exposures from ground broadcast applications are based on two published studies of occupational exposure rates involving hydraulic spray applications: Libich et al. (1984) and Nash et al. (1982). The analysis of both of these studies is detailed in SERA (1998). The Libich et al. (1984) study involved mixtures of 2,4-D, dichlorprop, and picloram. Although this study is very useful for assessing relative rates of exposure, the amounts handled by the workers are not specified, so this study is not suitable for calculating absolute occupational exposure rates. The study by Nash et al. (1982) provides all of the necessary information on 21 of 26 workers (i.e., Table V in Nash et al. 1982), including the amount handled, the duration of application, and the total urinary elimination of 2,4-D over a 6-day post-application period. For the remaining five workers, the amount handled was not recorded for four of the workers and 2,4-D was not detected in the urine of one of the remaining workers. In recent Forest Service risk assessments, this study was used to support occupational exposure rates of 9.6×10^{-5} mg/kg bw/lb a.i. with lower and upper 95% confidence limits of 4.9×10^{-6} and 1.9×10^{-3} mg/kg bw/lb a.i.

The re-analysis of these data was conducted excluding the four workers on which the data are not complete and using a trimmed mean (Gilbert 1987) to account for the one worker in which no 2,4-D was detected - i.e., omitting the data for the worker with no detectable 2,4-D in the urine as well as the data for the worker with the highest reported level of 2,4-D in the urine. These individual occupational exposure rates fit a log normal distribution [p=0.78 using the Kolmogorov-Smirnov test (Manugistics 1997) with an n of 20] with a mean of $2.4x10^{-4}$ mg/kg bw/lb a.i., a standard deviation of $5.48x10^{-4}$ and 95% confidence limits of $1.1x10^{-5}$ to $9.00x10^{-4}$ mg/kg bw/lb a.i.

4.2.1.3. Broadcast Aerial Applications. As discussed in SERA (1998), data on 2,4-D (Lavy et al. 1982) and (Nash et al. 1982) and for the three mixers using cypermethrin from the study by Chester et al. (1987) are useful for estimating exposure rates pertinent to aerial applications. The lack of an apparent relationship between estimated rates for dermal absorption and occupational exposure, as discussed above, suggests that it is appropriate to combine the data on cypermethrin with the data on 2,4-D.

Like data sets for ground applications, the individual occupational exposure rates fit a log normal distribution [p=0.91 using the Kolmogorov-Smirnov test (Manugistics 1997)]. There is at least a marginally significant (p=0.032) correlation between the log of the absorbed dose and the log of the amount handled, although the correlation coefficient between these two variables is low (r^2=0.19).

Using a log normal distribution, the mean of the rates is $3.08x10^{-5}$ mg/kg bw/lb a.i. with lower and upper 95% confidence limits of $1.08x10^{-6}$ to $1.16x10^{-4}$ mg/kg bw/lb a.i. These rates are applied to both pilots as well as mixer/loaders. Given the relatively minor and statistically insignificant differences in occupational exposure rates between pilots and mixer/loaders, separate exposure rates for these two groups are not justified. There are insufficient data on other job categories in aerial applications to support the derivation of additional occupational exposure rates.

Studies involving occupational exposure during aerial applications of 2,4,5-T suggest that flaggers—ground personnel who mark the area to be sprayed —are likely to have lower exposure rates than mixer/loaders. In a study by Lavy et al. (1980) involving exposure of aerial crews to 2,4,5-T, the amounts of 2,4,5-T handled are not specified and exposures are characterized in units of mg 2,4,5-T/kg bw based on urinalysis. Although this study cannot be used to calculate occupational exposure rates, information is reported on mixers and flagmen in two crews. Since each crew, by definition, handled the same amount of material per day, this information can be used to estimate relative differences in exposure. For mixers in the two crews, the daily excretion of 2,4,5-T was 0.065 mg/kg bw and 0.096 mg/kg bw. For the two flagmen in the first crew, the daily excretion was 0.002 mg/kg and 0.001 mg/kg. In the second crew, the daily excretion for both flagmen was 0.001 mg/kg. Thus, the average excretion rate for the mixers [0.081 mg/kg] was about 65-fold greater than the average rate for flagmen [0.00125 mg/kg]. Conversely, the exposure estimate for flagmen was about 1.5% of that estimated for mixers.

Similarly, Newton and Norris (1981) briefly report about exposure for mixer-loaders and flaggers in a helicopter crew spraying 2,4,5-T. Reported absorbed doses for mixer-loaders ranged from 0.016 to 0.063 mg/kg, in the range of absorbed doses reported by other investigators. A flagger, wearing a hat and long-sleeved shirt, absorbed 0.005 mg/kg. The report does not provide information regarding the amount of the chemical handled or sprayed or the duration of activities associated with the exposures. In a review, Lavy and Mattice (1985) provide similar information from an unpublished study: absorbed doses of 0.001 mg/kg for flagmen and 0.062 mg/kg for mixers. Thus, it seems reasonable to suggest that occupational exposure rates for flaggers, barring accidental direct sprays, will be about 10-100 lower than the rates for pilots or mixer/loaders.

4.2.2. Accidental Exposure Scenarios for Workers

4.2.2.1. Immersion or Contaminated Clothing -- Incidental occupational exposure may occur from improper handling or use of the pesticide, or from accidental contamination of the skin or clothing by a spill. All of these scenarios can be modeled using Fick's first law. Scenarios that use Fick's first law require an estimate of the permeability coefficient, K_p, expressed in cm/hour (Durkin et al. 1995, U.S. EPA 1992). If an experimental K_p is available for the compound of concern, it is used. Otherwise, the K_p is estimated based on Equation 5.

For this scenario, it is assumed that an individual immerses part of the body into the formulation for a short time, either through mischance or imprudent handling. The worst case scenario generally involves a worker placing both hands in a concentrated formulation for 1 minute. The surface area of the hands will be estimated at 0.084 m^2 (U.S. EPA 1992). Concentrations in units of g/L are equivalent to mg/mL, which, in turn, is equivalent to mg/cm^3. Using Ficks first law, the estimated absorbed dose (AD) is calculated as:

$$AD = K_p \text{ (cm/hour)} \cdot \text{Conc } (mg/cm^3) \cdot 1/60 \text{ hour} \cdot 840 \text{ } cm^2 \div 70 \text{ kg.} \quad \textbf{(22)}$$

Estimated doses for other immersed areas and durations can be calculated in a similar way. If, however, the scenario involves contaminated clothing (e.g., the chemical spilled inside of gloves), which might be worn for a long time, absorbed doses could be much higher. Thus, contaminated gloves worn for 1 hour would lead to an exposure 60 times greater than that described for the immersion scenario discussed above. Both of these scenarios—immersion of hands and wearing contaminated gloves—are typically presented in the risk assessment. These calculations are detailed in standard worksheet C02.

4.2.2.2. Accidental Spills -- In accidental spill scenarios, it is important to estimate the amount of liquid adhering to the surface of the skin. In one study, as much as 4 mg liquid/cm^2 of skin surface was retained on hands removed immediately from beakers containing water or ethanol (Mason and Johnson 1987). When beakers containing light paraffin oil were used, approximately twice this amount was retained. In most instances, using these values should result in a plausible upper estimate of retention because chemical loss from the skin surface due to

moving or washing is not taken into consideration. Thus, the amount of chemical transferred to the skin after a spill may be calculated as:

$$D_{Skin} = RF \cdot P \cdot A \quad (23)$$

where:
D_{Skin} = dose remaining on surface of skin (µg)
RF = retention factor (µg/cm^2) (for example, 4,000-8,000µg/cm^2)
P = proportion of compound in the liquid
A = skin area exposed (cm^2)

Any person handling a concentrated formulation or located near the area where the handling takes place may be subject to an accidental spill. This exposure scenario is different from the one involving immersion in that most of the liquid will run off the surface of the skin immediately after the spill unless the material is kept in contact with the skin by saturated clothing. If the clothing is saturated, the scenario outlined above applies. If the chemical spills on the skin but is not kept in contact with the skin, the exposure will be much less.

A typical spill scenario involves contamination of the lower legs. The surface area of the lower legs is taken as 2070 cm^2 (U.S. EPA 1992). The upper limit of the amount of liquid adhering to the surface of the skin is taken as 8 mg/cm^2 of skin (Mason and Johnson 1987). Assuming a density of 1.0 for the aqueous solution, this is equivalent to 0.008 mL/cm^2. Hence, the volume of liquid adhering to the skin is 16.56 mL [2070 cm^2 · 0.008 mL/cm^2]. Thus, for a given concentration (***C***) of the compound in units of mg/mL, the amount of compound adhering to the skin (***A***) can be estimated as 16.56 mL · ***C*** mg/mL. The absorbed dose is then calculated as in equation 11, using the amount deposited on the surface of the skin (x_0 in equation 11) and the first order dermal absorption rate constant (k in equation 11). These calculations are detailed in standard worksheet C03.

4.3. Exposure Scenarios for the General Public

4.3.1. General Considerations.

Any number of exposure scenarios may be constructed for the general public, based on varying assumptions concerning application rates, dispersion, canopy interception, and human activity. In general, several very conservative scenarios are developed. As discussed below, most of these scenarios should be regarded as extreme, some to the point of limited plausibility.

These exposure scenarios require various estimates of body weight, surface area, the consumption of contaminated food or water. These estimates are taken from published and well-documented sources. All of the specific values are summarized and documented in standard worksheet A04.

The anatomical values (i.e., body weights and skin surface areas) currently used are taken from various U.S. EPA sources (e.g., U.S. EPA 1989a,b; U.S. EPA 1995). For the most part, these values represent a consensus for common use. Other values could be proposed with equal or in some cases better documentation. For example, the U.S. EPA (1980) used 70 kg as the standard body weight for a man. This, in turn, was adopted from the International Commission on

Radiologic Protection Report on the Task Group on Reference Man (ICRP 1992). Other sources of information are available suggesting that slightly different values might be more appropriate or consistent. For example, Burmaster and Crouch (1997) summarize data indicating that 70 kg is about the mean weight of 18- to 19-year-old males and 64 kg is about the mean weight of women in their mid-forties. As summarized by U.S. EPA (1989b, Table 5-2 p. 5-5), time-weighted average body weights for individuals between the ages of 18 and 75 years are approximately 78.1 kg for men and 65.4 kg for women. The value of 70 kg is used as a reference weight for man because it has become a standard since the ICRP (1992) report. This weight is currently used by the U.S. EPA (1995) as a composite body weight for males and females. The weight of 64 kg for a woman is taken from U.S. EPA (1989b, Table 5-2 p. 5-5) for a women ranging in age from 25 to 35 years. Although other values could be used, usually they will not influence risk characterization substantially. The most important factor, particularly when comparing different scenarios or the same scenarios for different chemicals, is that the standard values are used consistently.

Many of the exposure scenarios for the general public involve a child. The child is incorporated into the scenario because the relationships of surface area and consumption rates to body weight result in estimated doses (mg chemical/kg body weight) for young children that are higher than those for adults (U.S. EPA 1989a). Dermal exposure scenarios that involve children use the same set of assumptions: the child is 2- to 3-years old, weighs 10–11 kg, and has a total body surface area of 0.6 m^2 or 6000 cm^2 for a body weight of 11 kg (U.S. EPA 1992). For most scenarios, the child is assumed to be naked, maximizing the surface area of the body in contact with the chemical. In all cases, there are linear relationships among the exposed surface area of the body, the estimated absorbed dose, and the subsequent risk.

Three scenarios for the consumption of contaminated media are usually developed as both general and accidental exposure scenarios. The contaminated media in these scenarios includes vegetation, water, and fish. If the consumed quantity of a chemical is known (e.g., as in the accidental ingestion of a known quantity of pesticide), this quantity is divided by body weight to convert the intake amount to a dose:

$$D_{(mg/kg)} = I_{(mg)} / BW_{(kg)} \quad \textbf{(24)}$$

where:

D = dose (mg/kg)

I = intake (mg)

BW = body weight (kg)

When material containing a known or estimated concentration of a chemical is consumed, the intake may be expressed as the product of the concentration and the quantity of contaminated material consumed:

$$I_{(mg)} = C_{(mg/kg)} \cdot Amt_{(kg)}$$

where:

C = concentration of compound in material (mg compound/kg material)

Amt = amount (kg) of material consumed **(25)**

In the case of contaminated fish, the concentration in the fish ($C_{(mg/kg)}$) is estimated as the product of the concentration in water (mg/L) and the bioconcentration factor (BCF in units of L/kg):

$$C_{Fish} = C_{Water} \cdot BCF \quad \textbf{(26)}$$

The specific methods for estimating the concentration in the various environmental media are detailed in the appropriate subsections below.

4.3.2. Direct Spray.

Direct sprays involving ground applications are modeled in a manner similar to accidental spills for workers (Section 4.2.2.2.). In other words, it is assumed that the individual is sprayed with a solution containing the compound and that an amount of the compound remains on the skin and is absorbed by first-order kinetics. As with the similar worker exposure scenarios, the first-order absorption kinetics are estimated from the empirical relationship of first-order absorption rate coefficients to molecular weight and octanol-water partition coefficients, as defined in Appendix 2, Worksheet A07a. The dose deposited (DD) on the child is estimated as the product of the amount adhering to the skin, the concentration (C) in the spray solution, and the surface area (0.008 mL/cm^2):

$$DD = 0.008 \text{ mL/cm}^2 \cdot C \text{ (mg/mL)} \cdot 6000 \text{ cm}^2 \quad \textbf{(27)}$$

The absorbed dose is then calculated as using the absorption rate, or range of rates and assuming that the child is washed completely 1 hour after being sprayed:

$$DD \text{ (mg)} \cdot AR \text{ (h}^{-1}\text{)} \cdot 1 \text{ hour} \div 11 \text{ kg.} \quad \textbf{(28)}$$

In a typical Forest Service risk assessment, a scenario is presented in which a naked child is sprayed directly during a ground application. The scenario also assumes that the child is completely covered (that is, 100% of the surface area of the body is exposed), which makes this an extremely conservative exposure scenario that is likely to represent the upper limits of plausible exposure. An additional scenario included in Forest Service risk assessments involves a young

woman who is accidentally sprayed over the feet and legs. The specific calculations used in these scenarios are detailed in Worksheets D01 (child) and D02 (woman).

4.3.3. Dermal Exposure from Contaminated Vegetation.

In this exposure scenario, it is assumed that the pesticide is sprayed at a given application rate and that an individual comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation. Some estimate of dislodgeable residue (DR) of the pesticide must be available (Durkin et al. 1995).

Immediately after the spray application, levels of exposure may approximate those involving contact with direct spray, as discussed above. Generally, after the liquid carrier dries, exposure levels are expected to decrease. For example, in a study by Harris and Solomon (1992), 2,4-D was applied to turf at a nominal rate of 11 $\mu g/cm^2$. Immediately after the liquid carrier dried, the dislodgeable residue of 2,4-D was 0.92 $\mu g/cm^2$, about a factor of 10 less than the nominal rate.

If no data are available on the dislodgeable residue, the assumption is made that the dislodgeable residue follows a pattern similar to that of 2,4-D (i.e., is one-tenth of the nominal applied rate). The dislodgeable residue immediately after the liquid carrier dries is then estimated as 0.1 of the nominal application rate.

The rate at which a chemical is transferred from the vegetation surface to the skin is referred to as the *transfer rate* and is assumed to be related to the dislodgeable residue. As detailed in Durkin et al. (1995, Equation 4, p. 68), the transfer rate (TR) may be calculated as the anti-log of:

$$TR = [(1.09 \cdot \log(DR \text{ a.i.}/cm^2)] + 0.05, \quad \textbf{(29)}$$

where DR is the dislodgeable residue and TR is the transer rate in units of μg compound/(cm^2 skin surface $\cdot$ hour).

The exposed dose (ED) is then calculated for an individual, wearing shorts and a short-sleeved shirt (5300 cm^2), in contact with the contaminated vegetation for 1 hour:

$$ED = TR \ \mu g/(cm^2 \cdot \text{hour}) \cdot 5300 \ cm^2 \cdot 1 \text{ hour}. \quad \textbf{(30)}$$

The absorbed dose is then calculated under the assumption of first order absorption (equation 11). Details of this exposure assessment are summarized in standard worksheet D03.

4.3.4. Contaminated Water

Water can be contaminated from runoff, as a result of leaching from contaminated soil, from a direct spill, or from unintentional contamination from aerial applications. Although most pesticides are chemically stable in pure aqueous solutions, they are degraded in natural waters by photolysis or hydrolysis, and concentrations in water are further reduced by biological degradations and dispersal. For most Forest Service risk assessments, the two types of estimates

made for the concentration of the pesticide in ambient water are acute/accidental exposure and longer-term exposure.

4.3.4.1. Acute Exposure/Spill

A standard scenario used in Forest Service risk assessments involves an acute exposure assuming that a young child (2- to 3-years old) consumes 1 L of contaminated water shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average depth of 1 m and a surface area of 1000 m^2 or about one-quarter acre. The details of this exposure scenario are presented in Worksheet D06. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation of the pesticide is considered.

This is an extremely conservative scenario dominated by arbitrary variability (see discussion of variability in Section 1). The actual concentrations in the water would depend heavily on the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed.

With some lipophilic pesticides, some of the estimates of the concentration of the pesticide in water from the spill of 200 gallons of a field solution exceed the solubility of the compound in water. In other words, some of the compound would precipitate from solution and would not be ingested under any plausible scenario. Consequently, for estimating the ingested dose, such concentrations are adjusted to the water solubility of the pesticide. This same approach is taken for all accidental spill scenarios involving water contamination in the ecological risk assessment (section 5).

4.3.4.2. Longer-term Exposures/Ambient Water.

Estimates of long-term exposures in ambient water may be based on monitoring studies or the use of environmental fate models. When ever monitoring data are available, this data is used in some way. Occasionally, studies may be available in which the concentration of the pesticide in ambient water can be directly associated with a known application of the compound. In such cases, empirical relationships between concentration in water and application rates may be developed. In other cases, monitoring data may indicate only general concentrations in water that cannot be associated with specific applications. Such studies are somewhat less useful directly in the exposure assessment but may serve as a 'reality check' on any modeled concentrations. The key limitation of environmental fate models is that they may be very closely linked to site specific environmental and climatic parameters and hence may not lead to accurate estimates of ambient concentrations that may be generally applied.

Whether or not monitoring data are available, a consistent set of environmental fate models are used. While there uncertainties in the application of any model, the approach taken in the risk assessments allows at least a relative characterization of plausible ambient concentrations under a variety of environmental and site-specific conditions (e.g., rain fall, soil types, and soil slope).

In the Forest Service risk assessments, GLEAMS (Knisel et al. 1992) is used to estimate ambient water concentrations. GLEAMS is a root zone model that can be used to examine the fate of chemicals in various types of soils under different meteorological and hydrogeological conditions. As with many environmental fate and transport models, the input and output files for GLEAMS can be complex. A complete and detailed description of the input files and GLEAM modeling used in the Forest Service risk assessments is given in Attachment 1.

The basic exposure scenario used for the modeling involves the compound being applied along a 10-acre right-of-way that is 50 feet wide and 8712 feet long. It is also assumed that a body of water runs along the length of the right-of-way and that the slope toward the water is 10 percent. Three types of soils are modeled: clay (high runoff potential), sand (low runoff potential), and loam (intermediate runoff potential). Annual rainfall rates ranging from 5 to 250 inches are used to reflect the variability of regional rainfall rates based on statistics from the U.S. Weather Service (1998) for 152 cities in 45 states covering the period from 1961 to 1990.

4.3.5. Consumption of Contaminated Fish.

Many chemicals may be concentrated or partitioned from water into the tissues of animals or plants in the water. This process is referred to as bioconcentration. Generally, bioconcentration is measured as the ratio of the concentration in the organism to the concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the concentration in the water is 1 mg/L, the bioconcentration factor (BCF) is 5 L/kg [5 mg/kg ÷ 1 mg/L]. As with most absorption processes, bioconcentration depends initially on the duration of exposure but eventually reaches steady state. Details regarding the relationship of bioconcentration factor to standard pharmacokinetic principles are provided in Calabrese and Baldwin (1993).

Usually there is at least one study available on the bioconcentration of a pesticide: a standardized 28-day assay using bluegill sunfish that is required as part of the registration process. The kinds of data reported in the study generally include the concentration of the pesticide in water, expressed as mg/L and the concentration of the pesticide in fish tissue (edible, non-edible, and total) at days 1, 7, 14, and 28. Additional time periods often are provided.

For both the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentration used in the bioconcentration study is compared with the concentrations derived in the exposure scenarios for contaminated water (see section 4.3.4). The closer these concentrations are to one another, the greater the degree of confidence (i.e., the less extrapolation) in the exposure assessment. In human health exposure assessments, only bioconcentration factors for the edible portion of the fish are used. Separate values are selected for the acute exposure scenario—usually the 1-day BCF—and the chronic exposure scenario—usually the 28-day BCF. For highly lipophilic compounds, the 28-day BCF may not represent steady state, and further kinetic analyses may be required to estimate the steady state BCF.

The acute exposure scenario is based on the assumption that an adult angler consumes fish taken from contaminated water shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average depth of 1 m and a surface area of 1000 m^2 or about one-quarter acre.

This is identical to the assumptions used in the acute drinking water scenario. Because this is an acute exposure scenario, the short term BCF is used and no dissipation or degradation is considered.

The chronic exposure scenario for the consumption of contaminated fish is constructed similarly to the acute scenario, as detailed in worksheet D09, except that estimates of pesticide concentrations in ambient water are based on the estimated longer-term concentrations in ambient water (see section 4.3.4) and the longer-term BCF for the edible portion of fish. Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations (U.S. EPA 1996), separate longer-term exposure estimates are made for these two groups, as illustrated in standard worksheet D08.

4.3.6. Consumption of Contaminated Vegetation.

Forest Service applications do not involve the treatment of crops. Thus, under normal circumstances and in most types of applications conducted as part of Forest Service programs, the consumption of vegetation contaminated is unlikely. Nonetheless, any number of scenarios could be developed involving either accidental spraying of crops or the spraying of edible wild vegetation, like berries. For most herbicides and particularly for longer-term scenarios, treated vegetation would probably show signs of damage from exposure to the pesticide, thereby reducing the likelihood of consumption that would lead to significant levels of human exposure.

Notwithstanding that assertion, it is conceivable that individuals could consume contaminated vegetation. One of the more plausible scenarios involves the consumption of contaminated berries after treatment of a right-of-way or some other area in which wild berries grow. The two accidental exposure scenarios are usually developed for the exposure assessment: one scenario for acute exposure (worksheet D04) and one scenario for longer-term exposure (worksheet D05). In both scenarios, the concentration of herbicide on contaminated vegetation is estimated. If available, compound specific residue data are used. If such data are not available, the empirical relationships between application rate and concentration in vegetation developed by Hoerger and Kenaga (1972) is used. These relationships are defined in worksheet A05a. For the acute exposure scenario, the estimated residue level is taken as the product of the application rate and the residue rate given in worksheet A05a.

For the longer-term exposure scenario, a duration of 90 days is used (i.e., a fruit bearing plant is treated on day 0 and consumed by an individual over a 90-day post-treatment period). The rate of decrease in the residues over time is usually estimated from a vegetation residue half-time. For most registered pesticides, particularly the herbicides, vegetation residue half-times are available or can be estimated from studies submitted to the U.S. EPA as part of the registration process.

For the acute exposure scenario, it is assumed that a woman consumes 1 lb (0.4536 kg) of contaminated fruit. Based on statistics summarized in U.S. EPA (1996), this consumption rate is approximately the mid-range between the mean and upper 95% confidence interval for the total vegetable intake for a 64 kg woman. The range of exposures is based on the range of

concentrations on vegetation from Hoerger and Kenaga (1972) and the range of application rates identified in the program description. The longer-term exposure scenario is constructed in a similar way, except that the estimated exposures include the range of vegetable consumption (U.S. EPA 1996) as well as the range of concentrations on vegetation, the range of application rates. For some herbicides, the kinetic data on residues may be adequate to estimate confidence intervals on the halftime and this information is also incorporated in the exposure assessment.

4.4. Terrestrial Animals

4.4.1. Overview.

Terrestrial animals might be exposed to any applied pesticide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. Estimates of oral exposure are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg body weight. For dermal exposure, the units of measure usually are expressed in mg of agent per cm^2 of surface area of the organism and abbreviated as mg/cm^2. In estimating dose, however, a distinction is made between the exposure dose and the absorbed dose. The *exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm^2 and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body weight. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal.

For the exposure assessments discussed below, general allometric relationships are used to model exposure (e.g., Boxenbaum and D'Souza 1990). These relationships dictate that, for a fixed level of exposure (e.g., concentrations of a chemical in food or water), small animals will receive a higher dose, in terms of mg/kg body weight, than large animals will receive.

Based on allometric relationship, it would be possible to model exposure in a very large number of nontarget terrestrial animals. This approach as been used in some past USDA assessments. This approach is no longer used because highly species specific exposure assessments are of little use in the absence of species specific dose-response assessments. Thus, if the pesticide- specific information indicates that large mammals may be more sensitive than smaller mammals (i.e., in contrast to the more general relationship noted above), both large and small mammals are modeled separately. Similarly, if the available information suggests that the compound under review may more toxic to birds than to mammals, separate exposure assessments are conducted for both birds (large and small) and mammals. The basic philosophy behind this approach is that the exposure assessment should not be more complicated than the dose-response assessment.

Generic estimates of exposure are given for a small mammal. A body weight of 20 g is used for a small mammal, which approximates the body weight of small mammals like mice, voles, shrews, and bats. Other body weights, food consumption, and caloric requirements for mammals and birds are taken from U.S. EPA (1993). The computational details for each exposure assessment presented in this section are provided in standard worksheets (worksheets F01 through F13). An overview of each of these exposure assessments are described in the following subsections.

4.4.2. Direct Spray – Wildlife species may be sprayed directly during the application of any pesticide. This exposure scenario is similar to the accidental exposure scenarios for the general public discussed in section 4.3.2. For an exposure scenario involving direct spray, the extent of dermal contact depends on the application rate, the surface area of the organism, and the rate of absorption.

Three groups of direct spray exposure assessments are typically conducted. The first, which is defined in worksheet F01, involves a 20 g mammal that is sprayed directly over one half of the body surface as the chemical is being applied. The range of application rates and the typical application rate are used to define the amount of pesticide deposited on the organism. The absorbed dose over the first day (i.e., a 24-hour period) is estimated using the assumption of first-order dermal absorption (equation 11). In the absence of data regarding dermal absorption in a small mammal, the estimated absorption rate for humans is used (see section 3.9). An empirical relationship between body weight and surface area (Boxenbaum and D'Souza 1990) is used to estimate the surface area of the animal when species-specific information is not available. The estimates of absorbed doses in this exposure scenario may bracket plausible levels of exposure for small mammals, based on uncertainties in the dermal absorption rate for the pesticide.

Other, perhaps more substantial, uncertainties affect the estimates for absorbed dose. For example, the estimate based on first-order dermal absorption does not consider fugitive losses from the surface of the animal and may overestimate the absorbed dose. Conversely, some animals, particularly birds and mammals, groom frequently, and grooming is likely to contribute to the total absorbed dose by direct ingestion of the compound residing on fur or feathers. Furthermore, other vertebrates, particularly amphibians, may have skin that is far more permeable than the skin of most mammals (Moore 1964).

Quantitative methods for considering the effects of grooming or increased dermal permeability are not available. As a conservative upper limit, the second exposure scenario, detailed in worksheet F02, is developed in which complete absorption over day 1 of exposure is assumed.

Because of the relationship of body size to surface area, very small organisms, like bees and other terrestrial insects, might be exposed to much greater amounts of pesticide per unit body weight, compared with small mammals. Consequently, a third exposure assessment is developed using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993) and the equation for body surface area proposed by Boxenbaum and D'Souza (1990). Because there is no information regarding the dermal absorption rate of most pesticides by bees, this exposure scenario, detailed in worksheet F03, also assumes complete absorption over the first day of exposure.

4.4.3. Indirect Contact – As in the human health risk assessment, the only approach for estimating the potential significance of indirect dermal contact is to assume a relationship between the application rate and dislodgeable foliar residue. The study by Harris and Solomon (1992) is used to estimate that the dislodgeable residue will be approximately 10 times less than the nominal application rate.

Unlike the human health risk assessment in which transfer rates for humans are available, there are no transfer rates available for wildlife species. As discussed in Durkin et al. (1995), the transfer rates for humans are based on brief (e.g., 0.5- to 1-hour) exposures that measure the transfer from contaminated soil to uncontaminated skin. Wildlife, compared with humans, are likely to spend longer periods of time in contact with contaminated vegetation. It is reasonable to assume that for prolonged exposures an equilibrium may be reached between levels on the skin, rates of absorption, and levels on contaminated vegetation, although there are no data regarding the kinetics of such a process.

Thus, no quantitative exposure assessment is made for this scenario. Often the direct spray scenarios, detailed above, results in exposure levels below those of toxicological concern, which somewhat diminishes concern about the inability to model this scenario directly.

4.4.4. Ingestion of Contaminated Vegetation or Prey – Since pesticides, particularly herbicides, may be applied to vegetation, uptake from contaminated vegetation is an obvious concern and separate exposure scenarios are developed for mammals and birds. Separate acute and chronic exposure scenarios are developed for a small mammal (worksheets F04 and F05) and large mammal (worksheets F10 and F11). In addition, the potential for adverse reproductive effects in birds after the consumption of contaminated insects is typically evaluated for acute exposure scenarios (worksheet F14).

As in the direct spray scenario, a small mammal is used because allometric relationships indicate that small mammals will ingest greater amounts of food per unit body weight, compared with large mammals. The amount of food consumed per day by a small mammal (i.e., an animal weighing approximately 20 g) is equal to about 15% of the mammal's total body weight (U.S. EPA 1989a). When applied generally, this value may overestimate or underestimate exposure in some circumstances. For example, a 20 g herbivore has a caloric requirement of about 13.5 kcal/day. If the diet of the herbivore consists largely of seeds (4.92 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 14% of its body weight [(13.5 kcal/day ÷ 4.92 kcal/g)÷20g = 0.137]. Conversely, if the diet of the herbivore consists largely of vegetation (2.46 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 27% of its body weight [(13.5 kcal/day ÷ 2.46 kcal/g)÷20g = 0.274] (U.S. EPA 1993, pp.3-5 to 3-6). While it is possible to model this kind of variability, the results might profoundly increase the apparent complexity of the risk assessment by adding several additional scenarios involving various species consuming various diets. A simpler approach is taken in this risk assessment by making the conservative assumption that 100% of the diet is contaminated and that the small mammal consumes leaves and leafy vegetables.

A large herbivorous mammal is included because empirical relationships of concentrations of pesticides in vegetation, discussed below, indicate that grasses may have substantially higher pesticide residues than other types of vegetation such as forage crops or fruits (worksheet A05a). Grasses are an important part of the diet for some large herbivores, but small mammals do not consume grasses as a substantial proportion of their diet. So, even though using residues from

grass to model exposure for a small mammal is the most conservative approach, it is not generally applicable to the assessment of potential adverse effects. Hence, in the exposure scenarios for large mammals, the consumption of contaminated range grass is modeled for a 70 kg herbivore, like a deer. Caloric requirements for herbivores and the caloric content of vegetation are used to estimate food consumption based on data from U.S. EPA (1993). Details of these exposure scenarios are given in worksheets F10 and F11.

The consumption of contaminated vegetation is also modeled for a large bird. This scenario is included when the pesticide under review causes reproductive impairment or other longer-term toxic effects in birds. For this exposure scenario, the consumption of range grass by a 4 kg herbivorous bird, like a Canada Goose, is modeled for both acute (worksheet F12) and chronic (worksheet F13) exposures.

For this component of the exposure assessment, the estimated amounts of pesticide residue in vegetation are based on the relationship between application rate and residue rates on different types of vegetation. As summarized in worksheet A05a, these residue rates are based on the relationships derived by Hoerger and Kenaga (1972). For chronic exposures, dissipation from vegetation is incorporated explicitly into the exposure assessment as detailed in worksheets F11 and F13.

The consumption of contaminated insects is modeled for a small bird. Except for insecticides, there are typically no monitoring data on the concentrations of pesticides in insects. The empirical relationships for residues in vegetation developed by Hoerger and Kenaga (1972) are used as surrogates, as detailed in worksheet F14.

In addition to the consumption of contaminated vegetation and insects, pesticides may reach ambient water and bioconcentrate in fish. Thus, a separate exposure scenario is developed for the consumption of contaminated fish by a predatory bird in both acute (worksheet F08) and chronic (worksheet F09) exposures. Because predatory birds usually consume more food per unit body weight than do predatory mammals (U.S. EPA 1993, pp. 3-4 to 3-6), a separate exposure scenario for a predatory mammal is not developed. The bioconcentration factors used for these risk assessments are based on bioconcentration factors in whole fish rather than the edible portion of fish which is used in the human health risk assessment. This is done because many predatory birds will consume the entire fish rather than just the muscle, which is typically considered as the edible portion for humans.

4.5. Terrestrial Plants

4.5.1. Overview – For herbicides, five exposure scenarios are typically considered quantitatively: direct spray, spray drift, runoff, wind erosion and the use of contaminated irrigation water. Unintended direct spray is expressed simply as the application rates considered in the risk assessment and should be regarded as an extreme/accidental form of exposure that is not likely to occur in most Forest Service applications. Estimates for the other routes of exposure are typically much less. All of the exposure scenarios are dominated by situational variability because the levels of exposure are highly dependent on site-specific conditions. Thus, the

exposure estimates are intended to represent conservative but plausible ranges that could occur; however, these ranges may overestimate or underestimate actual exposure in some cases. Spray drift is based on estimates of drift from a review of numerous field studies. The central estimate of drift is taken as the expected drift at 500 feet down wind from the application site with lower and upper estimates based on distances of 2500 feet and 100 feet, respectively. The proportion of the applied amount transported off-site from runoff is based on GLEAMS modeling of clay, loam, and sand. The amount of the compound that might be transported off-site from wind erosion is based on estimates of annual soil loss associated with wind erosion and the assumption that the compound is incorporated into the top 1 cm of soil. Exposure from the use of contaminated irrigation water is based on the same data used to estimate human exposure from the consumption of contaminated ambient water and may involve both monitoring studies as well as GLEAMS modeling.

4.5.2. Direct Spray – Unintended direct spray is expressed simply as the application rates considered in the risk assessment and should be regarded as an extreme/accidental form of exposure that is not likely to occur in most Forest Service applications.

4.5.3. Off-Site Drift – Because off-site drift is more or less a physical process that depends on droplet size and meteorological conditions rather than the specific properties of the herbicide, estimates of off-site drift can be made based on data for other compounds. When data are available on the compound under review, this data is of course used in lieu of or along with other estimates of drift, depending on the nature of the compound-specific information. The potential for spray drift was investigated in numerous field studies as reviewed by Bird (1995). The information from this review that is most often used in the risk assessment is summarized in worksheet A06. The monitoring studies on these compounds involved low-flight agricultural applications of pesticides and employed various types of nozzles under a wide range of meteorological conditions. The central estimates of off-site drift for single swath applications, expressed as a proportion of the nominal application rate, were approximately 0.03 at 100 feet, 0.002 at 500 feet, 0.0006 at 1000 feet, and 0.0002 at 2500 feet (Bird 1995, Figure 2, p. 204). Although multiple swath applications lead to higher rates of off-site deposition, they are less suitable for estimating drift from ground spray applications of pesticides.

Another approach to estimating drift involves the use of Stoke's law, which describes the viscous drag on a moving sphere. According to Stoke's law:

$$v = \frac{D^2 \cdot g}{18n} \quad \text{or} \quad v = 2.87 \cdot 10^5 \cdot D^2 \qquad \textbf{(31)}$$

where v is the velocity of fall (cm sec^{-1}), D is the diameter of the sphere (cm), g is the force of gravity (980 cm sec^{-2}), and n is the viscosity of air ($1.9 \cdot 10^{-4}$ g sec^{-1} cm^{-1} at 20°C) (Goldstein et al. 1974).

In typical backpack ground sprays, droplet sizes are greater than 100 μ, and the distance from the spray nozzle to the ground is 3 feet or less. In mechanical sprays, raindrop nozzles might be used. These nozzles generate droplets that are usually greater than 400 μ, and the maximum distance above the ground is about 6 feet. In both cases, the sprays are directed downward.

Thus, the amount of time required for a 100 μ droplet to fall 3 feet (91.4 cm) is approximately 3.2 seconds,

$$91.4 \div (2.87 \cdot 10^5(0.01)^2). \quad \textbf{(32)}$$

The comparable time for a 400 μ droplet to fall 6 feet (182.8 cm) is approximately 0.4 seconds,

$$182.8 \div (2.87 \cdot 10^5(0.04)^2). \quad \textbf{(33)}$$

For most applications, the wind velocity will be no more than 5 miles/hour, which is equivalent to approximately 7.5 feet/second (1 mile/hour = 1.467 feet/second). Assuming a wind direction perpendicular to the line of application, 100 μ particles falling from 3 feet above the surface could drift as far as 23 feet (3 seconds · 7.5 feet/second). A raindrop or 400 μ particle applied at 6 feet above the surface could drift about 3 feet (0.4 seconds · 7.5 feet/second).

For backpack applications, wind speeds of up to 15 miles/hour are allowed in Forest Service programs. At this wind speed, a 100 μ droplet can drift as far as 68 feet (3 seconds · 15 · 1.5 feet/second). Smaller droplets will of course drift further, and the proportion of these particles in the spray as well as the wind speed will affect the proportion of the applied herbicide that drifts off-site.

4.5.3.1. Soil Contamination – Studies on the environmental fate of a chemical in soil are usually required as part of the registration process, and field monitoring studies are often available on concentrations of the chemical in soil at various times after known application rates. As in the assessment of pesticide concentrations in ambient water, monitoring data in soil are always used in some way: either directly as the basis of the exposure assessment or indirectly in the limited validation of any environmental modeling.

In general, the off-site movement of a pesticide will be governed by its binding to soil, its persistence in soil, as well as site-specific topographic, climatic, and hydrological conditions. Although generic exposure models like GLEAMS cannot reflect all of the potential site-specific and situational variability, they are useful for identifying conditions under which off-site transfer through runoff, sediment loss, or percolation is likely to be most important. In order to encompass a wide range of plausible conditions, three types of soil are typically modeled using GLEAMS: clay, loam, and sand.

Model parameters are selected to yield upper estimates of runoff from clay and central estimates of runoff from loam and sand. The physical conditions of the application are identical to those

used in the estimate of water contamination, typically the application of the pesticide along a 10 acre right-of-way that is 50 feet wide and 8712 feet long. Details about the input files for the model are provided in Attachment 1.

In very sandy and porous soils, percolation into the soil column rather than runoff usually predominates, regardless of the rainfall rate. Particularly in areas with a relatively shallow water table, percolation could be associated with the contamination of ambient water. As discussed in the following section, this could in turn impact nontarget vegetation. At the other extreme, clay soils are likely to be associated with the highest levels of runoff and/or sediment loss but relatively little percolation into the soil column. Loam is likely to be associated with less runoff, compared with clay but more runoff compared with sand. For any given soil type, the proportion of run-off is directly related to the amount of rainfall.

The potential exposure of off-site vegetation depends greatly on the deposition of the pesticide in the runoff. Under some conditions, runoff could disperse over a relatively large area and be of no toxicological consequence. In other cases, local topographical conditions might favor the concentration of the runoff from a large treated area into a relatively small off-site area. This type of situational variability cannot be modeled generically. For most risk assessments, it is assumed that the runoff is dispersed over an area identical to the application site. For example, if approximately 0.004 of the applied amount is estimated to runoff from clay after 2 inches of rainfall, the effective off-site application rate would be 0.004 lb/acre at an application rate of 1 lb/acre.

Another factor that impacts the consequences of runoff involves the occurrence of multiple rainfalls. Heavy rain on multiple days immediately following application will result in greater amounts of runoff and more evenly dispersed rainfalls. Conversely, light rainfall would cause the pesticide to percolate into the soil with lesser amounts on the soil surface subject to runoff. Again, this type of situational variability cannot be modeled generically but is addressed to the extent possible in the risk characterization.

4.5.3.2. Wind Erosion – Wind erosion is a major transport mechanism for soil (e.g., Winegardner 1996). Although no specific incidents of nontarget damage from wind erosion may be available in the literature for the compound under review, this mechanism is associated with the environmental transport of several herbicides (Buser 1990) and is usually modeled for herbicide risk assessments.

Numerous models were developed for wind erosion (e.g., Strek and Spaan 1997, Strek and Stein 1997) and the quantitative aspects of soil erosion by wind are extremely complex and site specific. Field studies conducted on agricultural sites found that wind erosion may account for annual soil losses ranging from 2 to 6.5 metric tons/ha (Allen and Fryrear 1977). The upper range reported by Allen and Fryrear (1977) is nearly the same as the rate of 2.2 tons/acre (5.4 tons/ha) recently reported by the USDA (1998). The temporal sequence of soil loss (i.e., the amount lost after a specific storm event involving high winds) depends heavily on soil characteristics as well as meteorological and topographical conditions.

To estimate the potential transport of a pesticide by wind erosion, average soil losses ranging from 1 to 10 tons/ha·year, with a typical value of 5 tons/ha·year, is used. The value of 5 tons/ha·year is equivalent to 500 g/m^2 [1 ton=1000 kg and 1 ha = 10,000 m^2] or 0.05 g/cm^2 [1m^2=10,000 cm^2]. Using a soil density of 2 g/cm^3, the depth of soil removed from the surface per year would be 0.025 cm[(0.05 g/cm^2)÷ (2 g/cm^3)]. The average amount per day would be about 0.00007 cm/day [0.025 cm per year ÷ 365 days/year]. This central estimate is based on a typical soil loss rate of 5 tons/ha·year. Since the range of plausible rates of annual soil loss is 1 to 10 tons/ha·year, the range of soil loss per day may be calculated as 0.00001 cm/day [0.00007÷5 = 0.000014] to 0.0001 cm/day [0.00007×2=0.00014] .

The amount of pesticide that might be transported by wind erosion depends on several factors, including the application method, the depth of incorporation into the soil, the persistence of the pesticide in the soil, the wind speed, and the topographical and surface conditions of the soil. Under desirable conditions, like relatively deep (10 cm) soil incorporation, low wind speed, and surface conditions that inhibit wind erosion, it is likely that wind transport is substantial or significant. Typically, this component of the exposure assessments assumes that the pesticide is incorporated into the top 1 cm of soil. Thus, daily soil losses expressed as a proportion of applied amount are 0.00007 with a range of 0.00001-0.001.

As with the deposition of the pesticide in runoff, the deposition of the pesticide in contaminated soil from wind erosion will vary substantially with local conditions. For the risk assessment, neither concentration nor dispersion is considered quantitatively. Nonetheless, these factors together with the general and substantial uncertainties in the exposure assessment are considered in the risk characterization.

4.5.3.3. Contaminated Irrigation Water – Unintended direct exposure of nontarget plant species may occur through the use of contaminated ambient water for irrigation. Moreover, some studies have noted effects on nontarget vegetation from the use of irrigation water contaminated with herbicides (e.g., Bhandary et al. 1997; Bovey and Scifres 1971; Gomez de Barreda et al. 1993; Watson et al. 1989).

The levels of exposure associated with this scenario depend on the concentration of the pesticide in the ambient water used for irrigation and the amount of irrigation water that is applied. The concentration of the pesticide in water is taken as the same concentration or range of concentrations that form the basis for the risk assessments in the human health risk assessment as well as the risk assessment for terrestrial and aquatic animals.

The amount of irrigation water that may be applied depends largely on the climate, soil type, topography, and plant species under cultivation. Thus, the selection of an irrigation rate is somewhat arbitrary. Typically, plants require from 0.1 to 0.3 inches of water per day (Delaware Cooperative Extension Service 1999). In the absence of a general approach to determining and expressing the variability of irrigation rates, the application of 1 inch of irrigation water is used in the risk assessment, which is somewhat higher than the maximum daily irrigation rate for sandy

soil (0.75 inches/day) and substantially higher than the maximum daily irrigation rate for clay (0.15 inches/day) (Delaware Cooperative Extension Service 1999).

4.6. Aquatic Species.

The potential for effects on aquatic species is based on estimated concentrations of the pesticide in water that are identical to those used above for irrigation water which are in turn identical to those used in the human health risk assessment. As in the assessments for the consumption of contaminated water, estimates of concentrations of the pesticide in water are based on acute spills (see section 4.3.4.1) and longer-term exposure to ambient water (see section 4.3.4.2).

5. DOSE RESPONSE ASSESSMENT

5.1. Overview

The purpose of the dose-response assessment is to describe the degree or severity of risk as a function of dose. In classical toxicology, dose-response assessments are usually expressed as linear or non-linear equations such as probit analysis and the multistage model, respectively. Using these methods, the prevalence or magnitude of a response can be estimated for any dose level. In regulatory toxicology, this approach is the exception rather than the rule.

Most dose-response assessments in regulatory toxicology, as discussed below, result in point estimates. Although some methods in regulatory toxicology use dose-response models, the regulatory value used is a point estimate. For example, U.S. EPA cancer risk assessments usually employ a form of the multistage model or some other linear dose-response relationship that provide measures of variability or error. The estimate used in setting exposure criteria, however, is typically a point estimate that is a single value rather than a range of values. The results of other commonly used dose-response assessments, such as RfDs, and RfCs, are point estimates of doses that are not believed to be associated with any adverse effect and that are not directly related to a dose-response model.

The practice of relying on point estimates in regulatory toxicology is grounded in the history of this discipline (Dourson and Stara 1983). From its inception, the focus of regulatory toxicology has been the development of criteria (i.e., levels of exposure that are defined as *safe)*. Consequently, the methods used in regulatory toxicology are conservative.

Consistent with the recommendation of NRC (1983) that various groups within the federal government adopt common risk assessment methodologies, standard dose-response assessments are generally based on reference values, like RfDs, derived by other government agencies. This approach avoids a duplication of effort, capitalizes on the expertise of other organizations, and decreases the size, complexity, and cost of risk assessments.

In cases for which these standard approaches yield evidence of potential risk, other statistical methods such as categorical regression may be used to characterize the likelihood and severity of the risk. Categorical regression analysis is used as a tool to supplement RfDs and analogous values. The method defines a relationship between responses that can be categorized according to exposure dose and duration (factors that may influence the response) and estimates the probability that a group of animals subjected to a given exposure will be classified into a particular category (Dourson et al. 1997, Durkin et al. 1992, Guth et al. 1997).

5.2. RfDs and Similar Values

Quantitative toxicological assessments involve deriving dose levels associated with a negligible or at least defined level of risk. These dose levels are generally referred to as reference values in this document. Specific examples of various reference values are provided in Table 3.

TABLE 3: Dose-response assessments conducted by the federal government and related organizations

Acronym	Definition	Methodology Source
	Systemic Toxicity (Noncarcinogenic)	
RfD	*Reference Dose:* Oral dose (mg/kg/day) not likely to be associated with adverse effects over lifetime exposure, in the general population, including sensitive subgroups.	U.S. EPA 1989c
RfD_s	*Subchronic Reference Dose:* Oral dose (mg/kg/day) not likely to be associated with adverse effects over a less-than-lifetime exposure, in the general population, including sensitive subgroups. [The exposure duration to which this value applies is not clearly defined.]	U.S. EPA 1990
RfD_{rt}	*Reference Dose for Reproductive Toxicity:* Oral dose (mg/kg/day) not likely to be associated with adverse developmental effects, in the general population, including sensitive subgroups. Used to evaluate effects after single exposure episode.	U.S. EPA 1989c
RfC	*Reference Concentration:* Concentration in air (mg/m^3) not likely to be associated with adverse effects over lifetime exposure, in the general population, including sensitive subgroups.	U.S. EPA 1990
MRL	*Minimal Risk Level:* A route-specific (oral or inhalation) and duration-specific estimate of an exposure level that is not likely to be associated with adverse effects in the general population, including sensitive subgroups.	ATSDR 1992
1-Day HA	*1-Day Health Advisory:* A drinking water concentration (mg/L) not likely to cause adverse effects in the general population, including sensitive subgroups, after 1-day of exposure.	U.S. EPA 1989c
10-Day HA	*10-Day Health Advisory:* A drinking water concentration (mg/L) not likely to cause adverse effects in the general population, including sensitive subgroups, over a 10-day exposure period.	U.S. EPA 1989c
TLV	*Threshold Limit Value:* An air concentration (mg/m^3) not likely to cause adverse effects in exposed workers, over a normal period of work.	ACGIH 1992
	Carcinogenicity	
Slope Factor [q_1*]	*Cancer Potency Parameter:* A model-dependent measure of cancer potency $(mg/kg\text{-}day)^{-1}$ over lifetime exposure. [Often expressed as a q_1^* which is the upper 95% confidence limit of the first dose coefficient (q_1) from the multistage model.]	U.S. EPA 1987
Unit $Risk_{air}$	*Unit Risk for Inhalation Exposures:* The risk associated with a continuous lifetime exposure to an air concentration expressed $(mg/m^3)^{-1}$ or $(\mu g/m^3)^{-1}$.	U.S. EPA 1987
Unit $Risk_{water}$	*Unit Risk for Water Consumption:* The risk associated with a continuous lifetime exposure to a drinking water concentration expressed $(mg/L)^{-1}$ or $(\mu g/L)^{-1}$.	U.S. EPA 1987

Reference values fall into the broad categories of non-carcinogenic and carcinogenic effects. Consistent with the approaches taken by other government agencies, non-carcinogenic effects are assumed to have population thresholds (i.e., levels below which no adverse effects are expected for a given exposure route and duration). Reference values for non-carcinogenic effects are intended to be estimates of exposure levels at or below the threshold level.

The basic equation for deriving a reference value can be expressed as:

$$RRV = \frac{Th_{exp}}{\prod_{i=1}^{n} UF} \quad \textbf{(34)}$$

where:

Th_{exp} = *experimental threshold dose in units appropriate for the route of exposure*

UF_i = *one of the n numberof uncertainty factors*

The methods proposed for deriving reference values are similar to the methods used by U.S. EPA to derive RfDs and RfCs and by ATSDR to derive MRLs. Although the computations are simple, the toxicological judgments involved in deriving as reference value may be complex.

In assessing dose-severity relationships, the emphasis is on distinguishing the range of doses over which adverse effects were observed from the range of doses over which no adverse effects were observed. For oral reference values, as discussed above, units of dose usually are expressed as mg/kg/day, although different dose metameters may be used to reflect sensitivities among species. For inhalation reference values, the data are expressed as mg/m^3. Data on certain species may be censored from the analysis because they are atypical and do not serve as good animal models for effects in humans. An attempt is then made to determine the most sensitive toxicological endpoint. Usually, this is accomplished by identifying a toxicologically relevant series of effects that increase in severity as dose increases.

To derive the reference value, the experimental threshold is divided by the product of a series of uncertainty factors intended to account for differences between the experimental exposure and the conditions for which the reference value is derived. The uncertainty factors used by the U.S. EPA and ATSDR are presented in Table 4.

TABLE 4: Uncertainty factors used to derive reference values*

Factor	Definitions Basis	ATSDR	U.S. EPA
Interhuman	Use a 10-fold factor when extrapolating from valid experimental results using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among humans.	yes	yes
Experimental to human	Use a 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies on human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to humans. If adjustments to the dose metameter are adequate, this factor can be reduced or eliminated.	yes	yes
LOAEL to NOAEL	Generally use a 10-fold factor when deriving a reference value, RfD, or MRL from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs.	yes - UF always 10	yes -UF varies
Subchronic to chronic	Generally use a 10-fold factor when deriving a reference value or RfD from less than chronic results on experimental animals or humans. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs.	no	yes
Incomplete database	Generally use a 10-fold factor when deriving a reference value or RfD from valid results in experimental animals when the data are "incomplete." This factor is intended to account for the inability of any study to address all possible adverse outcomes.	no	yes
Modifying factor	Use professional judgment to determine an additional uncertainty factor that is >1 and ≤10 for deriving a reference value or RfD. The magnitude of the MF depends upon the professional assessment of the scientific uncertainties of the study and database not explicitly treated above. The default for the MF is 1	no	yes

*Source: ATSDR 1992

Generally, the risk assessment will use U.S. EPA RfDs as indices of 'acceptable' exposure. U.S. EPA RfDs generally provide a level of analysis, review, and resources that far exceed those that are or can be conducted in the support of most Forest Service risk assessments. In addition, it is desirable for different agencies and organizations within the federal government to use concordant risk assessment values.

Nonetheless, there are cases in which different RfDs for the same chemical are derived within the U.S. EPA and other cases in which the nature of the available data suggest the need to use alternative values to capture endpoint specific toxicities, dose-duration relationships, or dose-severity relationships as adequately as possible. Sometimes, the alternative values are less

conservative; at other times, the alternative values are more conservative. In either case, the purpose of deviating from the U.S. EPA RfDs is to characterize risk as clearly and thoroughly as possible. To avoid confusion, the acronym *RfD* is applied only to U.S. EPA values. Alternate values derived for a specific risk assessment are typically referred to as *reference values* with no abbreviation.

TLVs might serve as the basis for inhalation reference values if more appropriate values are not available, and might be adopted without modification as inhalation reference values for occupational exposure. For exposure scenarios involving the general public, inhalation RfCs will be adopted without modification as inhalation reference values for chronic exposure. When RfCs are not available, the TLV may be modified to account for the duration of daily exposure and sensitive subgroups within the general population. TLVs are designed to protect workers in occupational exposure settings during the work day (i.e., 8 hours/day). Inhalation reference values for the general public must be protective for the full 24-hour day. Consequently, the TLV will be reduced by one third (8 hours/24 hours) when applied to the general public. This adjustment is made with the assumption that exposures are equitoxic as long as the product of concentration and duration is constant (e.g., $c_1 \cdot d_1 = c_2 \cdot d_2$). This is an expression of Haber's law (Kennedy 1989) which is a reasonable approximation over limited ranges of concentration and duration. TLVs do not explicitly consider sensitive subgroups; therefore, the TLV will be adjusted for continuous exposure and further decreased by a factor of 10, according to U.S. EPA procedure, to account for sensitive subgroups.

The risk assessment may derive acute, subchronic, and chronic reference values. The definitions of acute, subchronic, and chronic exposure are vague, and to some extent, chemical specific. If 1-day, 10-day, or longer-term health advisories (HAs) are available (see Table 3), these values may be used to derive acute or subchronic reference values.

5.3. Cancer Potency.

For carcinogenic effects, cancer slope factors are derived, as described in U.S. EPA /ORD (1996) and U.S. EPA (1987). A major limitation in the use of cancer slope factors in risk assessments is that exposure scenarios often involve brief periods of time relative to the human life span. Most studies that serve as the basis for cancer potency factors are conducted over periods of time that approximate the lifetime of the animal. For short-term exposures, the U.S. EPA guidelines for carcinogenic risk assessment (U.S. EPA 1987) recommend that the effect of a short-term exposure on lifetime risk be calculated as:

$$R = \frac{SL_{(mg/kg/day)^{-1}} \cdot Dur_{st(days)} \cdot Dose_{st(mg/kg/day)}}{Life\ span_{(days)}}$$

where:

$$SL = slope\ (mg/kg/day)^{-1}$$
$$Dur_{st} = duration\ of\ study\ (days)$$
$$Dose_{st} = dose\ used\ in\ study\ (mg/kg/day)$$
$$Life\ span = life\ span\ of\ animal\ (days)$$

(35)

A problem with this approach, as discussed in U.S. EPA (1991a,b), is that lifetime risk for early stage carcinogens may be underestimated. Crump and Howe (1984) propose an approach for appropriately adjusting cancer risk from short-term exposure, but the algorithms have not been implemented. NRC (1986) proposes that the risk level be multiplied by 2.8 to account for the effects of early stage carcinogenesis, but the rationale for this recommendation is unclear.

5.4. Categorical Regression

Categorical regression analysis is a statistical tool that can be used in risk assessments to quantitatively estimate the probability of observing effects of varying severities. The major criteria for employing this method is that estimated levels of exposure exceed more easily understood criteria like RfD or NOAEL values and that the available data support a more detailed dose-response assessment in order to clarify or effectively capture the risk characterization. Although categorical regression is a well-developed method in statistics (McCullagh 1980), it is somewhat complex and used only sparingly in Forest Service risk assessments. Nonetheless, it is a sufficiently important tool that a discussion of the basic elements of this method is justified.

Many chemical and physical hazards may be expressed as quantal (i.e., all or none) responses. The most common response of this type is mortality. In such cases, the proportion (P) of animals responding and the doses at which these responses occur are usually fit to a dose response model. One model commonly used in risk assessment is the multistage model:

$$P = 1 - e^{q_0 + q_1 d + q_2 d^2 \ldots q_n d^n} \qquad \textbf{(36)}$$

where d is the dose, the qs are potency parameters, and n is the number of stages considered in the model (Crump and Howe 1984).

In some cases, population thresholds (i.e., dose below which no effect will occur) may be plausible or at least assumed. The existence of population thresholds is the basic premise behind the derivation of RfDs. In such cases, the population threshold (d_0) may be incorporated explicitly into the dose/response model:

$$P = 1 - e^{q_0 + q_1(d-d_0) + q_2(d-d_0)^2 \ldots q_n(d-d_0)^n} \quad \textbf{(37)}$$

where any negative value of d-d_0 is treated as zero.

Many other dose response models, such as the logit and probit, are commonly used in risk assessment. Both of these have the general form:

$$\Phi = \alpha + \beta \cdot d \quad \textbf{(38)}$$

where Φ is a transformation of the proportion responding (probits or logits), *d* is dose or a transformation of dose such as log dose, β is a slope or potency parameter (i.e., the relationship of dose to increasing response), and α is a measure of the background response (the response when dose is zero). In the probit model, the underlying assumption is that the distribution of individual tolerances in a population is normally distributed with respect to dose or some transformation of dose. Thus, a probit is a normal equivalent deviate or essentially a standard deviation from a central response of 50% (Finney 1971). The logistic function is based on the assumption that the proportion of responders, *p*, in the above equation is expressed as a logit, which is the logarithm of the ratio of the proportion of responders to the proportion of non-responders, often abbreviated as the *log(p/q)*, where *q* is 1-*p*.

Either the probit or logit models can be modified to consider additional explanatory variables (i.e., factors that influence the response) like duration of exposure expressed in some unit of time (t):

$$\Phi = \alpha + \beta_1 \cdot d + \beta_2 \cdot t \quad \textbf{(39)}$$

Although quantal dose-response models are useful for many kinds of effects, they are not specifically intended to describe an array of unrelated effects of differing severity. For data of that kind, Hertzberg and Miller (1985) and Hertzberg (1989) propose using categorical regression (McCullagh1980). In addition to incorporating different endpoints and levels of severity, the method accommodates both quantal and continuous data. With categorical regression, it is also possible to incorporate additional explanatory (independent) variables, like exposure duration. Thus, this method can be used to estimate risk under various exposure scenarios.

Categorical regression assumes that each effect level can be associated with a distribution (e.g., normal or logistic) and that the shape of the distributions of the various severity levels are identical but shift to the right as severity and dose increase, as illustrated in Figure 4. Thus, at any given dose, the probability of observing an effect at a particular severity level can be estimated.

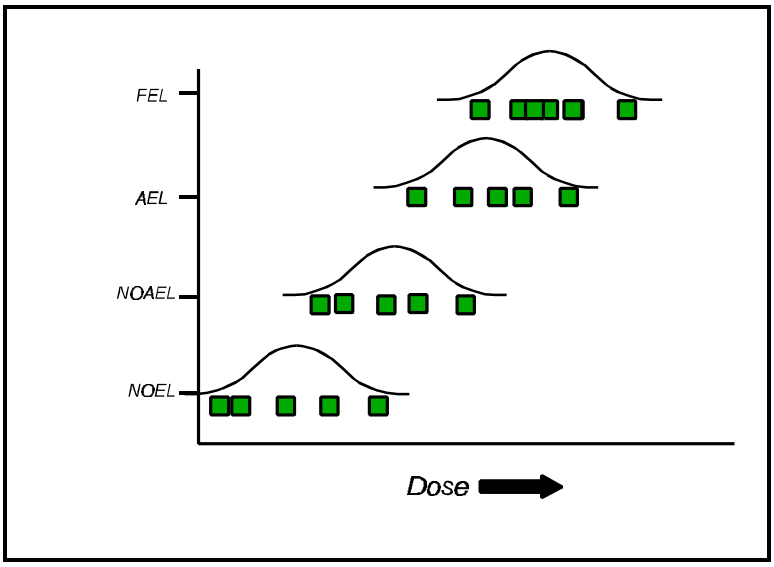

Figure 3: Conceptual overview of categorical regression.

Categorical regressions are conducted using the logistic model as a *link function*. That is, a logistic distribution is used to describe quantitatively the variability of NOELs, NOAELs, AELs, and FELs illustrated in Figure 3. This approach is similar to running simultaneous logistic regressions on severity categories:

$$\Phi_i = \log(p/q) = \alpha_i \beta \cdot \log_{10}(d) \quad \textbf{(40)}$$

where $_i$ is the probability of dose d being associated with the i^{th} severity level. Thus, for the four severity classifications (see Figure 4), three intercepts (αs) are estimated. These intercepts are associated with the boundary regions between the four severity levels and are referred to as cutpoint parameters. These, in turn, lead to three estimates of the cumulative probabilities associated with each severity class:

$$\hat{p}_1 = \frac{\exp(\alpha_1 + \beta \log d)}{1 + \exp(\alpha_1 + \beta \log d)} \quad \textbf{(41)}$$

$$\hat{p}_2 = \frac{\exp(\alpha_2 + \beta \log d)}{1 + \exp(\alpha_2 + \beta \log d)} \quad \textbf{(42)}$$

$$\hat{p}_3 = \frac{\exp(\alpha_3 + \beta \log d)}{1 + \exp(\alpha_3 + \beta \log d)} \quad \textbf{(43)}$$

An example of this type of analysis is given in Figure 5 using a β of -3 and α_1, α_2, and α_3 of 4, 6, and 8, respectively. In this figure, the left most (solid) line, labeled P_{NOEL} is the cumulative

probability of observing a NOEL. The center line is the probability of observing a NOEL or NOAEL, and the right most line is the probability of observing a NOEL, NOAEL, or AEL.

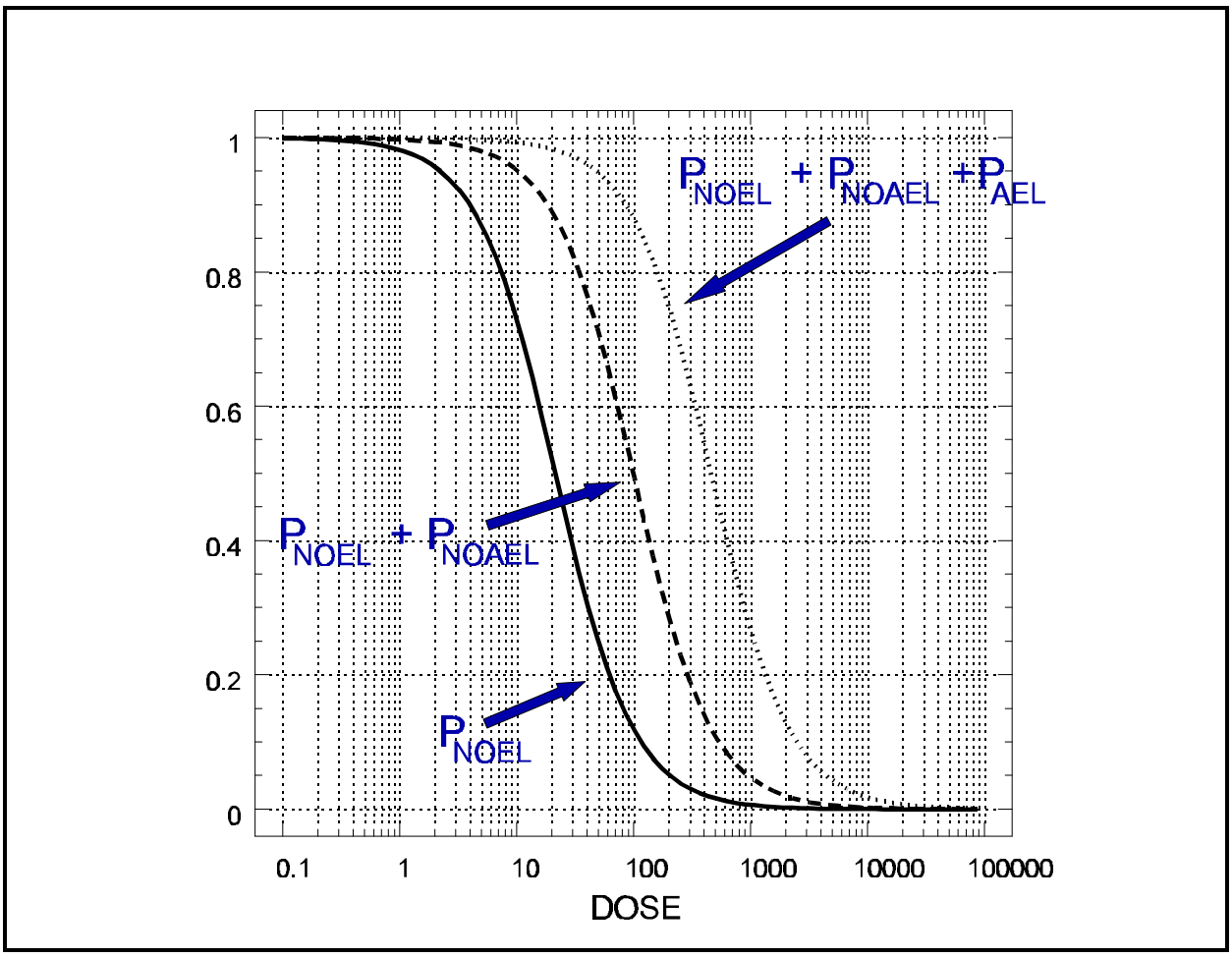

Figure 4: Cumulative probabilities for effects of different severity for example categorical regression.

As illustrated in Figure 4, the probability of observing effects of lesser severity decreases as the dose increases. For example, taking the left most curve in Figure 5, the probability of observing a NOEL decreases as dose increases because of the increasing likelihood of observing a NOAEL, AEL, or FEL. Similarly, taking the right most curve in Figure 5, probability of observing a NOEL, NOAEL, AEL decreases as dose increases because of the increasing likelihood of observing a FEL. This inverse relationship is dictated by the negative value of the slope, β, which in this example is -3. Sometimes, positive values for β are estimated, particularly when time is used as an explanatory variable. This approach indicates that the greater the dose or duration of exposure the less severe the response is expected to be. In most cases, this relationship is specious and may be related to additional experimental details in the data that need to be considered.

Most individuals involved in the use of risk assessments are accustomed to viewing response as positively related to dose. In other words, the response line or surface goes up as dose increases. As illustrated in Figure 5, this can be achieved by taking the expression $1-p_i$, where p_i is the result of Equations 41, 42, or 43. For example, the left most line in Figure 4 represents the probability of observing a NOEL (p) and the left most line in Figure 5 is the probability of observing an effect more severe than a NOEL and is calculated as 1-p. Similarly, the center line in Figure 5 is the probability of observing an effect more severe than a NOAEL (i.e., an AEL or FEL). The last line is the probability of observing an effect more severe than an AEL. Using the four-category classification scheme summarized in Table 1, this is equivalent to the probability of observing a FEL.

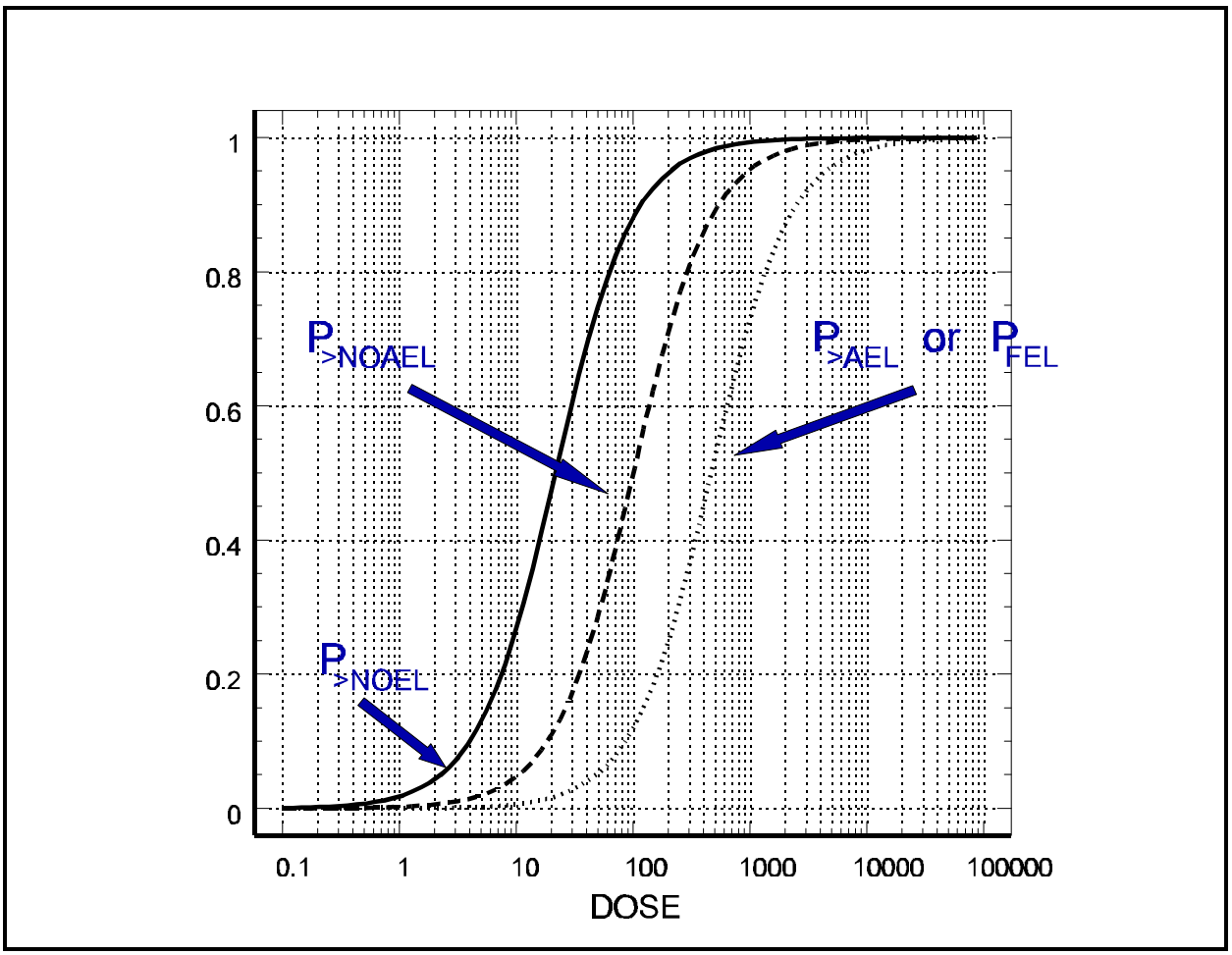

Figure 5: The example categorical regression in which cumulative probabilities are positively related to dose.

The probabilities of observing an effect of a given severity can be calculated using the following equations:

$$P_{NOAEL} = \hat{p}_1 \quad \textbf{(44)}$$

$$P_{NOAEL} = \hat{p}_2 - \hat{p}_1 \quad \textbf{(45)}$$

$$P_{AEL} = \hat{p}_3 - \hat{p}_2 \quad \textbf{(46)}$$

$$P_{FEL} = 1 - \hat{p}_3 \quad \textbf{(47)}$$

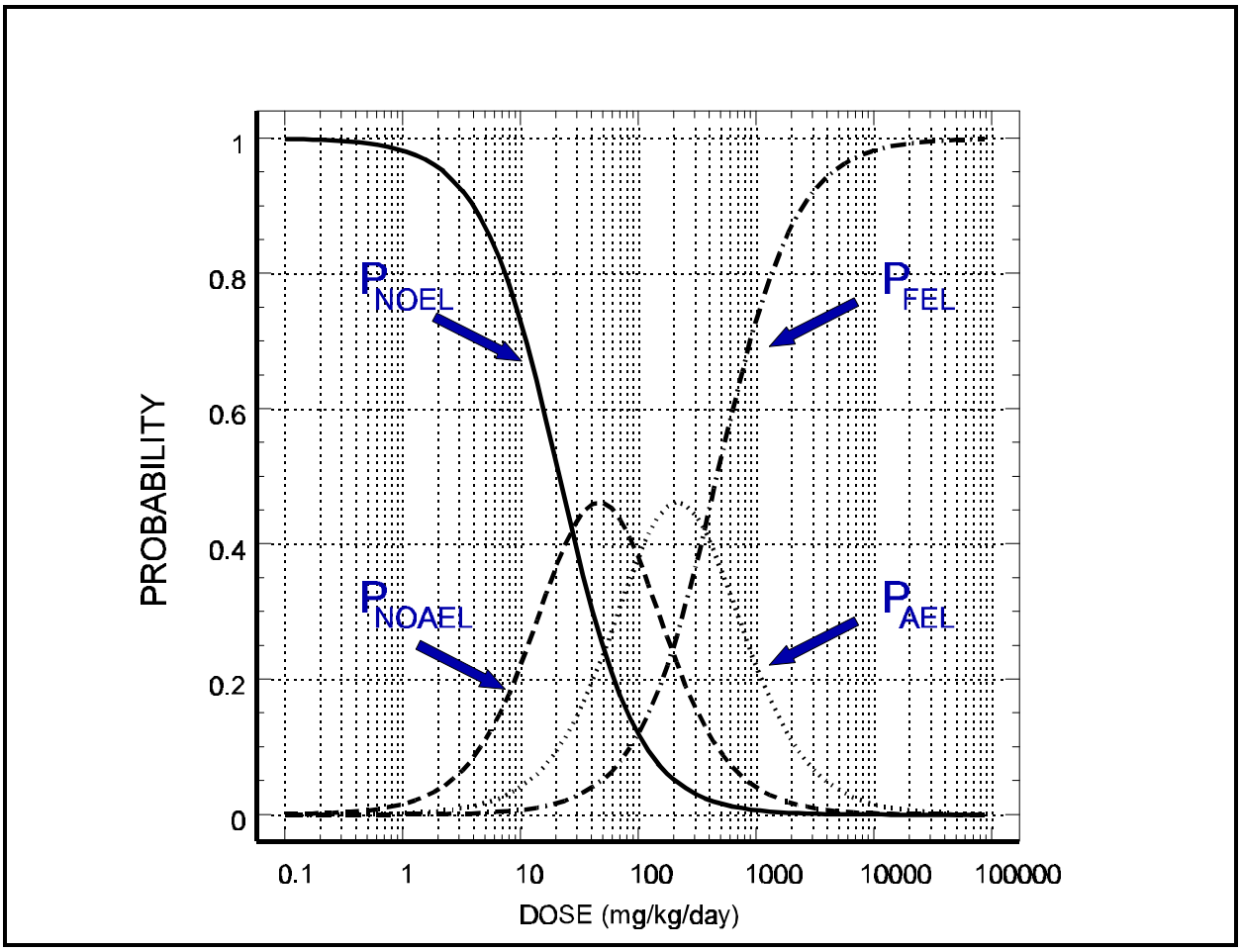

Figure 6: Probabilities of each severity level for the example categorical regression.

These probabilities are illustrated in Figure 6. The probability of observing a NOEL or FEL are both sigmoidal. The line for the NOEL is identical to the left most line in Figure 4 and the line for the FEL is identical to the right most line in Figure 5. These severity levels are essentially

unbounded: as dose increases towards infinity, the probability of observing a NOEL progressively decreases and the probability of observing a FEL progressively increases. For these severity levels, the probability of observing the effect will increase initially with increasing dose as, for example, NOAELs rather than NOELs are observed. As dose increases further, however, the probability of observing a NOAEL will decrease as the probability of observing an AEL or FEL increases. Similarly, the probability of observing an AEL will decrease as the probability of observing a FEL increases. Thus, in the four-category scheme, both NOAELs and AELs are bounded severity levels: NOAELs are bounded by NOELs and AELs and AELs are bounded by NOAELs and FELs.

The interpretation of the risk estimate from categorical regression depends on the unit of input to the categorical regression model. For the data sets presented in most analyses, the available toxicity data provide information at the dose group level but not at the individual animal level. When adequate data are available regarding the incidence of response within a dose group, the probability of observing a particular level of response (e.g., an adverse effect level) for an individual animal given that dose may be estimated. When the entire dose group is classified into one of the four severity categories, as in the current analysis, the method estimates the probability that a new animal group exposed to a given dose will be classified into a particular severity level. Only the latter type of estimate is used in the current analysis; however, when available, individual animal data regarding the incidence of a particular effect are compared to the categorical regression on severity.

5.5. Ecological Effects

In most respects, dose-response assessments for ecological effects are conceptually similar to the methods employed in the human health risk assessments with one major exception. Human health risk assessments focus on protecting the individual. This is why uncertainty factors, and sometimes very large uncertainty factors, are used to derive RfD values and why cancer risk is estimated using very conservative assumptions. In ecological risk assessment, the focus is on the population or community rather than the individual. Thus, the use of uncertainty factors is less common and the general methods for dose-response assessment are less conservative.

For terrestrial mammals, the dose-response assessment generally is based on the same data used to derive the RfD in the human health risk assessment: a NOAEL from a chronic exposure study. The data on other terrestrial animals, both birds and invertebrates, are often not as detailed as the available information on experimental mammals. Fewer toxicological endpoints are examined, and lifetime or chronic studies are seldom available at least for vertebrates.

For some terrestrial plants as well as some aquatic species, sensitive life-stage studies are often available. Such studies include egg-and-fry studies in fish, life-cycle toxicity studies in daphnia, as well as seed germination and growth studies in plants, all of which are required by the U.S. EPA for the registration of herbicides. The studies are obtained and assessed following the same criteria applied to studies for the human health risk assessment. The principal difference is that NOEL, NOEC, or LD or LC values are used directly rather than RfD values that involve the application of uncertainty factors.

Nonetheless, dose-response assessments can be complicated. As in the human health dose-response assessment, the nature of the available data as well as the potential risk may dictate the use of relatively complex dose-response analyses like categorical regression.

6. RISK CHARACTERIZATION

Risk characterization is the process of comparing the exposure assessment with the dose-response assessment to express the level of concern regarding a specific exposure scenario or set of scenarios (NRC 1983).

For systemic toxic effects, risk characterizations have been presented typically as either a Margin of Safety (MOS) or a Hazard Quotient (HQ). SERA generally prefers the HQ approach although the two methods are closely related.

A *margin of safety* is simply an experimental exposure level in animals, usually one that is not associated with adverse effects (i.e., *NOEL* or *NOAEL*), divided by an estimate of exposure:

$$MOS = \frac{NOAEL}{E_i} \quad \textbf{(48)}$$

Thus, as the exposure level decreases, the margin of safety increases.

A *hazard quotient* is the ratio of a projected level of exposure (E_i) divided by some index of an acceptable exposure or an exposure associated with a defined risk, such as an RfD. The RfD, in turn, is an experimental exposure level (i.e., *NOEL* or *NOAEL*) divided by an uncertainty factor (*UF*):

$$HQ = \frac{E_i}{NOAEL \div UF} \quad \textbf{(49)}$$

Consequently, as the level of projected human exposure decreases, the hazard quotient decreases.

The obvious and trivial difference between these two methods is that they are inversely related to each other. The significant difference between the *margin of safety* and the *hazard quotient* approach, however, is that the *hazard quotient* method is based on an explicit uncertainty factor, dependent on the quality of the available data.

Each of the above two equations can be rearranged in terms of the *NOAEL* as:

$$NOAEL = MOS \cdot E_i \quad \textbf{(50)}$$

$$NOAEL = \frac{E_i}{HQ \div UF} \quad \textbf{(51)}$$

Setting these two equations equal to each other:

$$MOS \cdot E_i = \frac{E_i}{HQ \div UF} \quad (52)$$

Eliminating E_i from both sides, the above equation simplifies to:

$$MOS = \frac{1}{HQ \div UF} = UF \div HQ \quad (53)$$

Thus, for a given exposure, the margin of safety is equal to the uncertainty factor used to derive the RfD divided by the hazard quotient. Equivalently, the hazard quotient is equal to uncertainty factor used to derive the RfD divided by the margin of safety:

$$HQ = UF \div MOS \quad (54)$$

The only time that these two methods will lead to differing interpretations of risk is when the acceptable margin of safety is set to a value other than the uncertainty factor used to derive the RfD or when the assessments use different NOAELs. Otherwise, the two methods are equivalent.

RfDs are intended to be conservative estimates that incorporate a substantial margin between a dose that does not cause adverse effects and doses that cause adverse effects. This difference is referred to as a *'margin of protection'*. If the margin of protection is substantial, adverse effects may not be observed or even induced when the hazard index is greater than unity (i.e., exposure exceeds the *presumably safe* level). In order to assess the plausibility and nature of inducing or observing adverse effects, the relationship of exposed dose to the severity of effects is further considered, either qualitatively or quantitatively.

As with the dose-response assessments, the distinction between AELs and FELs is central to characterizing risk. When applied to risk characterizations, however, the distinction between AELs and FELs may be subject to misinterpretation. Some and perhaps most of the exposure scenarios derived in a risk assessment may be associated with a low likelihood of a FEL based on the categorical regression analyses. In other words, no overt toxic effects are anticipated. This is not to be interpreted as suggesting that all of the exposure scenarios are acceptable or at least equally acceptable. Hazard indices may be exceeded by a substantial margin and may be in the region in which AELs are plausible. In such cases, humans subject to such exposures would probably be asymptomatic. Nonetheless, such individuals might experience subclinical changes that, if detected, would be regarded as justification for measures to reduce or eliminate the possibility of further exposure.

For carcinogenic effects, the risk associated with a given scenario and a single route of exposure can be expressed as:

$$P_{life\ span} = SL \cdot D_{Lifetime\ Average} \quad \textbf{(55)}$$

where:

P = *probability of observing a carcinogenic response from a single route of exposure*

SL = *slope factor in units specific to the route of exposure*

D = *lifetime average daily dose in units specific to the route of exposure*

If more than one route of exposure is associated with a carcinogenic response, the risk from all routes can be added:

$$P_{total} = P_{oral} + P_{inhalation} + P_{dermal} \quad \textbf{(56)}$$

A major source of uncertainty is introduced when the exposure duration for the scenario is substantially less than lifetime. This uncertainty cannot be quantified, but it is likely to result in underestimating risk if the compound affects early stages of the carcinogenic process.

In addition to these numerical expressions, the risk characterization section, more than any other part of the risk assessment, must explain the conclusions of the risk assessment in plain language. How this is done, specifically, depends largely on the nature of the perceived risk or the apparent lack of risk.

In some cases, a risk assessment may find no objective suggestion of an adverse effect based on the currently available data. In such cases, the risk characterization must clearly make the point that: ***Absolute safety cannot be proven and the absence of risk can never be demonstrated***. No chemical is studied for all possible effects and the use of data from laboratory animals to estimate hazard or the lack of hazard to humans of other species is an uncertain process. Thus, prudence dictates that normal and reasonable care should be taken in the handling of any chemical. In other instances, risks may be apparent and this too must be clearly stated both quantitatively and qualitatively.

The risk characterization for ecological risk assessments is mathematically similar to the HQ approach discussed above for the human health risk assessment. Conceptually, however, there is one substantial difference: the level of tolerable risk. In human health risk assessments, the fundamental concern is the individual. RfD values and other similar estimates are intended to represent population thresholds. Thus, if the level of exposure is below the RfD - i.e., the HQ is less than unity - no effects are anticipated in any individuals. In ecological risk assessment, concern is with populations of animals rather than individual animals. Thus, no attempt is made to

derive RfD-like estimates with the application of uncertainty factors. Instead, the level of exposure is typically divided by either a NOAEL, AEL, LD_{50}, LD_{25} or some other similar value. The specific value that is selected will depend on the nature of the available information as well as the species or groups of species under consideration and the specific rationale must be articulated on a case by case basis..

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