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Human Health Evaluation Manual Part A

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RISK ASSESSMENT GUIDANCE FOR SUPERFUND

Volume I: Human Health Evaluation Manual

Office of Emergency and Remedial Response
U.S. Environmental Protection Agency
Washington, D.C. 20460

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ABOUT THE REVISION . . .

WHAT IT IS

EPA's *Human Health Evaluation Manual* is a revision of the *Superfund Public Health Evaluation Manual* (SPHEM; October 1986); it is Volume I of the two-volume set called *Risk Assessment Guidance for Superfund*. This manual has three main parts: the baseline risk assessment (Part A); refinement of preliminary remediation goals (Part B); and evaluation of remedial alternatives (Part C). (Only Part A is included in the first distribution; see below.)

WHO IT'S FOR

Risk assessors, risk assessment reviewers, remedial project managers (RPMs), and risk managers involved in Superfund site cleanup activities will benefit from this revision.

WHAT'S NEW

This revision builds upon the process established in SPHEM and provides more detailed guidance on many of the procedures used to assess health risk. New information and techniques are presented that reflect the extensive Superfund program experience conducting health risk assessments at Superfund sites. Policies established and refined over the years -- especially those resulting from the proposed National Oil and Hazardous Substances Pollution Contingency Plan (NCP) -- have been updated and clarified. Additionally, the links between the human health evaluation, the environmental evaluation, and the remedial investigation/feasibility study (RI/FS) have been strengthened.

In Part A you will find:

For the risk assessor -- Updated procedures and policies, specific equations and variable values for estimating exposure, and a hierarchy of toxicity data sources.

For the risk assessment reviewer -- A baseline risk assessment outline for consistent presentation of risk information and format, and a reviewer's checklist to ensure appropriate quality and content of the risk assessment.

For the RPM -- A comprehensive overview of the risk assessment process in the RI/FS, a checklist for RPM involvement throughout the process, and a complete index for quick reference.

For the risk manager -- An expanded chapter on risk characterization (Chapter 8) to help summarize and present risk information for the decision-maker, and more detailed descriptions of uncertainties in the assessment.

DISTRIBUTION PLAN

This manual is being distributed as an interim final document while the proposed NCP is being finalized. After the final NCP is published, the manual will be updated and finalized. Parts B and C -- which were not distributed as interim final because they are highly dependent on possible revisions to the NCP -- will be added. Periodically, updates of portions of the manual will be distributed.

WHERE TO SEND COMMENTS

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NOTICE

The policies and procedures set forth here are intended solely as guidance to EPA and other government employees and contractors. This guidance does not constitute rulemaking by the Agency, and cannot be relied on to create a substantive or procedural right enforceable by any party in litigation with the United States. EPA may take action that is at variance with the policies and procedures in this manual and may change them at any time without public notice.

This interim final guidance is based on policies in the proposed revisions to the National Oil and Hazardous Substances Pollution Contingency Plan (NCP), which were published on December 21, 1988 (53 *Federal Register* 51394). The final NCP may adopt policies different than those in this manual and should, when promulgated, be considered the authoritative source. A final version of this manual will be published after the revised NCP is promulgated.

Following the date of its publication, this manual is intended to be used as guidance for all human health risk assessments conducted as part of Superfund remedial investigations and feasibility studies. Issuance of this manual does not invalidate human health risk assessments completed before (or in progress at) the publication date and based on previously released Agency guidance.

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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_ds), 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:

$$RfD = NOAEL \text{ or } LOAEL/(UF_1 \times UF_2 ... \times MF)$$

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 A 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 short duration of exposure 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 not 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.

ASSIGNING A WEIGHT OF EVIDENCE

In the first step of the evaluation, the vailable data are evaluated to determine the kelihood that the agent is a human carcinogen. he evidence is characterized separately for human tudies and animal studies as sufficient, limited, nadequate, no data, or evidence of no effect. The haracterizations of these two types of data are ombined, and based on the extent to which the gent has been shown to be a carcinogen in xperimental animals or humans, or both, the gent is given a provisional weight-of-evidence lassification. EPA scientists then adjust the rovisional classification upward or downward, ased on other supporting evidence of arcinogenicity (see Section 7.1.3). For a further lescription of the role of supporting evidence, see he EPA guidelines (EPA 1986a).

The EPA classification system for weight of vidence is shown in the box in the opposite olumn. This system is adapted from the ipr h taken by the International Agency for ch on Cancer (IARC 1982).

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

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 cla ation to indicate the strength of the e 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 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 $(\text{mg/kg-day})^{-1}$. 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:

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

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

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

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