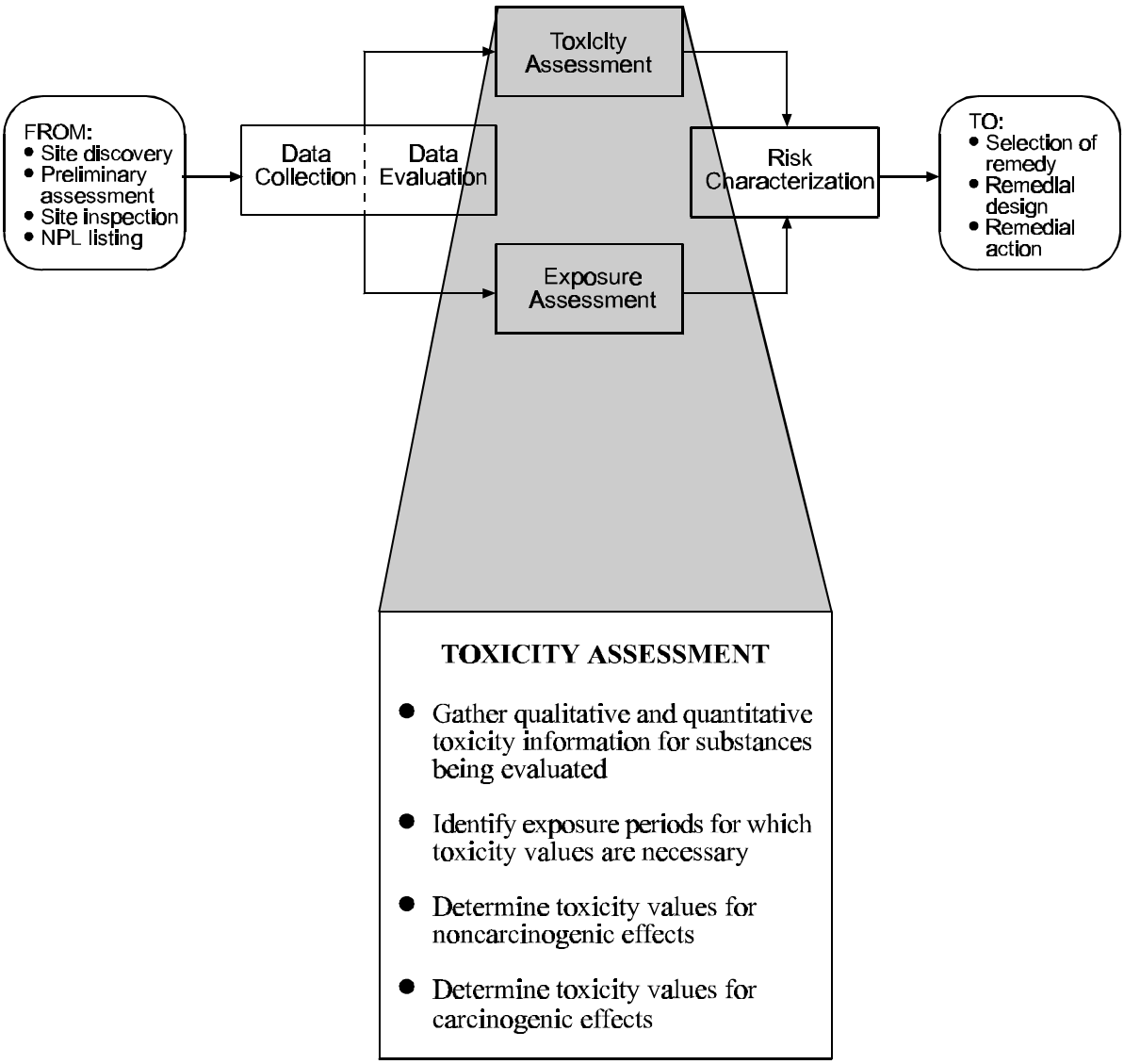
CHAPTER 7
TOXICITY ASSESSMENT



CHAPTER 7

TOXICITY ASSESSMENT

The purpose of the toxicity assessment is to weigh available evidence regarding the potential for particular contaminants to cause adverse effects in exposed individuals and to provide, where possible, an estimate of the relationship between the extent of exposure to a contaminant and the increased likelihood and/or severity of adverse effects.

Toxicity assessment for contaminants found at Superfund sites is generally accomplished in two steps: hazard identification and dose-response assessment. These two steps were first discussed in the National Academy of Sciences' publication entitled *Risk Assessment in the Federal Government - Managing the Process* and more recently in EPA's *Guidelines for Carcinogen Risk Assessment* (NAS 1983, EPA 1986). The first step, hazard identification, is the process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans. Hazard identification involves characterizing the nature and strength of the evidence of causation. The second step, dose-response evaluation, is the process of quantitatively evaluating the toxicity information and characterizing the relationship between the dose of the contaminant administered or received and the incidence of adverse health effects in the exposed population. From this quantitative dose-response relationship, toxicity values (e.g., reference doses and slope factors) are derived that can be used to estimate the incidence or potential for adverse effects as a function of human exposure to the agent. These toxicity values are used in the risk characterization step to estimate the likelihood of adverse effects occurring in humans at different exposure levels.

Toxicity assessment is an integral part of the overall Superfund site risk assessment. Although toxicity information is critical to the risk assessment, the amount of new toxicological evaluation of primary data required to complete this step is limited in most cases. EPA has performed the toxicity assessment step for numerous chemicals and has made available the resulting toxicity information and toxicity values, which have undergone extensive peer review. At some sites, however, there will be significant data analysis and interpretation issues that should be addressed by an experienced toxicologist. This chapter provides step-by-step guidance for locating EPA toxicity assessments and accompanying values, and advises how to determine which values are most appropriate when multiple values exist. Prior to this procedural discussion, background

ACRONYMS FOR CHAPTER 7

ADI = Acceptable Daily Intake
AIC = Acceptable Intake for Chronic Exposure
AIS = Acceptable Intake for Subchronic Exposure
CRAVE = Carcinogen Risk Assessment Verification Endeavor
ECAO = Environmental Criteria and Assessment Office
HAD = Health Assessment Document
HEA = Health Effects Assessment
HEAST = Health Effects Assessment Summary Tables
HEED = Health and Environmental Effects Document
HEEP = Health and Environmental Effects Profile
IRIS = Integrated Risk Information System
LOAEL = Lowest-Observed-Adverse-Effect-Level
NOAEL = No-Observed-Adverse-Effect-Level
NOEL = No-Observed-Effect-Level
RfD = Reference Dose (when used without other modifiers, RfD generally refers to chronic reference dose)
RfD_{dt} = Developmental Reference Dose
RfD_s = Subchronic Reference Dose

DEFINITIONS FOR CHAPTER 7

Acceptable Daily Intake (ADI). An estimate similar in concept to the RfD, but derived using a less strictly defined methodology. RfDs have replaced ADIs as the Agency's preferred values for use in evaluating potential noncarcinogenic health effects resulting from exposure to a chemical.

Acceptable Intake for Chronic Exposure (AIC). An estimate similar in concept to the RfD, but derived using a less strictly defined methodology. Chronic RfDs have replaced AICs as the Agency's preferred values for use in evaluating potential noncarcinogenic health effects resulting from chronic exposure to a chemical.

Acceptable Intake for Subchronic Exposure (AIS). An estimate similar in concept to the subchronic RfD, but derived using a less strictly defined methodology. Subchronic RfDs have replaced AISs as the Agency's preferred values for use in evaluating potential noncarcinogenic health effects resulting from subchronic exposure to a chemical.

Chronic Reference Dose (RfD). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Chronic RfDs are specifically developed to be protective for long-term exposure to a compound (as a Superfund program guideline, seven years to lifetime).

Developmental Reference Dose (RfD_{dt}). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of an exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of developmental effects. Developmental RfDs are used to evaluate the effects of a single exposure event.

Dose-response Evaluation. The process of quantitatively evaluating toxicity information and characterizing the relationship between the dose of a contaminant administered or received and the incidence of adverse health effects in the exposed population. From the quantitative dose-response relationship, toxicity values are derived that are used in the risk characterization step to estimate the likelihood of adverse effects occurring in humans at different exposure levels.

Hazard Identification. The process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans.

Integrated Risk Information System (IRIS). An EPA data base containing verified RfDs and slope factors and up-to-date health risk and EPA regulatory information for numerous chemicals. IRIS is EPA's preferred source for toxicity information for Superfund.

Lowest-Observed-Adverse-Effect-Level (LOAEL). In dose-response experiments, the lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

No-Observed-Adverse-Effect-Level (NOAEL). In dose-response experiments, an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered to be adverse, nor precursors to specific adverse effects. In an experiment with more than one NOAEL, the regulatory focus is primarily on the highest one, leading to the common usage of the term NOAEL to mean the highest exposure level without adverse effect.

No-Observed-Effect-Level (NOEL). In dose-response experiments, an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.

Reference Dose (RfD). The Agency's preferred toxicity value for evaluating noncarcinogenic effects resulting from exposures at Superfund sites. See specific entries for chronic RfD, subchronic RfD, and developmental RfD. The acronym RfD, when used without other modifiers, either refers generically to all types of RfDs or specifically to chronic RfDs; it never refers specifically to subchronic or developmental RfDs.

DEFINITIONS FOR CHAPTER 7
(continued)

Slope Factor. A plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used to estimate an upper-bound probability of an individual developing cancer as a result of a lifetime of exposure to a particular level of a potential carcinogen.

Subchronic Reference Dose (RfD_s). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a portion of a lifetime (as a Superfund program guideline, two weeks to seven years).

Toxicity Value. A numerical expression of a substance's dose-response relationship that is used in risk assessments. The most common toxicity values used in Superfund program risk assessments are reference doses (for noncarcinogenic effects) and slope factors (for carcinogenic effects).

Weight of Evidence Classification. An EPA classification system for characterizing the extent to which the available data indicate that an agent is a human carcinogen. Recently, EPA has developed weight-of-evidence classification systems for some other kinds of toxic effects, such as developmental effects.

information regarding EPA's methods for toxicity assessment is provided to assist the risk assessor in understanding the basis of the toxicity values and the limitations of their use. The steps of the toxicity assessment are illustrated in Exhibit 7-1.

Derivation and interpretation of toxicity values requires toxicological expertise and should not be undertaken by those without training and experience. Detailed guidance for deriving toxicity values is beyond the scope of this document. For those persons interested in obtaining additional information about EPA's methods for toxicity assessment, references to appropriate guidance documents are given throughout this chapter.

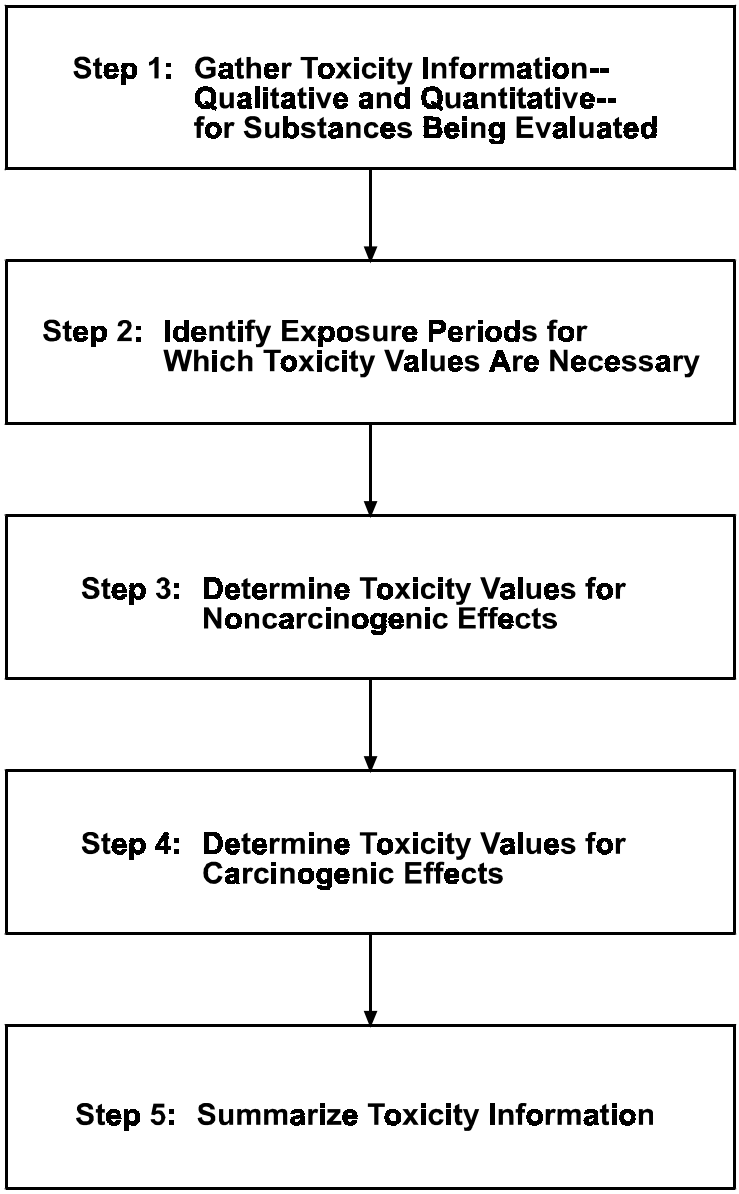
7.1 TYPES OF TOXICOLOGICAL INFORMATION CONSIDERED IN TOXICITY ASSESSMENT

This section summarizes information from several EPA documents (especially EPA 1989a, f) on the basic types of data used in toxicity assessment. As part of the hazard identification step of the toxicity assessment, EPA gathers evidence from a variety of sources regarding the potential for a contaminant to cause adverse health effects (carcinogenic and noncarcinogenic) in humans. These sources may include controlled epidemiologic investigations, clinical studies, and experimental animal studies. Supporting information may be obtained from sources such as *in vitro* test results and comparisons of structure-activity relationships.

7.1.1 HUMAN DATA

Well-conducted epidemiologic studies that show a positive association between an agent and a disease are accepted as the most convincing evidence about human risk. At present, however, human data adequate to serve as the sole basis of a dose-response assessment are available for only a few chemicals. Humans are generally exposed in the workplace or by accident, and because these types of exposures are not intentional, the circumstances of the exposures (concentration and time) may not be well known. Often the incidence of effects is low, the number of exposed individuals is small, the latent period between exposure and disease is long, and exposures are to mixed and multiple substances. Exposed populations may be heterogeneous, varying in age, sex, genetic constitution, diet, occupational and home environment, activity patterns, and other cultural factors affecting susceptibility. For these reasons, epidemiologic data require careful interpretation. If adequate human studies (confirmed for validity and applicability) exist, these studies are given first priority in the dose-response assessment, and animal toxicity studies are used as supportive evidence.

EXHIBIT 7-1
STEPS IN TOXICITY ASSESSMENT



Human studies having inadequate exposure-response information for a quantitative assessment are often used as supporting data. Such studies may establish a qualitative relationship between environmental exposures and the presence of an adverse effect in exposed human populations. For example, case reports of exposures resulting in effects similar to the types of effects observed in animals provide support for the conclusions drawn from the animal data.

7.1.2 ANIMAL DATA

The toxicity data base for most chemicals lacks sufficient information on toxic effects in humans. In such cases, EPA may infer the potential for the substance to cause an adverse effect in humans from toxicity information drawn from experiments conducted on non-human mammals, such as the rat, mouse, rabbit, guinea pig, hamster, dog, or monkey. The inference that humans and animals (mammals) are similar, on average, in intrinsic susceptibility to toxic chemicals and that data from animals can in many cases be used as a surrogate for data from humans is the basic premise of modern toxicology. This concept is particularly important in the regulation of toxic chemicals. There are occasions, however, in which observations in animals may be of uncertain relevance to humans. EPA considers the likelihood that the agent will have adverse effects in humans to increase as similar results are observed across sexes, strains, species, and routes of exposure in animal studies.

7.1.3 SUPPORTING DATA

Several other types of studies used to support conclusions about the likelihood of occurrence of adverse health effects in humans are described below. At the present time, EPA considers all of these types of data to be supportive, not definitive, in assessing the potential for adverse health effects in humans.

Metabolic and other pharmacokinetic studies may be used to provide insights into the mechanism of action of a particular compound. By comparing the metabolism of a compound exhibiting a toxic effect in an animal with the corresponding metabolism in humans, evidence for the potential of the compound to have toxic effects in humans may be obtained.

Studies using cell cultures or microorganisms may be used to provide insights into a compound's potential for biological activity. For example, tests for point mutations, numerical and structural chromosome aberrations, DNA damage/repair, and cell transformation may provide supportive evidence of carcinogenicity and may give information on potential mechanisms of carcinogenicity. It should be noted, however, that lack of positive results in short-term tests for genotoxicity is not considered a basis for discounting positive results in long-term carcinogenicity studies in animals.

Structure-activity studies (i.e., predictions of toxicologic activity based on analysis of chemical structure) are another potential source of supporting data. Under certain circumstances, the known activity of one compound may be used to estimate the activity of another structurally related compound for which specific data are lacking.

7.2 TOXICITY ASSESSMENT FOR NONCARCINOGENIC EFFECTS

This section summarizes how the types of toxicity information presented in Section 7.1 are considered in the toxicity assessment for noncarcinogenic effects. A reference dose, or RfD, is the toxicity value used most often in evaluating noncarcinogenic effects resulting from exposures at Superfund sites. Additionally, One-day or Ten-day Health Advisories (HAs) may be used to evaluate short-term oral exposures. The methods EPA uses for developing RfDs and HAs are described below. Various types of RfDs are available depending on the exposure route (oral or inhalation), the critical effect (developmental or other), and the length of exposure being evaluated (chronic, subchronic, or single event). This section is intended to be a summary description only; for additional details, refer to the appropriate guidelines and other sources listed as references for this chapter (especially EPA 1986b, EPA 1989b-f).

A <u>chronic RfD</u> is defined as an estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that

is likely to be without an appreciable risk of deleterious effects during a lifetime. Chronic RfDs are specifically developed to be protective for long-term exposure to a compound. As a guideline for Superfund program risk assessments, chronic RfDs generally should be used to evaluate the potential noncarcinogenic effects associated with exposure periods between 7 years (approximately 10 percent of a human lifetime) and a lifetime. Many chronic RfDs have been reviewed and verified by an intra-Agency RfD Workgroup and entered into the Agency's Integrated Risk Information System (IRIS).

FORMER TERMINOLOGY

Prior to the development of RfDs, noncarcinogenic effects of chronic exposures were evaluated using values called acceptable daily intakes (ADIs) or acceptable intakes for chronic exposure (AICs). While ADIs and AICs are similar in concept to RfDs, RfDs have been derived using a more strictly defined methodology and represent the Agency's preferred toxicity values. Furthermore, many chronic RfDs have been reviewed and verified by an intra-Agency RfD Workgroup; these verified RfDs represent an Agency consensus and are preferred over other RfDs that have not undergone such review (see Section 7.2.7, Verification of RfDs). Similarly, acceptable intakes for subchronic exposures (AISs) have been superseded by the more strictly defined subchronic RfD values. Therefore, the former terminology (ADI, AIC, AIS) should no longer be used in Superfund program risk assessments.

More recently, EPA has begun developing subchronic RfDs (RfD_ss), which are useful for characterizing potential noncarcinogenic effects associated with shorter-term exposures, and developmental RfDs (RfD_{dt}s), which are useful specifically for assessing potential developmental effects resulting from exposure to a compound. As a guideline for Superfund program risk assessments, subchronic RfDs should be used to evaluate the potential noncarcinogenic effects of exposure periods between two weeks and seven years. Such short-term exposures can result when a particular activity is performed for a limited number of years or when a chemical with a short half-life degrades to negligible concentrations within several months. Developmental RfDs are used to evaluate the potential effects on a developing organism following a single exposure event.

7.2.1 CONCEPT OF THRESHOLD

For many noncarcinogenic effects, protective mechanisms are believed to exist that must be overcome before the adverse effect is manifested. For example, where a large number of cells perform the same or similar function, the cell population may have to be significantly depleted before the effect is seen. As a result, a range of exposures exists from zero to some finite value that can be tolerated by the organism with essentially no chance of expression of adverse effects. In developing a toxicity value for evaluating noncarcinogenic effects (i.e., an RfD), the approach is to identify the upper bound of this tolerance range (i.e., the maximum subthreshold level). Because variability exists in the human population, attempts are made to identify a subthreshold level protective of sensitive individuals in the population. For most chemicals, this level can only be estimated; the RfD incorporates uncertainty factors indicating the degree or extrapolation used to derive the estimated value. RfD summaries in IRIS also contain a statement expressing the overall confidence that the evaluators have in the RfD (high, medium, or low). The RfD is generally considered to have uncertainty spanning an order of magnitude or more, and therefore the RfD should not be viewed as a strict scientific demarcation between what level is toxic and nontoxic.

7.2.2 DERIVATION OF AN ORAL RfD (RfD_o)

Identifying the critical study and determining the NOAEL. In the development of oral RfDs, all available studies examining the toxicity of a chemical following exposure by the oral route are gathered and judged for scientific merit. Occasionally, studies based on other exposure routes (e.g., inhalation) are considered, and the data are adjusted for application to the oral route. Any differences between studies are reconciled and an overall evaluation is reached. If adequate human data are available, this information is used as the basis of the RfD. Otherwise, animal study data are used; in these cases, a series of professional judgments are made that involve, among other considerations, an assessment of the relevance and scientific quality of the experimental studies. If data from several animal studies are being evaluated, EPA first seeks to identify the animal model that is most relevant to humans based on a defensible

biological rationale, for instance, using comparative metabolic and pharmacokinetic data. In the absence of a species that is clearly the most relevant, EPA assumes that humans are at least as sensitive to the substance as the most sensitive animal species tested. Therefore, as a matter of science policy, the study on the most sensitive species (the species showing a toxic effect at the lowest administered dose) is selected as the critical study for the basis of the RfD. The effect characterized by the "lowest-observed-adverse-effect-level" (LOAEL) after dosimetric conversions to adjust for species differences is referred to as the critical toxic effect.

After the critical study and toxic effect have been selected, EPA identifies the experimental exposure level representing the highest level tested at which no adverse effects (including the critical toxic effect) were demonstrated. This highest "no-observed-adverse-effect level" (NOAEL) is the key datum obtained from the study of the dose-response relationship. A NOAEL observed in an animal study in which the exposure was intermittent (such as five days per week) is adjusted to reflect continuous exposure.

The NOAEL is selected based in part on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented. The NOAEL for the critical toxic effect should not be confused with the "no-observed-effect level" (NOEL). The NOEL corresponds to the exposure level at which no effect at all has been observed; frequently, effects are observed that are not considered to be of toxicological significance. In some studies, only LOAEL rather than a NOAEL is available. The use of a LOAEL, however, requires the use of an additional uncertainty factor (see below).

MULTIPLE TOXIC EFFECTS AND RfDs

The RfD is developed from a NOAEL for the most sensitive, or critical, toxic effect based in part on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented. It should be remembered during the risk characterization step of the risk assessment that if exposure levels exceed the RfD, then adverse effects in addition to the critical toxic effect may begin to appear.

Applying uncertainty factors. The RfD is derived from the NOAEL (or LOAEL) for the critical toxic effect by consistent application of uncertainty factors (UFs) and a modifying factor (MF). The uncertainty factors generally consist of multiples of 10 (although values less than 10 are sometimes used), with each factor representing a specific area of uncertainty inherent in the extrapolation from the available data. The bases for application of different uncertainty factors are explained below.

- A UF of 10 is used to account for variation in the general population and is intended to protect sensitive subpopulations (e.g., elderly, children).

- A UF of 10 is used when extrapolating from animals to humans. This factor is intended to account for the interspecies variability between humans and other mammals.

- A UF of 10 is used when a NOAEL derived from a subchronic instead of a chronic study is used as the basis for a chronic RfD.

- A UF of 10 is used when a LOAEL is used instead of a NOAEL. This factor is intended to account for the uncertainty associated with extrapolating from LOAELs to NOAELs.

In addition to the UFs listed above, a modifying factor (MF) is applied.

- An MF ranging from >0 to 10 is included to reflect a qualitative professional assessment of additional uncertainties in the critical study and in the entire data base for the chemical not explicitly addressed by the preceding uncertainty factors. The default value for the MF is 1.[1]

To calculate the RfD, the appropriate NOAEL (or the LOAEL if a suitable NOAEL is not available) is divided by the product of all of the applicable uncertainty factors and the modifying factor. That is:

$$RfD = NOAEL \text{ or } LOAEL/(UF_1 \times UF_2 \ldots \times$$

MF)

Oral RfDs typically are expressed as one significant figure in units of mg/kg-day. These concepts are shown graphically in EPA (1989g). To date, most RfDs developed by EPA and included in the sources listed in Section 7.4 are based on administered doses, not absorbed doses (see box on page 7-10).

7.2.3 DERIVATION OF AN INHALATION RfD (RfD_i)

The methods EPA uses in the derivation of inhalation RfDs are similar in concept to those used for oral RfDs; however, the actual analysis of inhalation exposures is more complex than oral exposures due to (1) the dynamics of the respiratory system and its diversity across species and (2) differences in the physicochemical properties of contaminants. Additional information can be found in EPA's *Interim Methods for Development of Inhalation Reference Doses* (EPA 1989d).

Identifying the critical study and determining the NOAEL. Although in theory the identification of the critical study and the determination of the NOAEL is similar for oral and inhalation exposures, several important differences should be noted. In selecting the most appropriate study, EPA considers differences in respiratory anatomy and physiology, as well as differences in the physicochemical characteristics of the contaminant. Differences in respiratory anatomy and physiology may affect the pattern of contaminant deposition in the respiratory tract, and the clearance and redistribution of the agent. Consequently, the different species may not receive the same dose of the contaminant at the same locations within the respiratory tract even though both species were exposed to the same particle or gas concentration. Differences in the physicochemical characteristics of the contaminants, such as the size and shape of a particle or whether the contaminant is an aerosol or a gas, also influence deposition, clearance, and redistribution.

In inhalation exposures, the target tissue may be a portion of the respiratory tract or, if the contaminant can be absorbed and distributed through the body, some extrarespiratory organ. Because the pattern of deposition may influence concentrations at the alveolar exchange boundary or different tissues of the lung, the toxic health effect observed may be more directly related to the pattern of deposition than to the exposure concentration. Consequently, EPA considers the deposition, clearance mechanisms, and the physicochemical properties of the inhaled agent in determining the effective dose delivered to the target organ.

Doses calculated in animals are converted to equivalent doses in humans on the basis of comparative physiological considerations (e.g., ventilatory parameters, regional lung surface areas). Additionally, if the exposure period was discontinuous, it is adjusted to reflect continuous exposure.

Applying uncertainty factors. The inhalation RfD is derived from the NOAEL by applying uncertainty factors similar to those listed above for oral RfDs. The UF of 10 is used when extrapolating from animals to humans, in addition to calculation of the human equivalent dose, to account for interspecific variability in sensitivity to the toxicant. The resulting RfD value for inhalation exposure is generally reported as a concentration in air (in mg/m^3 for continuous, 24 hour/day exposure), although it may be reported as a corresponding inhaled intake (in mg/kg-day). A human body weight of 70 kg and an inhalation rate of 20 m^3/day are used to convert between an inhaled intake expressed in units of mg/kg-day and a concentration in air expressed in mg/m^3.

7.2.4 DERIVATION OF A SUBCHRONIC RfD (RfD_s)

The chronic RfDs described above pertain to lifetime or other long-term exposures and may be overly protective if used to evaluate the potential for adverse health effects resulting from substantially less-than-lifetime exposures. For such situations, EPA has begun calculating toxicity values specifically for subchronic exposure durations, using a method similar to that outlined above for chronic RfDs. EPA's Environmental Criteria and Assessment Office develops subchronic RfDs and, although they have been peer-reviewed by Agency and outside reviewers, RfDs values have not undergone verification by an intra-Agency workgroup (see Section 7.2.7). As a result,

subchronic RfDs are considered interim rather than verified toxicity values and are not placed in IRIS.

Development of subchronic reference doses parallels the development of chronic reference doses in concept; the distinction is one of exposure duration. Appropriate studies are evaluated and a subchronic NOAEL is identified. The RfD_s is derived from the NOAEL by the application of UFs and MF as outlined above. When experimental data are available only for shorter exposure durations than desired, an additional uncertainty factor is applied. This is similar to the application of the uncertainty factor for duration differences when a chronic RfD is estimated from subchronic animal data. On the other hand, if subchronic data are missing and a chronic oral RfD derived from chronic data exists, the chronic oral RfD is adopted as the subchronic oral RfD. There is no application of an uncertainty factor to account for differences in exposure duration in this instance.

7.2.5 DERIVATION OF DEVELOPMENTAL TOXICANT RfD (RfD_{dt})

In developing an RfD_{dt}, evidence is gathered regarding the potential of a substance to cause adverse effects in a developing organism as a result of exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse effects can include death, structural abnormality, altered growth, and functional deficiencies. Maternal toxicity also is considered. The evidence is assessed, and the substance is assigned a weight-of-evidence designation according to the scheme outlined below and summarized in the box in the opposite column. In this scheme, three levels are used to indicate the assessor's degree of confidence in the data: definitive evidence, adequate evidence, and inadequate evidence. The definitive and adequate evidence categories are subdivided as to whether the evidence demonstrates the occurrence or the absence of adverse effects.

WEIGHT-OF-EVIDENCE SCHEME FOR DEVELOPMENTAL TOXICITY

- Definitive Evidence for:
  - Human Developmental Toxicity
  - No Apparent Human Developmental Toxicity
- Adequate Evidence for:
  - Potential Human Developmental Toxicity
  - No Apparent Potential Human Developmental Toxicity
- Inadequate Evidence for Determining Potential Human Developmental Toxicity

After the weight-of-evidence designation is assigned, a study is selected for the identification of a NOAEL. The NOAEL is converted to an equivalent human dose, if necessary, and divided by uncertainty factors similar to those used in the development of an oral RfD. It should be remembered that the RfD_{dt} is based on a <u>short duration of exposure</u> because even a single exposure at a critical time (e.g., during gestation) may be sufficient to produce adverse developmental effects and that chronic exposure is not a prerequisite for developmental toxicity to be manifested. Therefore, RfD_{dt} values are appropriate for evaluating single event exposures, which usually are <u>not</u> adjusted based on the duration of exposure. Additional information on the derivation of RfD_{dt} values is available in EPA's *Proposed Amendments to the Guidelines for the Health Assessment of Suspect Developmental Toxicants* (EPA 1989e).

7.2.6 ONE-DAY AND TEN-DAY HEALTH ADVISORIES

Reference values that may be useful for evaluating potential adverse effects associated with oral exposures of shorter duration have been developed by the Office of Drinking Water. These values are known as One-day and Ten-day Health Advisories, which are issued as nonregulatory guidance. Health Advisory values are concentrations of contaminants in drinking water at which adverse health effects would not be expected to occur for an

exposure of the specified duration. The Health Advisory values are based on data describing noncarcinogenic effects and are derived by dividing a NOAEL or LOAEL by the appropriate uncertainty and modifying factors. They are based on a 10-kg child assumed to drink 1 liter of water per day, and a margin of safety is included to protect sensitive members of the population. One-day and Ten-day Health Advisories do not consider any carcinogenic risk associated with the exposure even if the compound is a potential carcinogen. For additional information on the derivation of Health Advisory values, refer to the Agency's guidance document (EPA 1989c).

7.2.7 VERIFICATION OF RfDs

EPA has formed an RfD Workgroup composed of members from many EPA offices to verify existing Agency RfDs and to resolve conflicting toxicity assessments and toxicity values within the Agency. The Workgroup reviews the information regarding the derivation of an RfD for a substance and summarizes its evaluations, conclusions, and reservations regarding the RfD in a standardized summary form from one to several pages in length. This form contains information regarding the development of the RfD, such as the chosen effect levels and uncertainty factors, as well as a statement on the confidence that the evaluators have in the RfD itself, the critical study, and the overall data base (high, medium, or low). Once verified, these data evaluation summaries are entered into IRIS and are available for public access.

Workgroup-approved RfDs are referred to as verified RfDs. Those RfDs awaiting workgroup approval are referred to as interim RfDs. At the time of this manual's publication, only chronic RfDs are being verified. No workgroup has been established to verify subchronic RfDs or developmental RfDs.

ABSORBED VERSUS ADMINISTERED DOSE

Toxicity values -- for both noncarcinogenic and carcinogenic effects -- are generally calculated from critical effect levels based on administered rather than absorbed doses. It is important, therefore, to compare such toxicity values to exposure estimates expressed as intakes (corresponding to administered doses), not as absorbed doses. For the few toxicity values that have been based on absorbed doses, either the exposure estimate or the toxicity value should be adjusted to make the values comparable (i.e., compare exposures estimated as absorbed doses to toxicity values expressed as absorbed doses, and exposures estimated as intakes to toxicity values expressed as administered doses). See Appendix A for guidance on making adjustments for absorption efficiency.

7.3 TOXICITY ASSESSMENT FOR CARCINOGENIC EFFECTS

This section describes how the types of toxicity information presented in Section 7.1 are considered in the toxicity assessment for carcinogenic effects. A slope factor and the accompanying weight-of-evidence determination are the toxicity data most commonly used to evaluate potential human carcinogenic risks. The methods EPA uses to derive these values are outlined below. Additional information can be obtained by consulting EPA's *Guidelines for Carcinogen Risk Assessment* (EPA 1986a) and Appendix B to IRIS (EPA 1989a).

7.3.1 CONCEPT OF NONTHRESHOLD EFFECTS

Carcinogenesis, unlike many noncarcinogenic health effects, is generally thought to be a phenomenon for which risk evaluation based on

presumption of a threshold is inappropriate. For carcinogens, EPA assumes that a small number of molecular events can evoke changes in a single cell that can lead to uncontrolled cellular proliferation and eventually to a clinical state of disease. This hypothesized mechanism for carcinogenesis is referred to as "nonthreshold" because there is believed to be essentially no level of exposure to such a chemical that does not pose a finite probability, however small, of generating a carcinogenic response. That is, no dose is thought to be risk-free. Therefore, in evaluating cancer risks, an effect threshold cannot be estimated. For carcinogenic effects, EPA uses a two-part evaluation in which the substance first is assigned a weight-of-evidence classification, and then a slope factor is calculated.

7.3.2 ASSIGNING A WEIGHT OF EVIDENCE

In the first step of the evaluation, the available data are evaluated to determine the likelihood that the agent is a human carcinogen. The evidence is characterized separately for human studies and animal studies as sufficient, limited, inadequate, no data, or evidence of no effect. The characterizations of these two types of data are combined, and based on the extent to which the agent has been shown to be a carcinogen in experimental animals or humans, or both, the agent is given a provisional weight-of-evidence classification. EPA scientists then adjust the provisional classification upward or downward, based on other supporting evidence of carcinogenicity (see Section 7.1.3). For a further description of the role of supporting evidence, see the EPA guidelines (EPA 1986a).

The EPA classification system for weight of evidence is shown in the box in the opposite column. This system is adapted from the approach taken by the International Agency for Research on Cancer (IARC 1982).

7.3.3 GENERATING A SLOPE FACTOR[2]

In the second part of the evaluation, based on the evaluation that the chemical is a known or probable human carcinogen, a toxicity value that defines quantitatively the relationship between dose and response (i.e., the slope factor) is calculated. Slope factors are typically calculated for potential carcinogens in classes A, B1, and B2. Quantitative estimation of slope factors for the chemicals in class C proceeds on a case-by-case basis.

Generally, the slope factor is a plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used in risk assessments to estimate an upper-bound lifetime probability of an individual developing cancer as a result of exposure to a particular level of a potential carcinogen. Slope factors should always be accompanied by the weight-of-evidence classification to indicate the strength of the evidence that the agent is a human carcinogen.

Identifying the appropriate data set. In deriving slope factors, the available information about a chemical is evaluated and an appropriate data set is selected. In choosing appropriate data sets, human data of high quality are preferable to animal data. If animal data are used, the species that responds most similarly to humans (with respect to factors such as metabolism, physiology, and pharmacokinetics) is preferred. When no clear choice is possible, the most sensitive species is given the greatest emphasis. Occasionally, in situations where no single study is judged most appropriate, yet several studies collectively support the estimate, the geometric mean

EPA WEIGHT-OF-EVIDENCE CLASSIFICATION SYSTEM FOR CARCINOGENICITY

Group	Description
A	Human carcinogen
B1 or B2	Probable human carcinogen
	B1 indicates that limited human data are available.
	B2 indicates sufficient evidence in animals and inadequate or no evidence in humans.
C	Possible human carcinogen
D	Not classifiable as to human carcinogenicity
E	Evidence of noncarcinogenicity for humans

of estimates from all studies may be adopted as the slope. This practice ensures the inclusion of all relevant data.

Extrapolating to lower doses. Because risk at low exposure levels is difficult to measure directly either by animal experiments or by epidemiologic studies, the development of a slope factor generally entails applying a model to the available data set and using the model to extrapolate from the relatively high doses administered to experimental animals (or the exposures noted in epidemiologic studies) to the lower exposure levels expected for human contact in the environment.

A number of mathematical models and procedures have been developed to extrapolate from carcinogenic responses observed at high doses to responses expected at low doses. Different extrapolation methods may provide a reasonable fit to the observed data but may lead to large differences in the projected risk at low doses. In keeping with EPA's *Guidelines for Carcinogen Risk Assessment* (EPA 1986a) and the principles outlined in *Chemical Carcinogens: A Review of the Science and Its Associated Principles* (OSTP 1985), the choice of a low-dose extrapolation model is governed by consistency with current understanding of the mechanism of carcinogenesis, and not solely on goodness-of-fit to the observed tumor data. When data are limited and when uncertainty exists regarding the mechanisms of carcinogenic action, the EPA guidelines and OSTP principles suggest that models or procedures that incorporate low-dose linearity are preferred when compatible with the limited information available. EPA's guidelines recommend that the linearized multistage model be employed in the absence of adequate information to the contrary. Among the other models available are the Weibull, probit, logit, one-hit, and gamma multihit models, as well as various time-to-tumor models. Most of these models are less conservative (i.e., predict lower cancer potency) than the linearized multistage model. These concepts and models are shown graphically in EPA (1989g) and OTA (1981).

In general, after the data are fit to the appropriate model, the upper 95th percent confidence limit of the slope of the resulting dose-response curve is calculated. This value is known as the slope factor and represents an upper 95th percent confidence limit on the probability of a response per unit intake of a chemical over a lifetime (i.e., there is only a 5 percent chance that the probability of a response could be greater than the estimated value on the basis of the experimental data and model used). In some cases, slope factors based on human dose-response data are based on the "best" estimate instead of the upper 95th percent confidence limits. Because the dose-response curve generally is linear only in the low-dose region, the slope factor estimate only holds true for low doses. Information concerning the limitations on use of slope factors can be found in IRIS.

Determining equivalent human doses. When animal data are used as a basis for extrapolation, the human dose that is equivalent to the dose in the animal study is calculated using the assumption that different species are equally sensitive to the effects of a toxicant if they absorb the same amount of the agent (in milligrams) per unit of body surface area. This assumption is made only in the absence of specific information about the equivalent doses for the chemical in question. Because surface area is approximately proportional to the 2/3 power of body weight, the equivalent human dose (in mg/day, or other units of mass per unit time) is calculated by multiplying the animal dose (in identical units) by the ratio of human to animal body weights raised to the 2/3 power. (For animal doses expressed as mg/kg-day, the equivalent human dose, in the same units, is calculated by multiplying the animal dose by the ratio of animal to human body weights raised to the 1/3 power.)

When using animal inhalation experiments to estimate lifetime human risks for partially soluble vapors or gases, the air concentration (ppm) is generally considered to be the equivalent dose between species based on equivalent exposure times (measured as fractions of a lifetime). For inhalation of particulates or completely absorbed gases, the amount absorbed per unit of body surface area is considered to be the equivalent dose between species.

Summary of dose-response parameters. Toxicity values for carcinogenic effects can be expressed in several ways. The slope factor is usually, but not always, the upper 95th percent confidence limit of the slope of the dose-response curve and is expressed as

$(mg/kg\text{-}day)^{-1}$. If the extrapolation model selected is the linearized multistage model, this value is also known as the q_1^*. That is:

Slope factor = risk per unit dose
= risk per mg/kg-day

Where data permit, slope factors listed in IRIS are based on absorbed doses, although to date many of them have been based on administered doses. (The qualifiers related to absorbed versus administered dose given in the box on page 7-10 apply to assessment of cancer risk as well as to assessment of potential noncarcinogenic effects.)

Toxicity values for carcinogenic effects also can be expressed in terms of risk per unit concentration of the substance in the medium where human contact occurs. These measures, called unit risks, are calculated by dividing the slope factor by 70 kg and multiplying by the inhalation rate (20 m^3/day) or the water consumption rate (2 liters/day), respectively, for risk associated with unit concentration in air or water. Where an absorption fraction less than 1.0 has been applied in deriving the slope factor, an additional conversion factor is necessary in the calculation of unit risk so that the unit risk will be on an administered dose basis. The standardized duration assumption for unit risks is understood to be continuous lifetime exposure. Hence, when there is no absorption conversion required:

air unit risk = risk per ug/m^3
= slope factor x 1/70 kg x $20m^3$/day x 10^{-3}

water unit risk = risk per ug/L
= slope factor x 1/70 kg x 2L/day x 10^{-3}

The multiplication by 10^{-3} is necessary to convert from mg (the slope factor, or q_1^*, is given in $(mg/kg\text{-}day)^{-1}$) to ug (the unit risk is given in $(ug/m^3)^{-1}$ or $(ug/L)^{-1}$).

7.3.4 VERIFICATION OF SLOPE FACTORS

EPA formed the Carcinogen Risk Assessment Verification Endeavor (CRAVE) Workgroup to validate Agency carcinogen risk assessments and resolve conflicting toxicity values developed by various program offices. Workgroup members represent many different EPA offices and are scientists experienced in issues related to both the qualitative and quantitative risk assessment of carcinogenic agents. Slope factors verified by CRAVE have undergone extensive peer review and represent an Agency consensus. CRAVE- verified review summaries (similar to RfD Workgroup summaries) are entered into the IRIS data base.

7.4 IDENTIFYING APPROPRIATE TOXICITY VALUES FOR SITE RISK ASSESSMENT

Using the methods outlined above, EPA has performed toxicity assessments for many chemicals found at Superfund sites and has made the results available for use. This section provides step-by-step methods for locating appropriate toxicity information, including numerical toxicity values, to be used in Superfund risk assessments. Because one's confidence in toxicity values depends heavily on the data base and the methods of extrapolation used in their development, guidance is also included for identifying the important information on which these values are based.

7.4.1 GATHER TOXICITY INFORMATION FOR CHEMICALS BEING EVALUATED

In the first step of the toxicity assessment, information is collected regarding the toxic effects that occur following exposure to the chemical being evaluated. Particular attention should be paid to the route of exposure, the frequency and length of exposure, and the doses at which the adverse effects are expected to occur. Chemicals having potential reproductive or developmental effects should be flagged. Later in the evaluation, special reference doses for developmental effects can be sought for these chemicals.

Several sources may provide useful toxicity information and references to primary literature, although only some of them should be used as sources for slope factors and reference doses (as explained below).

Integrated Risk Information System (IRIS).[3] IRIS is an EPA data base containing up-to-date health risk and EPA regulatory information for numerous chemicals. IRIS contains only those RfDs and slope factors that have been verified by the RfD or CRAVE Workgroups and consequently, is considered to be the preferred source of toxicity information. Information in IRIS supersedes all other sources. Only if information is not available in IRIS for the chemical being evaluated should the sources below be consulted. IRIS consists of a collection of computer files on individual chemicals. Existing information on the chemicals is updated as new scientific data are reviewed. New files and new chemicals are added as information becomes available. These chemical files contain descriptive and quantitative information in the following categories:

- oral and inhalation chronic reference doses;
- oral and inhalation slope factors and unit risks for chronic exposure to carcinogens;
- Health Advisories from EPA's Office of Drinking Water;
- EPA regulatory action summaries; and
- supplemental data on acute health hazards and physical/chemical properties.

To ensure access to the most up-to-date chemical information, IRIS is only available on-line. For information on how to access this data base, call IRIS User Support at 513-569-7254 or see the *Federal Register* notice regarding the availability of IRIS (EPA 1988a).

Should EPA regional staff have specific technical or scientific questions about any verification workgroup's analysis of particular data cited in IRIS, the Agency contact for a particular chemical (identified at the end of each IRIS file) should be consulted. If new data are identified suggesting that existing IRIS information may be outdated, or if there is concern or disagreement about the overall findings of particular files, the Agency IRIS coordinator should be consulted. The IRIS coordinator can assist in making arrangements should discussions with a verification workgroup be needed.

Health Effects Assessment Summary Tables (HEAST). Formerly "The Quarterly" and associated references, HEAST is a tabular presentation of toxicity information and values for chemicals for which Health Effects Assessments (HEAs), Health and Environmental Effects Documents (HEEDs), Health and Environmental Effects Profiles (HEEPs), Health Assessment Documents (HADs), or Ambient Air Quality Criteria Documents (AAQCDs) have been prepared. HEAST summarizes interim (and some verified) RfDs and slope factors as well as other toxicity information for specific chemicals. In addition, HEAST directs readers to the most current sources of supporting toxicity information through an extensive reference section. Therefore, HEAST is especially helpful when verified information for a chemical is not in IRIS. HEAST, which is updated quarterly, also provides a valuable pointer system for identifying current references on chemicals that are not in IRIS.

HEAST can be obtained upon request from the Superfund Docket (FTS or 202-382-3046). The Docket will mail copies of HEAST to callers and place requestors on a mailing list to receive an updated version quarterly. HEAs, HEEDs, HEEPs, HADs, and AAQCDs referenced in HEAST are available through EPA's Center for Environmental Research Information (CERI) in Cincinnati, OH (513-569-7562 or FTS 684-7562) or the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650 or 800-336-4700).

EPA criteria documents. These documents include drinking water criteria documents, drinking water Health Advisory summaries, ambient water quality

HIERARCHY OF TOXICITY INFORMATION

Because toxicity information may change rapidly and quickly become outdated, care should be taken to find the most recent information available. IRIS is updated monthly, provides verified RfDs and slope factors, and is the Agency's preferred source of toxicity information. Only if values are unavailable in IRIS should other information sources be consulted.

HEAST is the second most current source of toxicity information of importance to Superfund. Unlike IRIS, HEAST provides information regarding interim as well as verified RfDs and slope factors. Readers are directed to supporting toxicity information for interim and verified values in an extensive reference section of HEAST. HEAST information should only be sought for those chemicals not listed in IRIS.

Toxicity information, RfDs, and slope factors also can be found in other EPA documents. Although these values were developed by offices within the Agency, they have not necessarily been verified by the RfD or CRAVE Workgroups. The use of up-to-date verified information is preferred to the use of interim information and, therefore, toxicity information should be obtained from other EPA references only if information could not be found in IRIS or HEAST. Before using references other than those cited in IRIS or HEAST, check with ECAO at 513-569-7300 (FTS 684-7300) to see if more current information is available.

criteria documents, and air quality criteria documents, and contain general toxicity information that can be used if information for a chemical is not available through IRIS or the HEAST references. Criteria documents are available through NTIS at the address given above. Information on drinking water criteria documents can be obtained through the Safe Drinking Water Hotline (800-426-4791).

Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles. ATSDR is developing toxicological profiles for 275 hazardous substances found at Superfund sites. The first 200 substances to be addressed have been identified in *Federal Register* notices (EPA 1987, 1988b). These profiles contain general toxicity information and levels of exposure associated with lethality, cancer, genotoxicity, neurotoxicity, developmental and reproductive toxicity, immunotoxicity, and systemic toxicity (i.e., hepatic, renal, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, and dermal/ocular effects). Health effects in humans and animals are discussed by exposure route (i.e., oral, inhalation, and dermal) and duration (i.e., acute, intermediate, and chronic). Also included in the profiles are chapters on physicochemical properties, environmental fate, potential for human exposure, analytical methods, and regulatory and advisory status. Contact NTIS at the address given on the previous page for further information on the status or availability of a particular profile.

EPA's Environmental Criteria and Assessment Office (ECAO). ECAO may be contacted at 513-569-7300 (FTS 684-7300) for general toxicological information as well as for technical guidance concerning route-to-route extrapolations, toxicity values for dermal exposures, and the evaluation of chemicals without toxicity values. The requestor should identify their need for a "rapid response request" (within 48 hours) for interim guidance on Superfund health-related issues. Contractors must give the name and address of their RPM or regional risk assessment contact before ECAO will respond. RPMs and regional contacts will be sent a copy of ECAO's response to the contractor.

Open literature. A primary literature search may be valuable for determining whether new data are available that may affect IRIS information.

7.4.2 DETERMINE TOXICITY VALUES FOR NONCARCINOGENIC EFFECTS (RfDs)

After general toxicity information for the chemicals of concern has been located, the next step is to identify the appropriate toxicity values to be used in evaluating noncarcinogenic effects associated with the specific exposures being assessed. First, by referring to the exposure information generated in Chapter 6, the exposure periods for which toxicity values are

necessary and the exposure route for each chemical being evaluated should be determined. The appropriate toxicity values for the chemical for each exposure duration and route of exposure can then be identified using the sources listed above.

For Superfund risk assessments, chronic RfDs should be identified for evaluating exposure periods between seven years and a lifetime, subchronic RfDs for exposure periods between two weeks and seven years, and One- or Ten-day Health Advisories for oral exposure periods of less than two weeks. According to EPA (1988c), One-day Health Advisories are applicable to exposure periods as long as two weeks. Developmental RfDs should be identified for evaluating single exposure events and other very short exposures (e.g., one day). Note that for some substances and some exposure situations, more than one of the toxicity values listed above may be needed to adequately assess potential noncarcinogenic effects.

Because carcinogens also commonly evoke noncarcinogenic effects, RfDs should be sought for all chemicals being carried through the risk assessment, including carcinogens. The RfDs derived for carcinogens, however, are based on noncancer effects and should not be assumed to be protective against carcinogenicity. A sample format for summarizing RfDs and other toxicity values is shown in Exhibit 7-2. This information will be needed in the risk characterization step (see Exhibits 8-3 and 8-4).

7.4.3 DETERMINE TOXICITY VALUES FOR CARCINOGENIC EFFECTS (SLOPE FACTORS)

In this step of the toxicity assessment, appropriate toxicity values for evaluating the carcinogenic risks associated with exposure are identified. First, by referring to the exposure information generated in Chapter 6, the route of exposure for the potential carcinogens being evaluated should be identified. Slope factors for these chemicals can then be identified using the hierarchy of sources listed in the box on page 7-15. Slope factors for all potential carcinogens having a weight-of-evidence classification of A, B, or C should be sought. A notation of the EPA weight-of-evidence classification should always be included with the slope factor. A sample format for summarizing the required toxicity values is shown in Exhibit 7-3. This information will be needed in the risk characterization step (see Exhibit 8-2).

7.5 EVALUATING CHEMICALS FOR WHICH NO TOXICITY VALUES ARE AVAILABLE

If EPA-derived RfDs and slope factors are available for the chemicals being examined, these values should always be used in the risk assessment. Use of EPA-derived toxicity values prevents duplication of effort and ensures consistency among risk assessments. If EPA-derived toxicity values are not available, the following measures are recommended.

7.5.1 ROUTE-TO-ROUTE EXTRAPOLATION

For cases in which EPA-derived toxicity values are not available for the route of exposure being considered but are available for another route, EPA recommends contacting ECAO for guidance on route-to-route extrapolation. If toxicity information is not available from ECAO, a qualitative rather than quantitative evaluation of the chemical is recommended. The implications of the absence of this chemical from the risk estimate should be discussed in the uncertainty section.

7.5.2 DERMAL EXPOSURE

No RfDs or slope factors are available for the dermal route of exposure. In some cases, however, noncarcinogenic or carcinogenic risks associated with dermal exposure can be evaluated using an oral RfD or oral slope factor, respectively. EPA recommends contacting ECAO for guidance on appropriate methods for evaluating dermal exposure for specific chemicals; some general guidance for calculating intakes via the dermal route and making appropriate comparisons with oral RfD values is given in Appendix A. In brief, exposures via the dermal route generally are calculated and expressed as absorbed doses. These absorbed doses are compared to an oral toxicity value that has been

adjusted, if necessary, so that it too is expressed as an absorbed dose.

It is inappropriate to use the oral slope factor to evaluate the risks associated with dermal exposure to carcinogens such as benz(a)pyrene, which cause skin cancer through a direct action at the point of application. These types of skin carcinogens and other locally active compounds must be evaluated separately from the above method; consult ECAO for guidance. Generally only a qualitative assessment of risks from dermal exposure to these chemicals is possible. This does not apply to carcinogens such as arsenic, which are believed to cause skin cancer through a systemic rather than local action.

If information is not available from ECAO, the assessor should describe the effects of the chemical qualitatively and discuss the implications of the absence of the chemical from the risk estimate in the uncertainty section of the risk assessment.

7.5.3 GENERATION OF TOXICITY VALUES

If EPA-derived toxicity values are unavailable but adequate toxicity studies are available, one may derive toxicity values using Agency methodology. Any such derivation should be done in conjunction with the regional risk assessment contact, who will submit the derivation to ECAO for approval. Contact with ECAO should be established early in the process to eliminate any duplication of effort because ECAO may have information on the chemical being evaluated.

7.6 UNCERTAINTIES RELATED TO TOXICITY INFORMATION

Toxicity information for many of the chemicals found at Superfund sites is often limited. Consequently, there are varying degrees of uncertainty associated with the toxicity values calculated. Sources of uncertainty associated with toxicity values may include:

- using dose-response information from effects observed at high doses to predict the adverse health effects that may occur following exposure to the low levels expected from human contact with the agent in the environment;
- using dose-response information from short-term exposure studies to predict the effects of long-term exposures, and vice-versa;
- using dose-response information from animal studies to predict effects in humans; and
- using dose-response information from homogeneous animal populations or healthy human populations to predict the effects likely to be observed in the general population consisting of individuals with a wide range of sensitivities.

An understanding of the degree of uncertainty associated with toxicity values is an important part of interpreting and using those values. Therefore, as part of the toxicity assessment for Superfund sites, a discussion of the strength of the evidence of the entire range of principal and supporting studies should be included. The degree of confidence ascribed to a toxicity value is a function of both the quality of the individual study from which it was derived and the completeness of the supporting data base. EPA-verified RfDs found in IRIS are accompanied by a statement of the confidence that the evaluators have in the RfD itself, the critical study, and the overall data base. All EPA-verified slope factors are accompanied by a weight-of-evidence classification, which indicates the likelihood that the agent is a human carcinogen. The weight-of-evidence classification is based on the completeness of the evidence that the agent causes cancer in experimental animals and humans. These designations should be used as one basis for the discussion of uncertainty.

EXHIBIT 7-2

EXAMPLE OF TABLE FORMAT FOR TOXICITY VALUES: POTENTIAL NONCARCINOGENIC EFFECTS

Chemical	Chronic RfD[a] (mg/kg-day)	Confidence Level[b]	Critical Effect	RfD Basis/ RfD Source	Uncertainty and Modifying Factors
Oral Route					
Phenol	0.6*	Medium	Kidney and liver effects	Water[c]/ IRIS	UF = 1,000[d] for H,A,S,L MF = 1
Nitrobenzene	0.0005*	Medium	Hematologic, adrenal, kidney, and liver effects	Water[c]/ IRIS	UF = 10,000 for H,A,S,L MF = 1
Inhalation Route					
—	—	—	—	—	—

* Values for illustration only.

[a] Similarly formatted tables also could be used for subchronic and shorter-term toxicity values.

[b] Confidence level from IRIS, either high, medium, or low.

[c] RfD expressed as administered dose in drinking water, with assumed absorption fraction of 1.0.

[d] Uncertainty adjustment of 1,000 used to represent combined H, A, S, and L extrapolations.

Uncertainty adjustments: H = variation in human sensitivity;
A = animal to human extrapolation;
S = extrapolation from subchronic to chronic NOAEL;
L = extrapolation from LOAEL to NOAEL.

EXHIBIT 7-3

EXAMPLE OF TABLE FORMAT FOR TOXICITY VALUES: POTENTIAL CARCINOGENIC EFFECTS

Chemical	Slope Factor (SF) $(mg/kg\text{-}day)^{-1}$	Weight-of-Evidence Classification	Type of Cancer[a]	SF Basis/ SF Source
Oral Route				
Benzene	0.029*	A*	Leukemia	Water[b]/ IRIS
Chlordane	1.3*	B2*	--	Water[b]/ IRIS
Inhalation Route				
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* Values for illustration only.

[a] Identity type(s) of cancer in this table for Class A carcinogens only.

[b] Slope factor based on administered dose in drinking water and assumed absorption fraction of 1.0.

The discussion of uncertainty also should include an indication of the extent to which an analysis of the results from different studies give a consistent, plausible picture of toxicity. The greater the strength of the evidence, the greater one's confidence in the conclusions drawn. The following factors add to the strength of the evidence that the chemical poses a hazard to humans and should be considered:

- similar effects across species, strains, sex, and routes of exposure;
- clear evidence of a dose-response relationship;
- a plausible relationship among data on metabolism, postulated mechanism of action, and the effect of concern (see Section 7.1.3);
- similar toxicity exhibited by structurally related compounds (see Section 7.1.3); and
- some link between the chemical and evidence of the effect of concern in humans (see Section 7.1.1).

High uncertainty (low confidence; low strength of evidence) indicates that the toxicity value might change if additional chronic toxicity data become available. Low uncertainty (high confidence) is an indication that a value is less likely to change as more data become available, because there is consistency among the toxic responses observed in different species, sexes, study designs, or in dose-response relationships. The lower the uncertainty about toxicity values, the more confidence a decision-maker can have in the risk assessment results. Often, high confidence is associated with values that are based on human data for the exposure route of concern.

7.7 SUMMARIZATION AND PRESENTATION OF THE TOXICITY INFORMATION

This section discusses methods for presenting toxicity information in the risk assessment document for the chemicals being evaluated.

7.7.1 TOXICITY INFORMATION FOR THE MAIN BODY OF THE TEXT

A short description of the toxic effects of each chemical carried through the assessment in non-technical language should be prepared for inclusion in the main body of the risk assessment. Included in this description should be information on the effects associated with exposure to the chemical and the concentrations at which the adverse effects are expected to occur in humans. Toxicity values should be accompanied by a brief description of the overall data base and the particular study from which the value was derived. In addition, a notation should be made of the critical effect and any uncertainty factors used in the calculation. For any RfD value obtained from IRIS, a notation of the degree of confidence associated with the determination should also be included. To aid in the risk characterization, it should be indicated if absorption efficiency was considered and also what exposure averaging periods are appropriate for comparison with the value.

Summary tables of toxicity values for all chemicals should be prepared for inclusion in the main body of the risk assessment report. RfDs in the table should be accompanied with the uncertainty factors used in their derivation, the confidence rating given in IRIS (if applicable), and a notation of the critical effect. Slope factors should always be accompanied by EPA's weight-of-evidence classification.

7.7.2 TOXICITY INFORMATION FOR INCLUSION IN AN APPENDIX

If toxicity values were derived in conjunction with the regional risk assessment contact and ECAO for chemicals lacking EPA-derived values, a technical documentation/justification of the method of derivation should be prepared and included in the appendix of the risk assessment report. Included in this explanation should be a description of the toxic effects of the chemical such as information regarding the noncarcinogenic, carcinogenic, mutagenic, reproductive, and developmental effects of the compound. Also presented should be brief

descriptions (species, route of administration, dosages, frequency of exposure, length of exposure, and critical effect) of the studies from which the values were derived as well as the actual method of derivation. References for the studies cited in the discussion should be included.

ENDNOTES FOR CHAPTER 7

1. The MF is set less than one for a small number of substances to account for nutritional essentiality.

2. The slope factor is occasionally referred to as a cancer potency factor; however, use of this terminology is not recommended.

3. The quantitative risk values and supporting information found in IRIS represent a consensus judgement of EPA's Reference Dose Workgroup or Carcinogen Risk Assessment Verification Endeavor (CRAVE) Workgroup. These workgroups are composed of scientists from EPA's program offices and the Office of Research and Development. The concept of Agency-wide consensus is one of the most valuable aspects of IRIS.

REFERENCES FOR CHAPTER 7

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