

# Chapter 12 Inhalation Toxicity Assessment

## Table of Contents

12.1	Introduction . . . . .	<u>1</u>
12.1.1	Hazard Identification and Dose-Response Information . . . . .	<u>1</u>
12.1.2	Dose-Response Assessment Methods . . . . .	<u>5</u>
12.2	Hazard Identification . . . . .	<u>8</u>
12.2.1	Weight of Evidence – Human Carcinogenicity . . . . .	<u>9</u>
12.2.2	Identification of Critical Effect(s) – Non-Cancer Endpoints . . . . .	<u>11</u>
12.3	Dose-Response Assessment for Cancer Effects . . . . .	<u>12</u>
12.3.1	Determination of the Point of Departure (POD) . . . . .	<u>13</u>
12.3.2	Derivation of the Human Equivalent Concentration . . . . .	<u>14</u>
12.3.3	Extrapolation from POD to Derive Carcinogenic Potency Estimates . . . . .	<u>17</u>
12.4	Dose-Response Assessment for Derivation of a Reference Concentration . . . . .	<u>19</u>
12.4.1	Determination of the Point of Departure and Human Equivalent Concentration . . . . .	<u>20</u>
12.4.2	Application of Uncertainty Factors . . . . .	<u>22</u>
12.5	Sources of Chronic Dose-Response Values . . . . .	<u>24</u>
12.6	Acute Exposure Reference Values . . . . .	<u>26</u>
12.7	Evaluating Chemicals Lacking Health Reference Values . . . . .	<u>31</u>
12.7.1	Use of Available Data Sources . . . . .	<u>31</u>
12.7.2	Route-to-Route Extrapolation . . . . .	<u>31</u>
12.8	Dose-Response Assessment for Mixtures . . . . .	<u>32</u>
	References . . . . .	<u>35</u>



## 12.1 Introduction

The purpose of the toxicity assessment is to weigh available evidence regarding the potential for toxicity in exposed individuals (**hazard identification**) and to quantify the toxicity by deriving an appropriate dose-response value (**dose-response assessment**). Toxicity assessment is the second part of the general risk equation. Although the toxicity assessment is an integral and important part of the overall air toxics risk assessment, it is usually accomplished prior to the risk assessment. EPA has completed this toxicity assessment for many HAPs and has made available the resulting toxicity information and dose-response values, which have undergone extensive peer review (see Appendix C).<sup>1</sup>

**Risk =  $f$  (metric of exposure, metric of toxicity)**

**Toxicity Assessment is a 2-Step Process:**

1. **Hazard Identification** – What types of effects does the chemical cause? Under what circumstances?
2. **Dose-response Assessment** – How potent is the chemical as a carcinogen and/or for noncancer effects?

In most air toxics risk assessments, little new toxicological evaluation of primary data will be required. However, it is important to understand how the available data were analyzed to produce the dose-responses values used in a risk assessment. In the risk characterization step, the risk assessor will need to describe the nature of the available toxicological evidence and the uncertainties inherent in the development of the dose-response values used in the inhalation risk assessment (see Chapter 13).

Additionally, in the event that there are significant data analysis and interpretation issues, or if a dose-response value does not exist and needs to be developed for a particular air toxic of interest, this chapter provides information about how to locate toxicity assessments, accompanying dose-response values, and relevant guidance documents. However, development and interpretation of toxicity information and dose-response values requires toxicological expertise and should not be undertaken by those without appropriate training and experience.

### 12.1.1 Hazard Identification and Dose-Response Information

As part of the hazard identification step, evidence is gathered from a variety of sources regarding the potential for an air toxic to cause adverse health effects in humans. These sources may include human data, experimental animal studies, and supporting information such as *in vitro* laboratory tests. The source of data affects the overall uncertainties in the resulting human dose-response values, as discussed below.

- **Human data.** Human toxicity data associated with exposures to air toxics may be located in epidemiological studies, controlled exposure studies, or studies of accidental exposures. Well-conducted epidemiological studies that show a positive association between exposure to a chemical and adverse health effects often provide evidence about human health effects associated with chronic exposures. Such data, however, are available only for a limited number of air toxics. Epidemiological data also are very difficult to interpret, because the number of exposed individuals may be small, the incidence of effects may be low, doses are usually not well-characterized, and there may be complicating factors such as simultaneous exposure to multiple chemicals and heterogeneity among the exposed group in terms of age, sex, diet, and other factors. Controlled exposure studies provide stronger evidence, since both the exposure duration and exposure concentrations are more accurately known. However, such studies with humans are generally limited to acute exposure durations. Studies reporting health effects associated with accidental exposures may be helpful, although exposure concentrations to air toxics may be high, and effects may be acute rather than chronic. Also note that small sample size is often a significant limitation to interpreting controlled and accidental exposure studies.
- Epidemiology** is the study of the distribution and determinants of disease or health status in a population.
- **Animal data.** The toxicity database for most air toxics is drawn from experiments conducted on non-human mammals such as rats, mice, rabbits, guinea pigs, hamsters, dogs, or monkeys. The underlying assumption is that the susceptibility of humans and these animals to the effects of the chemicals is broadly similar because we share many common biological attributes (e.g., similar organs, similar and, in some cases, identical metabolic processes). However, some observations in animals may be of uncertain relevance to humans (e.g., if tumors are observed in an animal experiment, but the organ in which the tumor is formed does not exist in humans). Also, it is necessary to adjust the results from animal studies to humans due to differences in body mass, anatomy, metabolic rate, and other species-specific factors (see, for example, Section 12.3.3). This is why derivation of dose-response values from animal studies requires considerable expertise.
  - **Supporting data.** Metabolic, pharmacokinetic, and genotoxicity studies are sometimes used to infer the likelihood of adverse effects in humans. Metabolic studies on absorption, distribution, metabolism, and elimination can provide information about the mechanisms of toxicity associated with a particular chemical in humans. In physiologically based pharmacokinetic (PBPK) models,<sup>(a)</sup> the body is subdivided into a series of anatomical or physiological “compartments” that represent specific organs or lumped tissue and organ groups, and the behavior of the chemical is modeled in each compartment. Data on a chemical’s pharmacokinetics, genotoxicity, and possible mode of action can be used to refine a toxicity assessment. In some cases, computer models using structure-activity relationships (i.e., predictions of toxicological activity based on analysis of chemical structure) also may be used as supporting evidence. EPA considers these types of data to be supportive, not definitive, evidence of a chemical’s toxicity.

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<sup>a</sup>A PBPK model estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion.

Information from these sources is considered in the hazard and dose-response assessment steps in characterizing a chemical with regard to the type(s) of effect a chemical produces (the hazard) and the circumstances in which this occurs, as well as the level of exposure required to produce that effect. The output of the dose-response assessment is the relationship between **dose** (the level of exposure) and the resulting **response** (the increased incidence and/or severity of adverse effects). A dose-response assessment is the process of quantitatively evaluating toxicity information, characterizing the relationship between the dose of the contaminant received (or the inhalation exposure concentration, for inhalation assessments) and the incidence of adverse health effects in the exposed subjects (which may be animal or human) and then, as appropriate, extrapolating these results to human populations. Depending on the type of effect and the chemical, there are two types of dose-response values that traditionally may be derived: predictive cancer risk estimates, such as the **inhalation unit risk estimate (IUR)**, and predictive non-cancer estimates, such as the **reference concentration (RfC)**.<sup>(b)</sup> Both types of dose-response values may be developed for the same chemical, as appropriate.

#### Inhalation Dose-Response Values<sup>(a)</sup>

**Inhalation Unit Risk (IUR):** The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent via inhalation per  $\mu\text{g}/\text{m}^3$  over a lifetime. The interpretation of the IUR would be as follows: if  $\text{IUR} = 2 \times 10^{-6} \mu\text{g}/\text{m}^3$ , not more than 2 excess tumors are expected to develop per 1,000,000 people if exposed continuously for a lifetime to 1  $\mu\text{g}$  of the chemical per cubic meter of inhaled air. The number of expected tumors is likely to be less; it may even be none.

**Reference Concentration (RfC):** An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive sub-populations) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Generally used in EPA's noncancer health assessments.

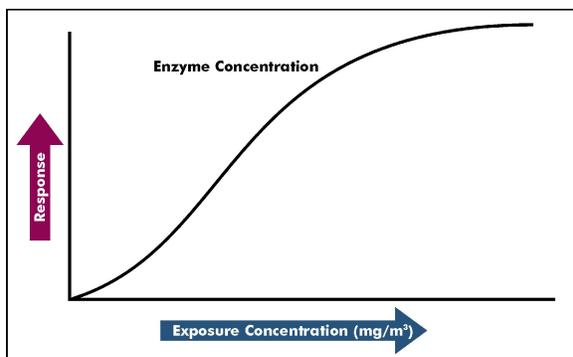
<sup>(a)</sup>The phrase "dose-response" is used generally here and elsewhere in the document. EPA's values for inhalation, however, are derived for exposure concentration, although with consideration of dose. Consideration of the relationship between exposure concentration, dose, and dosimetry (how the body handles a chemical once it is inhaled) is inherent in the derivation of these exposure concentration-response values.

The relationship of dose to response can be illustrated as a graph called a **dose-response curve**. There are two general types of response data that may be considered and graphed. One is termed "continuous" and refers to responses such as the severity in changes to a physiological parameter in a given individual as dose increases (see Exhibit 12-1, A). The second describes the incidence of a particular response in a population (see Exhibit 12-1, B). By convention, dose or exposure is represented on the x-axis; response on the y-axis (Exhibit 12-1).

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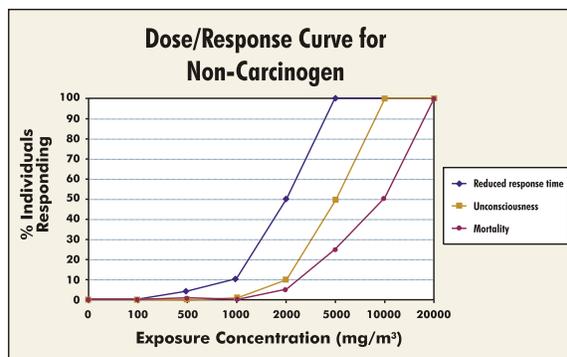
<sup>b</sup>While the majority of RfCs are derived for effects other than cancer, RfCs may be derived for all effects, including cancer, when a non-linear mode of action has been demonstrated for carcinogenicity.

## Exhibit 12-1. Examples of Dose-Response Curves



### A. Continuous Response Data

Simple example of a dose-response curve for graded responses of a specific physiological parameter to increasing exposure.



### B. Different Responses in a Population

Simple example of the incidence of three different effects in an exposed population in response to different exposure concentrations (over the same duration).

While the primary focus of this chapter is on description of dose-response values relevant to chronic (long-term) exposures, the information reviewed for developing those values may include effects associated with acute (short-term) exposures. Additionally, information on acute exposures is essential to the development of acute exposure reference values (see Section 12.6).

- **Acute exposures** are usually relatively short in duration, but relatively high in concentration and may result in immediate respiratory and sensory irritation, chemical burns, narcosis, eye damage, and various other effects. Acute exposures also may result in longer-term health effects.
- **Chronic exposures** are usually relatively long in duration, but relatively low in concentration and may result in health effects that do not show up immediately and that persist over the long term, such as cardiovascular disease, respiratory disease, liver and kidney disease, reproductive effects, neurological damage, and cancer.

Generally, chronic reference values are derived for exposure periods between seven years and a lifetime. Acute reference values (see section 12.6) are generally developed for very short exposures (e.g., hours to days; Exhibit 12-2). For intermediate exposures, subchronic reference values are available from some sources (e.g., ATSDR). Most air toxics risk assessments will focus on chronic and acute evaluations; however, under more limited circumstances, subchronic evaluations may be performed.

### Exhibit 12-2. Reference Values of Different Durations

In the Agency's *Review of the Reference Dose and Reference Concentration Processes*,<sup>2</sup> it was recommended that in addition to the traditional chronic reference value (i.e., RfC or RfD) included in the IRIS database, values of several shorter durations also be developed, where possible. As a first step in this direction, the *Review* proposed the following definitions. EPA currently is considering these and other recommendations made in the *Review*. These definitions are based on exposure durations for humans, and were not intended to be rigid specifications, but simply general descriptions of the relevant exposure time period.

- **Acute:** Exposure by the oral, dermal, or inhalation route for 24 hours or less.
- **Short-term:** Repeated exposure<sup>(a)</sup> by the oral, dermal, or inhalation route for more than 24 hours, up to 30 days.
- **Longer-term:** Repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10 percent of the life span in humans<sup>(b)</sup> (more than 30 days up to 90 days in typically used laboratory animal species<sup>(c)</sup>).
- **Chronic:** Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10 percent of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species).

<sup>(a)</sup>A repeated exposure may be either continuous, periodic, or intermittent. A continuous exposure is a daily exposure for the total duration of interest. A periodic exposure is one occurring at regular intervals (e.g., inhalation exposure 6 hours/day, 5 days/week; or oral exposure 5 days/week). An intermittent exposure is one in which there is no effect of one exposure on the effect of the next; this definition implies sufficient time for the chemical and its metabolites to clear the biological system before the subsequent (i.e., noncumulative pharmacokinetics). A periodic exposure may or may not be intermittent.

<sup>(b)</sup>An average of 70 years is typical default used for chronic exposures.

<sup>(c)</sup>Examples of typically used laboratory species include rats, mice, and rabbits.

#### 12.1.2 Dose-Response Assessment Methods

Depending on whether a substance causes cancer and whether its dose-response curve is thought to have a threshold, EPA may use either of two approaches in a dose-response assessment. One approach produces a predictive estimate (e.g., inhalation cancer risk estimate), and the other produces a reference value (e.g., RfC). Historically, the use of a predictive estimate has been limited to cancer assessment. That is, dose-response assessments for cancer have been expressed as predictive cancer risk estimates based on an assumption that any amount of exposure poses some risk. Assessments of effects other than cancer usually have been expressed as reference values at or below which no harm is expected. Many substances have been assessed both ways: the first for cancer and the second for adverse effects other than cancer. While this use of predictive estimates for cancer and reference values for other effects is still the practice for the vast majority of chemicals, EPA now recognizes that there are chemicals for which the data support an alternate approach.

An important aspect of dose-response relationships is whether the available evidence suggests the existence of a threshold. For many types of toxic responses, there is a **threshold dose** or dose rate below which there are thought to be no adverse effects from exposure to the chemical. The human body has defenses against many toxic agents. Cells in human organs, especially in the liver and kidneys, break down many chemicals into less toxic substances that can be eliminated from the body in urine and feces. In this way, the human body can withstand some chemical exposure (at doses below the threshold) and still remain healthy. For example, many air toxics are naturally occurring substances to which people routinely receive trace exposures at non-toxic levels.

Identification of a threshold dose depends on the type of response and the way in which the toxic chemical produces it. EPA has developed guidelines<sup>3</sup> for assessing the dose-response for various types of adverse effects, which provide more information about evaluating evidence to determine if a threshold exists.

*All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy.*

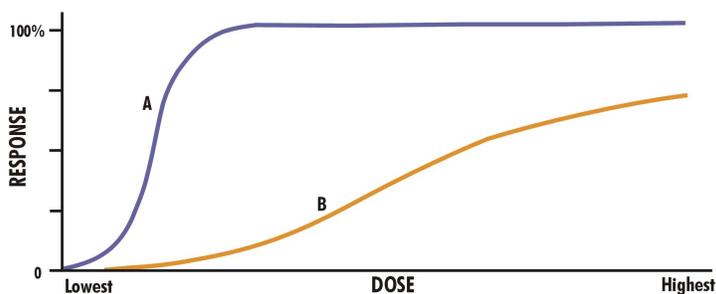
– Paracelsus

Both the point at which the dose-response curve begins to ascend (its threshold, which may be zero) and the slope of the curve (its steepness) provide information about the toxicity of a chemical (Exhibit 12-3). The potency of a chemical is a measure of its strength as a toxicant compared with other chemicals.

Therefore, the lower the threshold dose, the more potent (or toxic) the

chemical. The slope of the curve is a measure of the range of doses from the threshold dose (at which the adverse effect is first measured) to the dose at which the effect is complete (i.e., higher doses produce no additional incidence of that effect, although other adverse effects may begin to appear). The steeper the dose-response curve, the smaller the range between the first appearance of an effect and a substantial response.

#### Different Responses Exhibit Different Dose-Response Curves

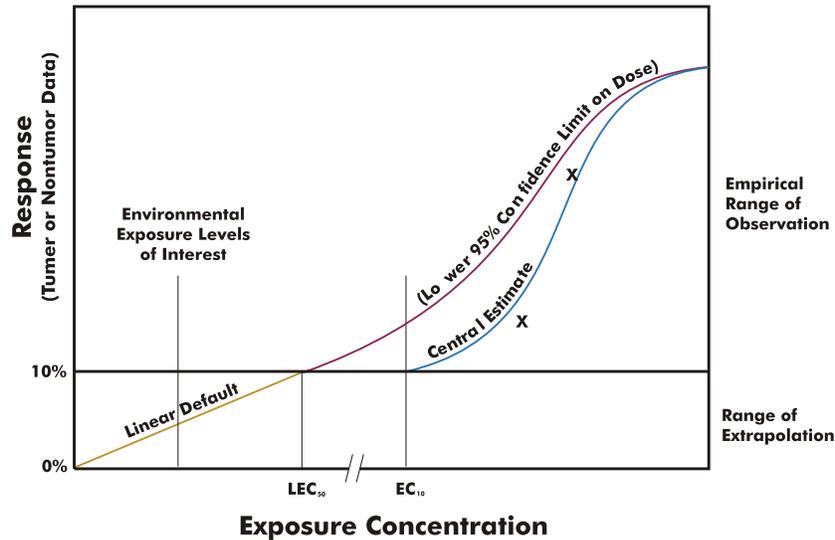


Line A – A sharp increase in response with increasing dose

Line B – A more gradual increase in response with increasing dose

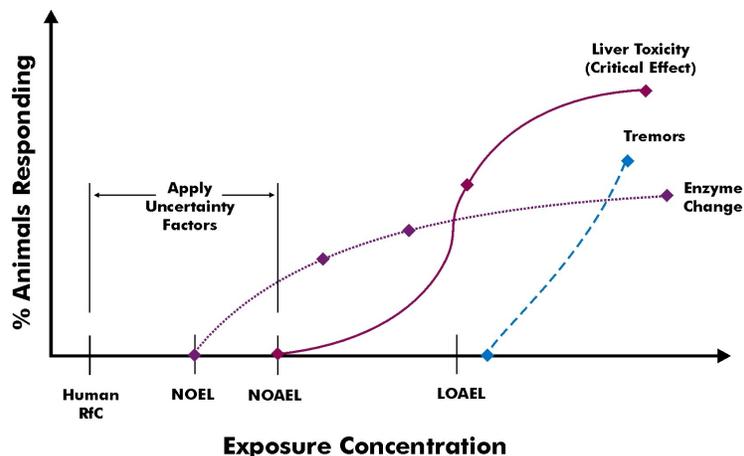
## Exhibit 12-3. Dose-Response Relationships for Carcinogens and Noncarcinogens

### A. Example Linear Carcinogen



In the absence of clear evidence to the contrary, EPA assumes as a matter of science policy that even a very low exposure to a cancer-causing pollutant can increase the risk of cancer (albeit a small amount). Experimental data are used to construct a dose-response relationship and identify the point of departure – the dose that can be considered to be near or in the range of observed responses and, thus, no significant extrapolation is needed. To estimate the dose-response relationship at doses below the point of departure, the dose-response relationship between the point of departure and zero is assumed to be linear. Thus, at doses below the point of departure, with each unit of increase in exposure (dose), there is an increase in cancer response. Where evidence supports the acceptance of a non-linear mode of action, a reference concentration approach may be employed, as shown in “B” below.  $LEC_{50}$  = lethal effective concentration for 50 percent of the population;  $EC_{10}$  = effective concentration that causes an observable adverse effect in 10 percent of the population.

### B. Example Non-linear Approach



A dose may exist below the minimum health effect level for which no adverse effects occur. EPA typically assumes that at low doses the body's natural protective mechanisms prevent or repair any damage caused by the pollutant, so there is no ill effect at low doses. Even long-term (chronic) exposures below the threshold are not expected to have adverse effects. The dose-response relationship (the response occurring with increasing dose) varies with pollutant, individual sensitivity, and type of health effect. NOEL = no-observed-effect-level; NOAEL = no-observed-adverse-effect-level; LOAEL = lowest-observed-adverse-effect-level.

Epidemiologic and toxicologic data on air toxics typically result from exposure levels that are high relative to environmental levels. Therefore, **low-dose extrapolation** (prediction) is necessary to derive an appropriate dose-response value. For a few air toxics (e.g., the criteria air pollutants ozone and carbon monoxide), data are sufficient to characterize dose-response relationships at environmental levels. In such cases, there is no need for extrapolation of toxicity data to lower doses. Such is not the case for most air toxics. Low-dose extrapolation requires either information or assumptions about the type of dose-response curve likely under low dose situations. EPA risk assessment guidelines provide more detailed information on how EPA performs low-dose extrapolation for chemicals with various toxic effects, such as developmental effects or neurotoxic effects.<sup>(3)</sup>

## 12.2 Hazard Identification

The hazard identification, which is usually part of an existing dose-response assessment for each chemical, provides a summary of the available toxicity information for the air toxics being studied, and includes the weight of evidence determination and identification of critical effects. This step should answer the following questions:

- Can exposure to a chemical be linked causally to particular health effects?
- Could these effects occur at environmentally relevant concentrations?
- What is the nature and strength of the evidence of causation?

By definition, all HAPs and many other air toxics have the potential to cause adverse effects in the exposed population. Exhibit 12-4 provides examples of cancer and non-cancer effects, and Appendix C identifies which HAPs have been associated with carcinogenic (cancer) effects or non-cancer effects, along with the strength and ratings of the toxicity evidence that has been evaluated by EPA or other international environmental agencies.

### Items to Include in the Hazard Identification of an Air Toxics Risk Assessment

- List of chemicals detected
- Summaries of toxic effects and quality of the toxicological evidence
- Discussion that focuses the risk assessment on chemicals most likely to cause adverse effects

### Exhibit 12-4. Examples of Adverse Health Effects

- Birth defects
- Tremors
- Infertility
- Skin rash
- Melanoma

An air toxics risk assessment should include in its hazard identification a summary of the quality of the toxicological evidence (i.e., the nature and strength of the evidence of causation) for the chemicals of concern. Study factors such as the route of exposure used, the type and quality of health effects, the biological plausibility of findings, and the consistency of findings across studies all contribute to the strength of the hazard identification statement.

### 12.2.1 Weight of Evidence – Human Carcinogenicity

A major determination made during the hazard identification step concerns the potential of a chemical to cause cancer in humans. This determination, which involves considering (or weighing) all the available evidence, is called the weight of evidence determination. This determination is complicated by possible inadequacies of the published studies, as well as differences in body processes between people and laboratory animals. EPA's *Guidelines for Carcinogen Risk Assessment* guide scientists in interpreting available studies to assess the potential human carcinogenicity of environmental pollutants. (EPA's carcinogen risk assessment guidelines were first published in 1986. Revisions were proposed in 1996 and 2001 and the July 1999 draft of the revisions was adopted as interim guidance. A subsequent 2003 draft of the Guidelines has been released for public and scientific review prior to adoption as final. The guidelines are available on the web.)<sup>4</sup> When compared with EPA's original 1986 guidelines, the 1999 interim Guidelines recommend a more comprehensive evaluation of the evidence with regard to a chemical's potential mode of action, and a more complete description of the context of a chemical's carcinogenic potential (e.g., "likely carcinogenic by inhalation and not likely carcinogenic by oral exposure"). The weight of evidence determination now includes one of five descriptors, and is accompanied by additional text that more completely summarizes EPA's interpretation of the evidence. The narrative statements consider the quality and adequacy of data and the consistency of responses induced by the agent in question (see Exhibit 12-5).

**Exhibit 12-5. Information Regularly Included in a Narrative Statement Describing the Characterization of Weight of Evidence for Carcinogenicity (1999 Interim Guidelines)**

- Name of agent and Chemical Abstracts Services number, if available
- Conclusions (by route of exposure) about human carcinogenicity, using one of five standard descriptors: "Carcinogenic to Humans" "Likely to be Carcinogenic to Humans" "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" "Data are Inadequate for An Assessment of Human Carcinogenic Potential" "Non Likely to be Carcinogenic to Humans".
- Summary of human and animal tumor data on the agent or its structural analogues, their relevance, and biological plausibility
- Other key data (e.g., structure-activity data, toxicokinetics and metabolism, short-term studies, other relevant toxicity or clinical data)
- Discussion of possible mode(s) of action and appropriate dose-response approach(es)
- Conditions of expression of carcinogenicity, including route, duration, and magnitude of exposure

Source: EPA (1999) *Guidelines for Carcinogen Risk Assessment. Review Draft*<sup>(4)</sup>

Many existing carcinogen assessments were developed pursuant to EPA's 1986 *Guidelines for Carcinogen Risk Assessment*, which used a simpler but less informative weight of evidence system (see Exhibit 12-6).

Information bearing on the qualitative assessment of carcinogenic potential may be gained from human epidemiological data, animal studies, comparative pharmacokinetic and metabolism studies, genetic toxicity studies, structure-activity relationship (SAR) analysis, and other studies of an agent's properties. Information from these studies helps to elucidate potential modes of action and biological fate and disposition.

**Exhibit 12-6. EPA's Weight of Evidence Classification for Carcinogens (1986 Guidelines)**

- Group A: Human Carcinogen (sufficient evidence of carcinogenicity in humans)
- Group B: Probable Human Carcinogen (B1 - limited evidence of carcinogenicity in humans; B2 - sufficient evidence of carcinogenicity in animals with inadequate or lack of evidence in humans)
- Group C: Possible Human Carcinogen (limited evidence of carcinogenicity in animals with inadequate or lack of human data)
- Group D: Not Classifiable as to Human Carcinogenicity (inadequate or no evidence)
- Group E: Evidence of Noncarcinogenicity for Humans (no evidence of carcinogenicity in adequate studies)

*Source: EPA (1986). Guidelines for Carcinogen Risk Assessment<sup>(4)</sup>*

Upon such consideration, both EPA systems assign a consensus interpretation to the weight of evidence, evaluating the likelihood that the agent is a human carcinogen. Toxicological 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 chemical is given a weight of evidence classification.

Generally, no single factor is determinative. For example, strength of association is one of the criteria for causality. A strong association between exposure and cancer in animals is more likely to indicate causality than a weak association. However, finding of a large cancer incidence in a single study must be balanced against the lack of consistency as reflected by null results from other equally well-designed and well-conducted studies. In this situation, the positive association of a single study may either suggest the presence of chance, bias, confounding factors, or different exposure conditions. On the other hand, evidence of weak but consistent associations across several studies suggests either causality or that the same confounder may be operating in all of these studies.

If information is available to consider the mode of action for carcinogenicity, the carcinogenicity assessment will evaluate that information and draw conclusions that influence the dose-response method for the substance. If the evidence is sufficient to support a conclusion of nonlinear dose-response, then the information on carcinogenicity may be considered in combination with the information on other effects in deriving a reference value such as an RfC (see section 12.4). Otherwise, a linear dose-response approach leading to a predictive risk estimate, such as an IUR, will usually be pursued. If the information supports it, the guidelines also accommodate the development of a non-linear predictive risk estimate.

## Biological Effects of Carcinogens

**Carcinogens** are chemicals that induce cancers. Examples include:

- *4-Aminobiphenol*, which targets the bladder;
- *Benzene*, which targets the tissue that make white blood cells;
- *Asbestos*, which targets the lung's tissue;
- *Benzidene*, which targets the bladder;
- *Beryllium*, which targets the lungs;
- *Chromium*, which targets the respiratory tract;
- *Radionucleotides*, which targets bone marrow and the lungs; and
- *Vinyl chloride*, which targets the liver.

There are various types of carcinogens, including:

- **Primary Carcinogens:** A primary carcinogen is a substance that is carcinogenic as it occurs in the environment.
- **Procarcinogen:** A procarcinogen is a substance that becomes carcinogenic only after conversion from some benign form. Most environmental carcinogens are of this type.
- **Cocarcinogen:** A cocarcinogen is a substance that is not carcinogenic by itself, but potentiates the carcinogenic effect of other chemicals.

Chemicals also can serve as **mutagens**, causing changes in genetic material that can disrupt cell function and lead to cancer or other health problems.

### 12.2.2 Identification of Critical Effect(s) – Non-Cancer Endpoints

As part of the characterization of the available information on non-cancer health effects (or including cancer, if a threshold mode of action has been established), the targets of chemical toxicity within the body are identified, along with what have been termed “critical effects” associated with the toxicity. A **critical effect** is described as “either the adverse effect that first appears in the dose scale as dose is increased, or as a known precursor to the first adverse effect.” Underlying this designation is the assumption that if the critical effects are prevented, then all other adverse effects observed at higher exposure concentrations or doses are also prevented.<sup>(c)</sup> Note that not all observed effects in toxicity studies are considered adverse effects. The identification of the critical effect(s) depends on a comprehensive review of the available data with careful consideration of the exposure conditions associated with each observed effect, so that comparisons of effect levels or potential reference values are made on a common basis (see Section 12.4). A more comprehensive discussion of hazard identification and the evaluation of the underlying database for non-cancer effects is included in the EPA documents *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (1994) and *A Review of the Reference Dose and Reference Concentration Process* (2002).<sup>5</sup>

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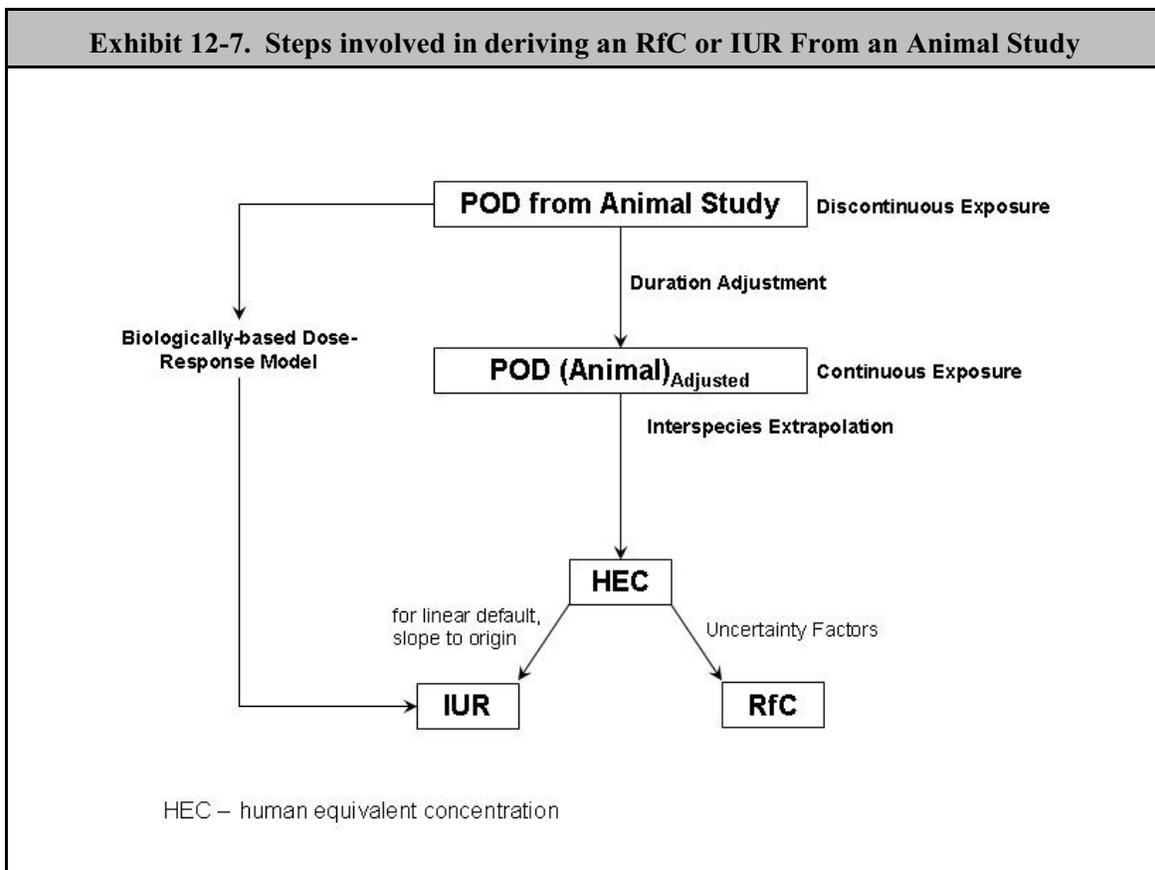
<sup>c</sup>A similar, more recent term, “key event,” is defined as “an empirically observed precursor” to an adverse effect (e.g., liver cancer or other liver toxicity) consistent with a particular mode of action. The phrase “mode of action” refers to the way a given chemical may act in the body to initiate one or more adverse effects.

### 12.3 Dose-Response Assessment for Cancer Effects

The process for deriving a quantitative dose-response estimate for cancer (e.g., a cancer slope factor) involves the following three steps:

1. Determination of the concentration associated with the point of departure or POD (Section 12.3.1);
2. Derivation of the human equivalent concentration corresponding to the POD (Section 12.3.2); and
3. Extrapolation from the POD (expressed as human equivalent concentration) to derive carcinogenic potency estimates (Section 12.3.3).

The first two steps are also performed in the derivation of reference values such as the RfC (Exhibit 12-7); in that case, these steps are followed by the application of uncertainty factors (see Section 12.4).



### 12.3.1 Determination of the Point of Departure (POD)

Dose-response assessment for cancer and other effects begins with identification of the point of departure (an exposure concentration or intake) from the experimental data. This point (in terms of its human equivalent), while within the range of observation, is the point from which extrapolation begins, either for the purposes of deriving a cancer risk estimate (the IUR) or a RfC for non-cancer health effects.

#### Example POD for Benzene

EPA's characterization of the carcinogenic effects of benzene was updated in 1998. The IUR for benzene is based on epidemiologic studies showing clear evidence of a causal association between exposure to benzene and leukemia. The specific mechanisms by which benzene and its metabolites lead to cancer remain uncertain.

EPA selected the Rinsky et al. 1981 epidemiologic study of 1,165 Pliofilm rubber male workers at three facilities in Ohio as the data set for the dose-response relationship for determining the IUR. The workers had been employed between 1940 and 1965 and were followed through 1981. Rinsky et al. expanded the study to include additional workers and published it in 1987. The Rinsky data suffers - as many epidemiologic studies do - from uncertainties about exposure levels in the early years. There are no measurements of benzene in the facilities' air prior to 1946, so exposures for these years must be estimated.

Using one set of exposure estimates with the Rinsky et al. study, EPA concluded that exposure to benzene increases the risk of leukemia at a level of 40 ppm-years of occupational exposure (8 hours/day, 5 days/week, 50 weeks/year). Below this number, the shape of the dose-response curve cannot be determined. Converting the occupational exposure of 40 ppm-years to an equivalent lifetime of environmental exposure yields 120 ppb, as a POD, below which the shape of the dose-response curve is uncertain.

EPA decided there is not sufficient evidence to demonstrate that the dose-response relationship below the POD is non-linear. As a science policy default, EPA assumed low-dose linearity for extrapolation from the POD to zero. Given a range of plausible exposure estimates for the Rinsky et al. study, the Agency determined that the benzene inhalation unit risk at  $1 \mu\text{g}/\text{m}^3$  ranges from  $7.1 \times 10^{-3}$  to  $2.5 \times 10^{-2}$  depending on the exposure estimates and modeling approach used to derive the POD.

*Source: U.S. EPA. 1998. Carcinogenic Effects of Benzene: An Update. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. EPA/600/P-97/001F.; Rinsky, R.A., Young, R.J., and Smith, A.B. 1981. Leukemia in benzene workers. American Journal of Industrial Medicine. 2(3) 217:245.*

The POD may be the traditional no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), or **benchmark concentration (BMC)**.<sup>(d)</sup> EPA has recommended the use of the BMC approach, where possible, because the traditional use of the LOAEL or NOAEL in determining the POD has long been recognized as having several limitations (and

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<sup>d</sup>Note that the corresponding value for ingestion exposures is the benchmark dose (BMD). This often is used as the general term for the BMC/BMD process.

generally is not used in dose-response for cancer effects. In particular, the LOAEL-NOAEL approach:

- Is limited to one of the doses in the study and thus is dependent on study design;
- Does not account for variability and uncertainty in the estimate of the dose-response relationship;
- Does not account for the slope of the dose-response curve; and
- Cannot be applied, where there is no NOAEL, except through the application of an uncertainty factor.

If the dose-response data are of high quality, a mathematical dose-response model may be fitted to the data to determine a more precise POD than the NOAEL or LOAEL. When a model is used, the POD is calculated as the statistical lower confidence limit of the dose at which there is a low toxic response (usually 5 or 10 percent incidence in populations with an effect or a change in a physiological measurement indicating adversity).<sup>(6)</sup> The selection of the response percentage is intended to coincide with the sensitivity limit of the experimental design or professional judgment. This calculated POD is called the BMC.

The BMC approach is an alternate way of determining the point of departure for low-dose extrapolation. It can be used in cancer and noncancer risk assessment as the starting point for linear low-dose extrapolation, calculation of a margin of exposure, or application of uncertainty factors for calculating RfCs or other dose-response values. BMC methods involve fitting various mathematical models for dose-response to reported data and using the different results to select a BMC that is associated with a predetermined benchmark response, such as a 10 percent increase in the incidence of a particular lesion or a 10 percent decrease in body weight gain (Exhibit 12-8). EPA has developed the Benchmark Dose Software (BMDS) to facilitate these operations. BMDS currently offers 16 different mathematical models that can be fit to the laboratory data. EPA plans to continually improve and expand the BMDS system.<sup>6</sup>

It is likely that there will continue to be situations that are not amenable to BMC modeling and for which a NOAEL or LOAEL approach should be used. In some cases, there may be a combination of benchmark doses and NOAELs to be considered in the assessment of a particular agent.

### **12.3.2 Derivation of the Human Equivalent Concentration**

Because inhalation toxicity studies typically involve discontinuous exposures (e.g., animal studies routinely involve inhalation exposures of 6 hours per day, 5 days per week), the POD will usually need to be extrapolated to a continuous exposure scenario (as appropriate for the RfC and IUR). This duration adjustment step is essential in interpreting inhalation studies, but is not routinely necessary for the interpretation of oral exposures. Operationally, this is accomplished

by applying a concentration-duration product, or **C × t product**<sup>(e)</sup> for both the number of hours in a daily exposure period and the number of days per week that the exposures are performed. For example, for a POD of 100 mg/m<sup>3</sup> derived from an animal study in which animals are exposed by inhalation for 6 hours per day, 5 days per week, the adjustment to a continuous

$$100 \text{ mg/m}^3 \times \frac{6}{24} \times \frac{5}{7} = 18 \text{ mg/m}^3 \quad (\text{Equation 12-1})$$

exposure concentration would consider both hours per day and days per week:

Thus, 18 mg/m<sup>3</sup> is the POD concentration adjusted for continuous exposure versus 100 mg/m<sup>3</sup> unadjusted. This approach assumes there is no dose-rate effect (i.e., that the same total inhaled material produces the same effect regardless of the time over which this material was inhaled).

**Exhibit 12-8. Example Derivation of Benchmark Dose Level**

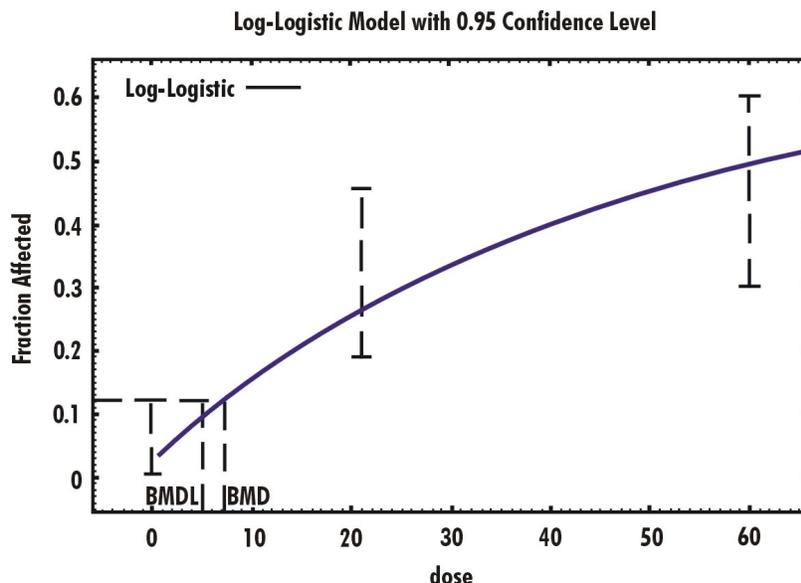


Illustration of the computation of a benchmark dose (BMD) and BMDL (a lower one-sided confidence limit on the BMD) for an extra risk of 0.10 (as suggested by the BMDS guidance document), using a one-sided 95 percent confidence interval. A number of models were fit to the data, and the log-logistic model illustrated provides the best fit to the example data. The predicted curve comes well within the confidence limits for each data point. Other data and models are illustrated in examples provided in the BMDS guidance document.<sup>(6)</sup>

<sup>e</sup>“C × t” is a component of Haber’s Law that refers to the default assumption (in lieu of information to the contrary) that effects observed are related to the cumulative exposure or “area under the curve” (quantified by concentration, C, multiplied by duration, t). It is noted that when going from a discontinuous inhalation exposure regimen to a continuous exposure, the result will always be a lower value for concentration, thus providing an automatic margin of protectiveness for chemicals for which C alone (vs. C × t) may be appropriate, while providing the appropriate conversion for substances for which cumulative exposure is the appropriate measure.<sup>(4)</sup>

Exposures documented from human occupational epidemiological studies are most often reported as 8-hr time-weighted averages (TWAs) and therefore, also are discontinuous. Adjustment of these exposures is usually done as part of the dosimetric adjustment to derive a human equivalent concentration (HEC), rather than as a discrete step, and is explained below in Section 12.3.3. The duration adjustment step also is explicitly incorporated into physiologically based pharmacokinetic (PBPK) models used to extrapolate an animal or occupational study-derived POD into an HEC.

After duration adjustment, the POD is converted into a **human equivalent concentration (HEC)** from the experimental animal dose. This conversion may be done using default methods specific to the particular chemical class of concern or more refined methods such as PBPK modeling.

The Agency's inhalation dosimetry methodology<sup>(5)</sup> provides a recommended hierarchy, as well as default generalized procedures for deriving **dosimetric adjustment factors (DAFs)** for this extrapolation. Application of DAFs to an animal exposure value yields an estimate of the corresponding concentration relevant to humans (i.e., the HEC) given differences in physiology and in the form of the pollutant that influence how the chemical exerts its effect. The DAF depends on the chemical category (i.e., gas or particle) and whether the adverse effect occurs in the respiratory tract or outside of the respiratory tract. HECs are derived using DAFs for both RfC development (noncancer effects) and IUR development (cancer).

**Choice of a Default DAF for Extrapolation from Animal Data  
Depends on the Physical and Chemical Properties of the Pollutant**

**Gases**

- Category 1 (effect in respiratory system) – default DAF based on inhalation rate, and surface area of target portion of respiratory tract
- Category 2 (some characteristics intermediate or common to category 1&3) – default DAF is the more restrictive of the defaults for category 1 & 3
- Category 3 (systemic effect[s]) – default DAF based on blood:air partition coefficient

**Particles**

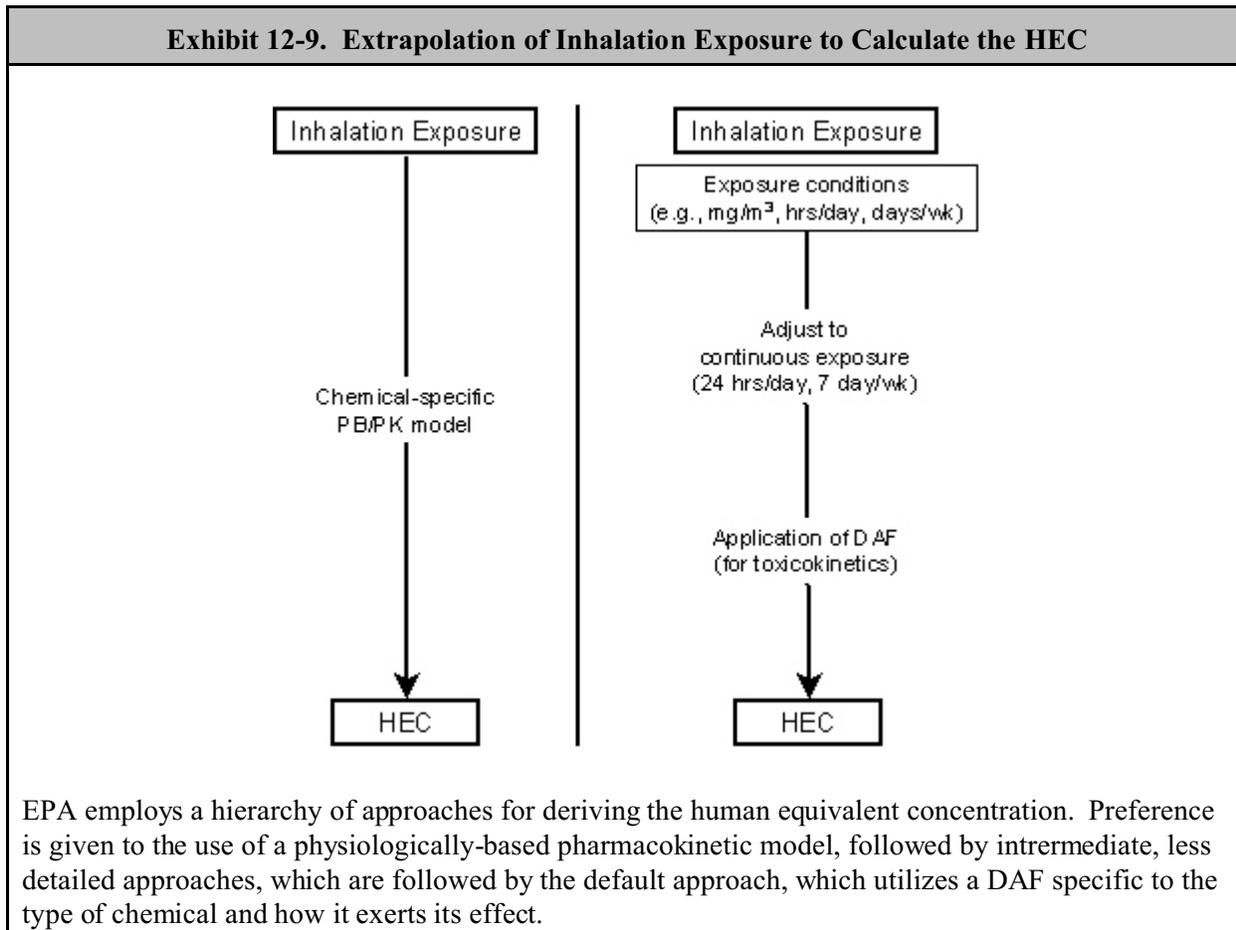
- Respiratory toxicant – default DAF based on fractional deposition, inhalation rate, and surface area of target portion of respiratory tract
- Systemic toxicant – default DAF based on inhalation rate, body weight, and fractional deposition

*Source: U.S. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry.<sup>(5)</sup>*

When data are adequate to support it, the preferred EPA approach for calculating a HEC is to use a chemical-specific PBPK model parameterized for the animal species and regions (e.g., of the respiratory tract) involved in the toxicity (Exhibit 12-9).

In PBPK models, the body is subdivided into a series of anatomical or physiological “compartments” that represent specific organs or tissue and organ groups. The transfer of chemicals between compartments is described by a set of differential equations. The parameters of the model are of three types: physiological parameters (such as tissue perfusions or tissue volumes), physicochemical parameters (such as partition coefficients that describe the degree of partitioning of a given chemical to a given tissue), and biochemical parameters describing metabolic processes. The structure of a PBPK model is determined by the intended use of the model, the biochemical properties of the chemical studied, and the effect site of concern.

**Exhibit 12-9. Extrapolation of Inhalation Exposure to Calculate the HEC**



With sufficient data, a PBPK model is capable of calculating internal doses to a target organ in an animal from any exposure scenario and then estimating what human exposure would result in this same internal dose (i.e., the HEC). A formal DAF is not calculated in this process; rather, the model itself serves as a DAF in estimating HECs. However, constructing a PBPK model is an information-intensive process, requiring much chemical-specific data. Consequently, these models are usually available for only a subset of chemicals. For example, EPA’s IRIS toxicity assessment for vinyl chloride relies on a PBPK model.

### 12.3.3 Extrapolation from POD to Derive Carcinogenic Potency Estimates

Observable cancer rates in laboratory or human occupational epidemiologic studies tend to be several orders of magnitude higher than cancer risk levels that society is willing to tolerate from involuntary chemical exposures. To obtain observable results, laboratory studies need to be

conducted at exposures usually well above environmentally relevant concentrations. Thus, extrapolation from the POD-HEC to lower doses is usually necessary. This extrapolation is performed consistent with the mode of action, if adequately supported. Where the mode of action supports a biologically-based model and the data set is not rich enough to support a biologically based model, a non-linear reference concentration approach is employed (see Section 12.4.2). When the data are insufficient to support a mode of action decision, or where the data support a linear mode of action, a linear extrapolation is employed.

For linear extrapolation, a straight line is drawn from the point of departure expressed as a human equivalent dose to the origin (i.e., zero incremental dose, zero incremental response) to give an incremental probability dose unit. That is, the slope of the line expresses extra risk per dose unit (e.g., the IUR, expressed as extra risk per  $\mu\text{g}/\text{m}^3$  of lifetime exposure). EPA's 1999 proposed guidelines<sup>(4)</sup> for carcinogen risk assessment recommend the use of the lowest effective dose using a 10 percent response level ( $\text{LED}_{10}$ ) (as estimated by the lower one-sided confidence limit on the benchmark concentration [or  $\text{BMCL}_{10}$ ]) as the POD for linear extrapolation. This approach is to draw a straight line between the estimated point of departure, generally, as a default, the  $\text{LED}_{10}$ . The  $\text{LED}_{10}$  is the lower 95 percent limit on a dose that is estimated to cause a 10 percent response. The linear extrapolation approach to assessing risk is considered generally conservative of public health, including sensitive subpopulations, in the absence of specific information about the extent of human variability in sensitivity to effects.

The inhalation cancer dose-response value derived by linear extrapolation is the IUR. It is presented as an upper-bound estimate of the excess cancer risk resulting from a lifetime (assumed 70-year) of continuous exposure to an agent at a concentration of  $1 \mu\text{g}/\text{m}^3$  in air. As illustrated previously in Exhibit 12-2(A), risk is the product of the slope and the estimated exposure. The IUR is a plausible upper-bound estimate of the risk (i.e., the risk is not likely to be higher but may be lower and may be zero). When adequate human epidemiology data are available, maximum likelihood estimates may be used instead of upper bounds to generate the IUR. When only animal data are available and linear extrapolation is used, the IUR is derived from the largest linear slope that is consistent with the data (within the upper 95 percent confidence limit). In other words, the true risk to humans, while not identifiable, is not likely to exceed the upper-bound estimate (the IUR), and is likely to be lower. This means that any estimate of risk for air toxics using an IUR is likely to be protective of all potentially exposed populations. In addition, this means that air toxics risk estimates are likely to be conservative, that is, protective of public health.

The evidence for the carcinogenic mode of action may lead to a conclusion that the dose-response relationship is nonlinear, with response falling much more quickly than linearly with dose, or may be most influenced by individual differences in sensitivity. In some cases this may be due to the mode of carcinogenic action being a secondary effect of toxicity or of an induced physiological change that is itself a threshold phenomenon. EPA does not generally try to distinguish between modes of action that might imply a "true threshold" from those with a nonlinear dose-response relationship. Except in unusual cases where extensive information is available, it is not possible to distinguish between

Risk = EC × IUR, where

EC = lifetime estimate of continuous inhalation exposure to an individual air toxic  
IUR = the corresponding inhalation unit risk estimate for that air toxic

these empirically. Therefore, as a matter of science policy, nonlinear probability functions are only fitted to the response data to extrapolate quantitative low-dose risk estimates when the carcinogenic mechanism of the toxicant is very well-understood. When the evidence indicates a non-linear dose response function containing a significant change in slope, and alternate nonlinear approach may be considered. For example, when carcinogenesis can be shown to be a secondary effect of threshold toxicity, the EPA draft carcinogen guidelines recommend derivation of a reference concentration.

#### **12.4 Dose-Response Assessment for Derivation of a Reference Concentration**

The reference concentration is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive sub-populations) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC is expressed as a chronic exposure level to the chemical in ambient air (in units of milligrams of the substance per cubic meter of air, or mg/m<sup>3</sup>). This value is usually derived for use with effects other than cancer. But when a chemical's carcinogenicity has been shown to be associated with a nonlinear mode of action (see Agency's Cancer Guidelines),<sup>(4)</sup> a reference concentration may be derived for use with all effects, including cancer.

Inherent in the derivation of a reference concentration is the recognition of an exposure level likely to be without an appreciable risk of adverse effects (e.g., a sub-threshold level for adverse effects). The objective of this type of dose-response assessment, then, is to estimate that exposure level for humans. The RfC is derived after a thorough review of the health effects database for an individual chemical and identification of the most sensitive and relevant endpoint (the "critical effect") along with the principal study(ies) demonstrating that endpoint. In addition to an analysis of the study data available for the chemical, risk assessors also use uncertainty factors to account for differences in sensitivity between humans and laboratory animals, the possibility of heightened sensitivity of some population groups (e.g., people with respiratory disease, very young children, the aged), and any limitations of the database. The methodology for derivation of an inhalation reference concentration is described in detail in EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*.<sup>(5)</sup>

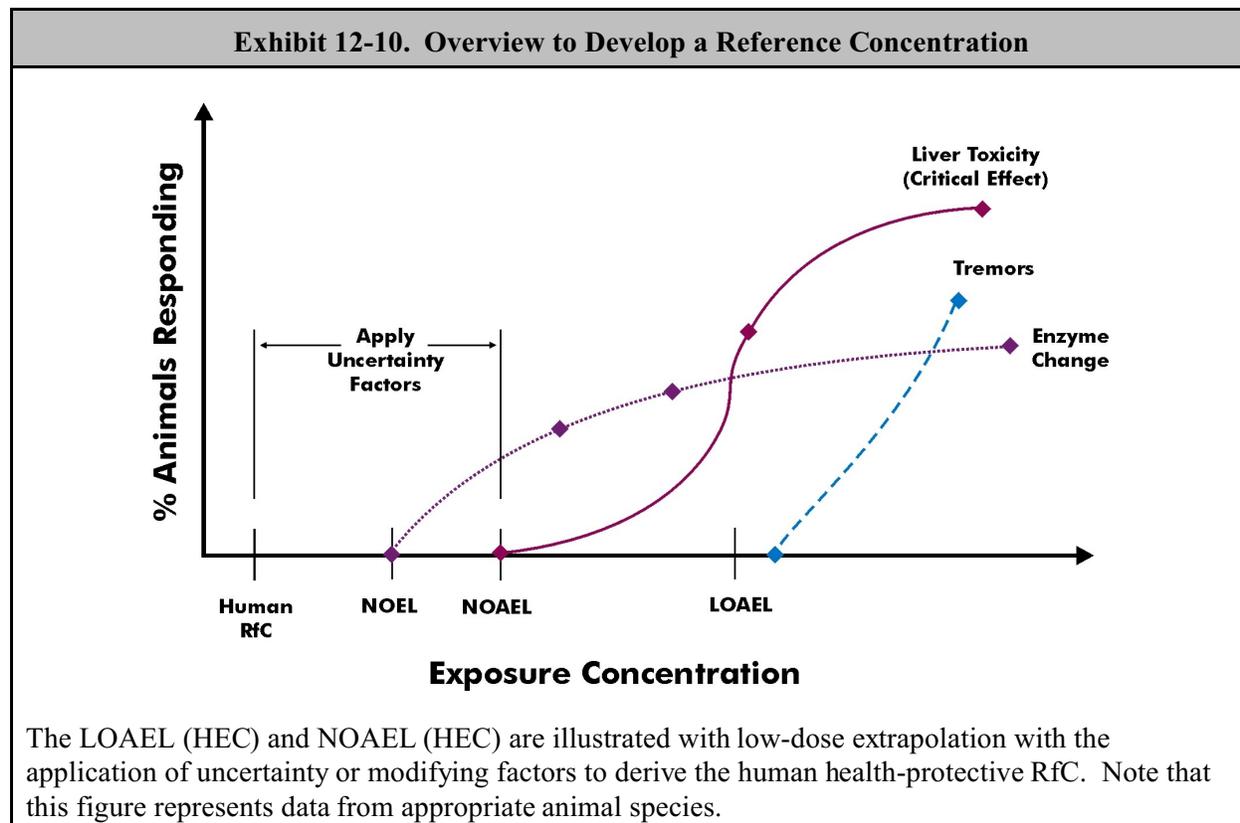
The first part of this type of assessment, which involves a careful qualitative and quantitative analysis of the study data, parallels that performed for linear cancer dose-response assessment (i.e., derivation of the point of departure in terms of a human equivalent concentration [POD<sub>HEC</sub>]). The qualitative analysis is described in Section 12.2.2, while the quantitative analysis is described in Sections 12.3.1 and 12.3.2. The latter part of this type of assessment involves the application of uncertainty factors to address limitations of the data used (e.g., the factors raised above).

In IRIS, EPA includes with each RfC a statement of high, medium, or low confidence based on the completeness of the database for that substance. High confidence RfCs are considered less likely to change substantially with the collection of additional information, while low confidence RfCs may be especially vulnerable to change.<sup>(5)</sup>

### 12.4.1 Determination of the Point of Departure and Human Equivalent Concentration

In earlier sections (Section 12.2.2, 12.3.1 and 12.3.2) the analysis of the database and identification of the critical effect, as well as the derivation of the POD in terms of human equivalent concentrations are discussed.

In developing a dose-response assessment, toxicologists evaluate the available data for a substance. Studies of high quality are selected, and the assessment is focused on the most appropriate studies. As the RfC is a chronic value, preference is given to long-term studies over short-term ones, to studies using animals that exhibit effects similar to those experienced by humans, to studies using an appropriate exposure route (e.g., inhalation exposure for developing an RfC), and to studies showing a clear pattern of increasing frequency or severity of response with increasing dose. Toxicologists use the information to identify the **critical effect** (i.e., the adverse effect that appears at the lowest dose). Afterwards, appropriate human data are chosen as the basis for the RfC or, if human data are not adequate, data from the most appropriate species are identified. If this is not known, the data from the most sensitive species is usually chosen. This analysis is described in Section 12.2.2. The objective in identifying the critical effect or effects is to identify the effect(s) - among all those associated with exposure to the chemical of interest - that occur at the lowest exposure and would lead to derivation of the lowest RfC (Exhibit 12-10).



Using the dose-response relationship for the critical effect, toxicologists identify the POD from the experimental data. This exposure concentration (in terms of its human equivalent) which marks the boundary between the range of observation and that of extrapolation, is the point from

which extrapolation begins for derivation of a RfC. The POD may be derived from benchmark modeling (see Section 12.3.1 regarding the derivation of a BMCL). If the data do not meet requirements for benchmark modeling, the POD is derived by the use of a statistical analysis to identify the **no-observed-adverse-effect-level**, or **NOAEL**, defined as the highest dose level administered to laboratory animals that did not cause statistically or biologically significant observable adverse effects after chronic (usually lifetime) exposure in the studied population. In some cases, a LOAEL is used in the absence of a NOAEL. In either case, the POD is transformed into a continuous inhalation exposure (e.g., from an intermittent animal exposure, 6 hours/day, 5 days/week) and then into a human equivalent concentration (as described in Section 12.3.2). In order for the appropriate critical effect to be identified, a comparison of PODs across different endpoints is done in terms of human equivalent concentrations (or potential RfC values, which incorporate the application of UFs, need to be compared).<sup>(5)</sup>

#### **Derivation of RfC Using BMC Methodology – 1,3-dichloropropene**

A review of the available animal studies indicated changes to the surface cells of the nasal portion of the respiratory tract as the critical effect for 1,3-dichloropropene. Benchmark modeling was performed on the data demonstrating this effect. The seven statistical models for dichotomous data from the Agency's benchmark dose modeling software (BMDS Version.1b) were applied to the incidence data for the adjusted administered doses. The best model fit was determined by eliminating all models that did not have a statistically significant goodness-of-fit ( $p < 0.05$ ). The remaining models were then ranked by best visual fit of the data, especially for the lower doses, as observed in the graphical output of the Benchmark Dose Software. The model with statistically significant goodness-of-fit and best visual and statistical fit was used to estimate the BMC at 10 percent risk and the 95 percent lower confidence limit of the BMC (the BMCL). The gamma, logistic, multistage, Weibull, and quantal-quadratic models provided statistically significant fits. The gamma model was the best fit overall because it provided the best visual fit. This model yielded a  $BMC_{10}$  of  $5.9 \text{ mg/m}^3$  and a  $BMCL_{10}$  of  $3.7 \text{ mg/m}^3$ .

The  $BMCL_{10}$  was identified as the POD and was adjusted from experimental conditions to a continuous inhalation exposure value ( $POD_{adj}$ ). Because the critical target was the nasal mucosa, algorithms for extrathoracic effects for Category 1 gases were used to adjust continuous animal exposure concentration to HEC. The  $POD_{HEC}$  for a Category 1 gas was derived by multiplying the animal  $BMCL_{10}$  by an interspecies dosimetric adjustment for gas:respiratory effects in the extrathoracic area of the respiratory tract. Using default values, the adjustment factor was equal to 0.2. For example, for 1,3-dichloropropene:

$$POD_{HEC} = BMCL_{10}(HEC) = BMCL_{10} (adj) \times 0.2 = 3.7 \times 0.2 = 0.7 \text{ mg/m}^3$$

The  $POD_{HEC}$  was divided by uncertainty factors for interspecies extrapolation (UF of 3) and intraspecies variation (UF of 10) and rounded to one significant figure to yield the RfC for 1,3-dichloropropene:

$$RfC = POD_{HEC} / 30 = 0.02 \text{ mg/m}^3$$

## 12.4.2 Application of Uncertainty Factors

The RfC is an estimate derived from the  $POD_{HEC}$  for the critical effect (based on either a  $BMCL_{HEC}$ ,  $NOAEL_{HEC}$  or  $LOAEL_{HEC}$ ) by consistent application of UFs. The UFs are applied to account for recognized uncertainties in the use of the available data to estimate an exposure concentration appropriate to the assumed human scenario. The general formula for deriving an RfC from a  $POD_{HEC}$  is:

$$RfC(mg/m^3) = \frac{POD_{HEC}(mg/m^3)}{UF} \quad (\text{Equation 12-2})$$

A UF of 10, 3, or 1 is applied for each of the following extrapolations used to derive the RfC (see Exhibit 12-11):

- Animal to human;
- Human to sensitive human populations;
- Subchronic to chronic;
- LOAEL to NOAEL; and
- Incomplete to complete database.

The UFs are generally an order of magnitude (10), although incorporation of dosimetry adjustments or other information may result in the use of reduced UFs for RfCs (3 or 1). The composite UF applied to an RfC will vary in magnitude depending on the number of uncertainties involved; however, an RfC will not be derived when use of the data involves more than four areas of extrapolation. The composite UF when four factors are used generally is reduced from 10,000 to 3,000 in recognition of the lack of independence and the conservatism of these factors.

The 2002 Agency review of the reference dose (RfD)/reference concentration process<sup>(2)</sup> encouraged the development of guidance in the area of chemical-specific adjustment factors (CSAFs). These factors utilize specific data to replace the default UFs for interspecies or inter-individual variation. The review panel noted, however, that the CSAF approach for any single substance is determined principally by the availability of relevant data. For many substances there are relatively few data available to serve as an adequate basis to replace defaults for interspecies differences and human variability with more informative CSAFs.

Because of this procedure to address the lack of information on the translation from experimental data to a human scenario, the resulting RfC for many HAPs is on the order of 100 to 300 times lower than the NOAEL actually observed in the animal testing (see Exhibit 12-12). This reflects the lowering of the RfC to address the uncertainties in the extrapolations mentioned above. For those HAPs that have had their effects well documented in human studies, the RfC may be much closer to the highest concentration at which an adverse effect was not observed (e.g., within a factor of 3 to 10).

**Exhibit 12-11. Uncertainty Factors Used in the Derivation of an Inhalation RfC**

Standard Uncertainty Factors	Processes Considered in UF Purview
<p><b>A = Animal to human</b>                      Extrapolation from valid results of long-term studies on laboratory animals when results of studies of human exposure are not available or are inadequate. Intended to account for the uncertainty in extrapolating laboratory animal data to the case of average healthy humans.</p>	<ul style="list-style-type: none"> <li>• Pharmacokinetics/Pharmacodynamics</li> <li>• Relevance of laboratory animal model</li> <li>• Species sensitivity</li> </ul>
<p><b>H = Human to sensitive human</b>                      Extrapolation of valid experimental results for studies using prolonged exposure to average healthy humans. Intended to account for the variation in sensitivity among the members of the human population.</p>	<ul style="list-style-type: none"> <li>• Pharmacokinetics/Pharmacodynamics</li> <li>• Sensitivity</li> <li>• Differences in mass (children, obese)</li> <li>• Concomitant exposures</li> <li>• Activity Pattern</li> <li>• Does not account for idiosyncrasies</li> </ul>
<p><b>S = Subchronic to chronic</b>                      Extrapolation from less than chronic exposure results on laboratory animals or humans when there are no useful long-term human data. Intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs.</p>	<ul style="list-style-type: none"> <li>• Accumulation/Cumulative damage</li> <li>• Pharmacokinetics/Pharmacodynamics</li> <li>• Severity of effect</li> <li>• Recovery</li> <li>• Duration of study</li> <li>• Consistency of effect with duration</li> </ul>
<p><b>L = LOAEL to NOAEL</b>                      Derivation from a LOAEL instead of a NOAEL. Intended to account for the uncertainty in extrapolating from LOAELs to NOAELs.</p>	<ul style="list-style-type: none"> <li>• Severity</li> <li>• Pharmacokinetics/Pharmacodynamics</li> <li>• Slope of dose-response curve</li> <li>• Trend, consistency of effect</li> <li>• Relationship of endpoints</li> <li>• Functional vs histopathological evidence</li> <li>• Exposure uncertainties</li> </ul>
<p><b>D = Incomplete to complete data</b>                      Extrapolation from valid results in laboratory animals when the data are “incomplete”. Intended to account for the inability of any single laboratory animal study to adequately address all possible adverse outcomes in humans.</p>	<ul style="list-style-type: none"> <li>• Quality of critical study</li> <li>• Data gaps</li> <li>• Power of critical study/supporting studies</li> <li>• Exposure uncertainties</li> </ul>
<p><i>Source: U.S. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry.<sup>(5)</sup></i></p>	

<b>Exhibit 12-12. Examples of the Use of Uncertainty Factors in Deriving RfCs</b>	
<b>RfC from NOAEL Example: Diesel Engine Emissions</b>	<b>RfC from LOAEL Example: Toluene</b>
<p><i>Toxicity data:</i> 144 µg chemical/m<sup>3</sup> air (NOAEL<sub>HEC</sub> from chronic rodent study)</p> <p><i>Uncertainty factors:</i> 3 x 10 = 30</p> <p>3 = animal-to-human extrapolation 10 = human to sensitive human subpopulations</p> <p>RfC = 144/30 = 4.8 µg/m<sup>3</sup> = 0.005 mg/m<sup>3</sup></p>	<p><i>Toxicity data:</i> 119 mg chemical/m<sup>3</sup> air (LOAEL<sub>HEC</sub> from chronic occupational study)</p> <p><i>Uncertainty factors:</i> 10 x 10 x 3 = 300</p> <p>10 = human to sensitive human subpopulations 10 = LOAEL-to-NOAEL extrapolation 3 = database deficiencies</p> <p>RfC = 119/300 mg/m<sup>3</sup> = 0.4 mg/m<sup>3</sup></p>
<p>NOAEL<sub>HEC</sub> = No-Observed-Adverse-Effect Level (Human Equivalent Concentration) LOAEL<sub>HEC</sub> = Lowest-Observed-Adverse-Effect Level (Human Equivalent Concentration)</p> <p>Source: EPA's IRIS database <a href="http://www.epa.gov/IRIS/">http://www.epa.gov/IRIS/</a>.</p>	

In some of the older IRIS assessments a “modifying factor” may have been applied in addition to the traditional uncertainty factors. It had been used with professional judgement when it was determined that another uncertainty factor was needed; its magnitude depended upon the professional assessment of scientific uncertainties of the study and database not explicitly treated via the other uncertainty factors.<sup>(5)</sup> The 2002 Agency review of the RfD/RfC process, however, recommended against continued use of the modifying factor. It was felt that the traditional factors could account for any remaining uncertainties.<sup>(2)</sup>

## 12.5 Sources of Chronic Dose-Response Values

Appendix C provides a current listing of appropriate chronic dose-response values (i.e., RfCs or comparable values and IURs) for HAPs.<sup>(f)</sup> References for acute exposure levels are provided below in Exhibit 12-13. Hazard identification and dose-response assessment information for chronic exposure, presented in Appendix C, was obtained from various sources and prioritized according to (1) conceptual consistency with EPA risk assessment guidelines, and (2) level of review received. The prioritization process was aimed at incorporating into our assessments the best available science with respect to dose-response information. The sources listed below were used, and provide this information for chemicals beyond the 188 Clean Air Act hazardous air pollutants listed in Appendix C.

- **U.S. Environmental Protection Agency (EPA).** EPA has developed dose-response assessments for chronic exposure to many pollutants. These assessments typically specify an RfC (to protect against effects other than cancer) and/or IUR (to estimate the probability of

<sup>f</sup>As noted earlier, see <http://www.epa.gov/ttn/atw/toxsource/summary.html> for a current listing of this information.

contracting cancer). Background documents, particularly for the more recent files, also contain information on physical and chemical properties, toxicokinetics, and hazard characterization. EPA disseminates dose-response assessment information in several forms, based on the level of review. Dose-response assessments that have achieved full intra-agency consensus are incorporated in the **Integrated Risk Information System (IRIS)**, which is regularly updated and available on-line ([www.epa.gov/iris](http://www.epa.gov/iris)). All IRIS assessments since 1996 also have undergone independent external peer review. In the past, dose-response assessments for some substances were prepared by the EPA Office of Research and Development, but were never submitted for EPA consensus. EPA has assembled the results of many such assessments in the **Health Effects Assessment Summary Tables (HEAST)**. Although the values in HEAST have undergone some review and have the concurrence of individual Agency program offices, they have not had enough review to be recognized as Agency-wide consensus information. In addition, since HEAST has not been updated since 1997, other sources described here are, for many chemicals, more reliable.

- **Agency for Toxic Substances and Disease Registry (ATSDR).** ATSDR, which is part of the US Department of Health and Human Services, develops and publishes Minimum Risk Levels (MRLs) for many toxic substances. The MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (other than cancer) over a specified duration of exposure. MRLs are derived for acute (1-14 days), intermediate (>14-364 days), and chronic (365 days and longer) exposures by inhalation and oral routes. ATSDR describes MRLs as substance-specific estimates to be used by health assessors to select environmental contaminants for further evaluation. MRLs are presented with only one significant figure and are considered to be levels below which contaminants are unlikely to pose a health threat. Exposures above an MRL do not necessarily represent a threat, and MRLs are therefore not intended for use as predictors of adverse health effects or for setting cleanup levels. The MRL data undergo a rigorous review process, including internal ATSDR review, peer reviews, and public comment periods. Appendix C shows the ATSDR chronic MRL where no IRIS value is available, because the MRL's concept, definition, and derivation are philosophically consistent (though not identical) with EPA's guidelines for assessing noncancer effects. ATSDR publishes MRLs as part of pollutant-specific toxicological profile documents, and also in regularly-updated on-line tables.<sup>7</sup>
- **California Environmental Protection Agency (CalEPA).** The CalEPA Office of Environmental Health Hazard Assessment (OEHHA) has developed dose-response assessments for many substances, based both on carcinogenicity and health effects other than cancer. The process for developing these assessments is similar to that used by EPA to develop IRIS values and includes significant external scientific peer review. The non-cancer information includes inhalation health risk guidance values expressed as chronic inhalation reference exposure levels (RELs). CalEPA defines the REL as a concentration level at (or below) which no health effects are anticipated, a concept that is substantially similar to EPA's approach to non-cancer dose-response assessment. Appendix C shows the chronic REL (including both final and proposed values) where no IRIS RfC/RfD or ATSDR MRL exists. CalEPA's quantitative dose-response information on carcinogenicity by inhalation exposure is expressed in terms of the IUR, defined similarly to EPA's IUR. Appendix C shows specific CalEPA UREs where no IRIS values exist. CalEPA's dose response assessments for carcinogens and noncarcinogens are available on-line.<sup>8</sup>

- **International Agency for Research on Cancer (IARC).** The IARC, a branch of the World Health Organization, coordinates and conducts research on the causes of human cancer and develops scientific strategies for cancer control. The IARC sponsors both epidemiological and laboratory research, and disseminates scientific information through meetings, publications, courses and fellowships. As part of its mission, the IARC assembles evidence that substances cause cancer in humans and issues judgments on the strength of evidence. IARC's categories are Group 1 (carcinogenic in humans), Group 2A (probably carcinogenic), Group 2B (possibly carcinogenic), Group 3 (not classifiable), and Group 4 (probably not carcinogenic). The categorization scheme may be applied to either single chemicals or mixtures; however, IARC does not develop quantitative dose-response metrics such as UREs. IARC's categories for substances are included in Appendix C to support or augment EPA's weight-of-evidence (WOE) determinations, which do not cover all substances and in some cases may be out-of-date. The list of IARC evaluations to date is available on-line (<http://193.51.164.11/monoeval/grlist.html>).

Additionally, the EPA has compiled fact sheets for the 188 CAA hazardous air pollutants and makes them available on the Air Toxics website (<http://www.epa.gov/ttn/atw/hapindex.html>). This collection is called the **Health Effects Notebook for Hazardous Air Pollutants**, and provides for each HAP a summary of available information in the following categories: hazard summary, physical properties, uses, sources and potential exposure, and health hazard information. These fact sheets are useful for describing hazards associated with the 188 HAPs.

## 12.6 Acute Exposure Reference Values

Many air pollutants can cause adverse health effects after acute or short-term exposures lasting from a few minutes to several days. For some pollutants, acute exposures may be of greater concern than chronic exposures. The severity of effects from acute exposures may vary widely. Agency-wide guidance on how to assess toxic effects from short-term exposures is currently being developed. This guidance for Acute Reference Exposure (ARE) levels is intended to assist acute risk assessment activities. A variety of other short-term, acute exposure limits are also described in Exhibit 12-12.<sup>9</sup> Appendix C provides a current listing of acute dose-response values for HAPs.

Methods for dose-response assessment of acute exposures are usually similar to the approach for chronic exposure, with their derivation involving the identification of a "critical effect," determination of a NOAEL or comparable value for that effect, and application of uncertainty factors (e.g., animal to human population). However, the process by which most acute inhalation dose-response assessment values are derived differs from the chronic RfC methodology in two important ways. First, "acute" may connote exposure times varying from a few minutes to two weeks. The time frame for the value is critical, because the safe dose (or the dose that produces some defined effect) may vary substantially with the length of exposure. Second, some acute dose-response assessments include more than one level of severity. A typical assessment may have values for level 1 (at which only mild, transient effects may occur), level 2 (above which irreversible or other serious effects may occur), and level 3 (above which life-threatening effects may occur). Therefore, many acute assessments present dose-response assessment values as a matrix, with one dimension being length of exposure and the other a severity-of-effect category.

**Exhibit 12-13. Examples of Available Short-Term, Acute Exposure Levels**

Acronym	Full Name	Group or Agency	Purpose/Definition	Source/Website
<b>AEGL</b>	Acute Exposure Guideline Level	National Research Council (NRC) National Advisory Committee (NAC)	<p>The AEGLs represent short-term threshold or ceiling exposure values intended for the protection of the general public, including susceptible or sensitive individuals, but not hypersusceptible or hypersensitive individuals. The AEGLs represent biological reference values for this defined human population and consist of three biological endpoints for four different single emergency (accidental) exposure periods (30 minutes, 1 hour, 4 hours, and 8 hours). In some instances, AEGLs also are developed for 5 or 10 minutes. The biological endpoints are defined as follows:</p> <ul style="list-style-type: none"> <li>• AEGL-1 is the airborne concentration (expressed as parts per millions [ppm] or milligrams [mg]/meters [m]<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but excluding “hypersusceptible” individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that could produce mild odor, taste, or other sensory irritations.</li> <li>• AEGL-2 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but excluding “hypersusceptible” individuals, could experience irreversible or other serious, long-lasting effects or impaired ability to escape. Airborne concentrations below the AEGL-2 but at or above AEGL-1 represent exposure levels that may cause notable discomfort.</li> <li>• AEGL-3 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but excluding “hypersusceptible” individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL-3 but at or above AEGL-2 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impaired ability to escape.</li> </ul>	<a href="http://search.nap.edu/books/0309072948/html/">http://search.nap.edu/books/0309072948/html/</a>
<b>ARE</b>	Acute Reference Exposure	U.S. Environmental Protection Agency	<p>The ARE is an informed estimate of the highest inhalation exposure (concentration and duration) that is not likely to cause adverse effects in a human population, including sensitive subgroups, exposed to that scenario, even on an intermittent basis.<sup>10</sup> For these purposes, acute exposures are single continuous exposures lasting 24 hours or less; AREs may be derived for any duration of interest within that period. “Intermittent” implies sufficient time between exposures such that one exposure has no effect on the health outcome produced by the next exposure. EPA is in the process of finalizing the methodology for development of AREs.</p>	

**Exhibit 12-13. Examples of Available Short-Term, Acute Exposure Levels**

Acronym	Full Name	Group or Agency	Purpose/Definition	Source/Website
<b>BEI</b>	Biological Exposure Indices	American Conference of Governmental Industrial Hygienists	BEIs <sup>®</sup> are health-based values for use by industrial hygienists in making decisions regarding safe levels of exposure to various chemical and physical agents found in the workplace.	<a href="http://www.acgih.org/TLV/">http://www.acgih.org/TLV/</a>
<b>CEEL</b>	Community Emergency Exposure Level	National Research Council (NRC) National Advisory Committee (NAC)	CEELs are ceiling exposure values for the public applicable to emergency exposures of foreseeable magnitude and duration, usually not exceeding 1 hour. Three CEELs were established: <ul style="list-style-type: none"> <li>• CEEL-1: Concentration above which discomfort, for example eye and nose irritation or headaches, becomes increasingly common;</li> <li>• CEEL-2: Concentration above which disability, for example, severe eye or respiratory irritation, becomes increasingly common;</li> <li>• CEEL-3: Concentration above which death or life-threatening effects, for example, pulmonary edema, cardiac failure, or cancer, become increasingly common.</li> </ul>	Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances (NRC, 1993)
<b>EEGL</b>	Emergency Exposure Guidance Level	NAS Committee on Toxicology	Exposure levels judged to be acceptable for military personnel performing tasks during emergency situations. Not considered safe exposure level for routine or normal operations.	
<b>ERPG</b>	Emergency Response Planning Guideline	American Industrial Hygiene Association's (AIHA) Emergency Response Planning Committee	These guidelines are intended for application by persons trained in emergency response planning. <p>ERG-1: The maximum concentration in air below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor.</p> <p>ERG-2: The maximum concentration in air below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair their abilities to take protective action.</p> <p>ERG-3: The maximum concentration in air below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.</p>	<a href="http://www.bnl.gov/scapa/erpgpref.htm">http://www.bnl.gov/scapa/erpgpref.htm</a>  <a href="http://www.bnl.gov/scapa/scapawl.htm">http://www.bnl.gov/scapa/scapawl.htm</a>
<b>IDLH</b>	Immediately Dangerous to Life or Health Concentration	National Institute for Occupational Safety and Health (NIOSH)	An immediately dangerous to life or health condition is one "that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment. The purpose of establishing an IDLH is to ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment.	NIOSH Respirator Decision Logic [NIOSH 1987],  <a href="http://www.cdc.gov/niosh/idlh/intrid14.html">http://www.cdc.gov/niosh/idlh/intrid14.html</a>

**Exhibit 12-13. Examples of Available Short-Term, Acute Exposure Levels**

Acronym	Full Name	Group or Agency	Purpose/Definition	Source/Website
<b>LOC</b>	Level of Concern	U.S. Environmental Protection Agency, Federal Emergency Management Agency, U.S. Department of Transportation	Defined by the Technical Guidance for Hazards Analysis (a guide developed to assist in planning for accidental chemical releases). As the concentration of an extremely hazardous substances in air above which there may be serious irreversible health effects or death as a result of a single exposure for a relatively short period of time. In the 1987 Technical Guidance for Hazards Analysis document, an LOC was estimated by using one-tenth of the IDLH level published by the National Institute for Occupational Safety and Health. For the purposes of offsite consequence analysis performed as part of accidental release requirements under Section 112(r) of the CAA, this value is superceded by ERPG-2 values as available, and the Agency intends to supercede those values with AEGL-2 values as they are developed and adopted.	Technical Guidance for Hazards Analysis. Emergency Planning for Extremely Hazardous Substances. (USEPA, FEMA, USDOT, 1987). 61 FR 31672; June 20, 1996
<b>MRL</b>	Acute Minimum Risk Levels	U.S. Agency for Toxic Substances and Disease Registry (ATSDR)	The MRL is an estimate of human exposure to a substance that is likely to be without an appreciable risk of adverse effects (other than cancer) over a specified duration of exposure, and can be derived for acute exposures by the inhalation and oral routes. Unlike the one-hour focus of most of the other values listed here, acute MRLs are derived for exposures of 1 to 14 days duration.	<a href="http://www.atsdr.cdc.gov/mr/ls.html">http://www.atsdr.cdc.gov/mr/ls.html</a>
<b>REL</b>	Reference Exposure Level	California EPA Office of Environmental Health Hazard Assessment (OEHHA)	The acute REL is an exposure that is not likely to cause adverse effects in a human population, including sensitive sub-populations, exposed to that concentration for one hour on an intermittent basis. RELs are based on the most sensitive, relevant, adverse health effect reported in the medical and toxicological literature. RELs are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety. Since margins of safety are incorporated to address data gaps and uncertainties, exceeding the REL does not automatically indicate an adverse health impact. OEHHA has defined the lowest available acute severity level as the REL.	<a href="http://www.oehha.ca.gov/air/pdf/acutere1.pdf">http://www.oehha.ca.gov/air/pdf/acutere1.pdf</a>
<b>SPEGL</b>	Short-term Public Emergency Exposure Guidance Level	National Academy of Sciences (NAS) Committee on Toxicology	The NAS develops short-term public emergency exposure guidance levels (SPEGLs) to apply to the exposures of the general public to contaminants during airborne chemical releases; SPEGLs are generally set at a level of 0.1 to 0.5 times the EEGL and are measured as 60 minute or 8 hour exposure time frames.	<i>Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents.</i> 1986. National Academy Press, National Academy of Sciences, Washington, D.C.

**Exhibit 12-13. Examples of Available Short-Term, Acute Exposure Levels**

<b>Acronym</b>	<b>Full Name</b>	<b>Group or Agency</b>	<b>Purpose/Definition</b>	<b>Source/Website</b>
<b>STEL</b>	Short-Term Exposure Limit	American Conference of Governmental Industrial Hygienists (ACGIH)	STELs are time weighted average (TWA) guidelines for the control of short term exposure in the workplace. These are important supplements to the eight-hour TWA exposure standards which are more concerned with the total intake over long periods of time. Generally, STELs are established to minimize the risk of the occurrence in nearly all workers of: intolerable irritation; chronic or irreversible tissue change; and narcosis to an extent that could precipitate industrial accidents, provided the eight hour TWA exposure standards are not exceeded. STELs are recommended for those substances only when there is evidence either from human or animal studies that adverse health effects can be caused by high short term exposure. STELs are expressed as airborne concentrations of substances, averaged over a period of 15 minutes.	

## 12.7 Evaluating Chemicals Lacking Health Reference Values

### 12.7.1 Use of Available Data Sources

If EPA-derived IRIS assessments are available for the chemicals being examined, these values should generally be used in the risk assessment. Use of IRIS or other EPA-derived dose-response values prevents duplication of effort in toxicity assessment and ensures consistency in the dose-response values among risk assessments. If EPA-derived dose-response values are not available, the other sources described in Section 12.6 should be given next priority. Use of these sources in a hierarchical manner has been implemented in tables developed for the 188 hazardous air pollutants (see Appendix C and <http://www.epa.gov/ttn/atw/toxsource/table1.pdf>). The Toxicology Excellence for Risk Assessment (TERA) maintains a database of international dose-response values (see [www.TERA.org/iter](http://www.TERA.org/iter)).

If those sources also lack inhalation dose-response values, then route-to-route extrapolation (discussed below) may be considered. This approach, however, may be quite detailed, and requires assistance from a professional toxicologist. If all sources and approaches have been researched, and no dose-response value is available, 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.

### 12.7.2 Route-to-Route Extrapolation

For cases in which appropriate dose-response values are not available for the route of exposure being considered, but are available for another route, it may be possible to use route-to-route extrapolation. Route-to-route extrapolation is recommended only from oral to inhaled exposure and only for carcinogens. The ability to perform quantitative route-to-route extrapolation is critically dependent on the amount and type of data available. Regardless of the toxic endpoint being considered, a minimum of information is required to construct plausible dosimetry for the routes of interest. This information includes both the nature of the toxic effect and a description of the relationship between exposure and the toxic effect.

Data from other routes of exposure may be useful to derive an RfC (for carcinogens only; discussed below) only when respiratory tract effects and/or “first pass” effects can be ruled out. First pass effects are cases where metabolism takes place in the portal-of-entry tissues, prior to entry into the systemic circulation. The respiratory tract can exhibit a first-pass effect after inhalation. Unless the first-pass effect and dosimetry are adequately understood, there can be substantial error introduced in route-to-route extrapolation that does not account for these considerations.

**Route to route extrapolations should only be done by qualified toxicologists.**

Oral toxicity data should *not* be used for route-to-route extrapolation in the following cases (unless these effects can be accounted for in a PBPK model):

- When groups of chemicals have different toxicity by the two different routes (e.g., metals, irritants, and sensitizers);
- When a first-pass effect by the respiratory tract is expected;

- When a first-pass effect by the liver is expected;
- When a respiratory tract effect is established, but dosimetry comparison cannot be clearly established between the two routes;
- When the respiratory tract is not adequately studied in the oral studies; and
- When short-term inhalation studies, dermal irritation, in vitro studies, or characteristics of the chemical indicate potential for portal-of-entry effects at the respiratory tract, but studies themselves are not adequate for an RfC development.

The actual impact of exposure by different routes can only be estimated by taking account of factors that influence absorption at the portal of entry, such as (1) physicochemical characteristics of the chemical; (2) exposure factors; and (3) physiologic parameters. The preferred method for performing route-to-route extrapolation involves the development of a PBPK model that describes the disposition of the chemical for the routes of interest. As previously discussed, PBPK models account for fundamental physiologic and biochemical parameters and processes such as blood flow, ventilatory parameters, metabolic capacities, and renal clearance, tailored by the physicochemical and biochemical properties.

If appropriate toxicity information is not available, a qualitative rather than quantitative evaluation of the chemical is recommended. The implications of the absence of the chemical from the risk estimate should be discussed in the uncertainty section.

## 12.8 Dose-Response Assessment for Mixtures

The recommended approach for assessing risks from exposure to a mixture of pollutants (e.g., coke oven emissions, diesel exhaust, etc.) is to utilize a dose-response assessment developed for that mixture or a mixture judged similar.<sup>11 12</sup> Where such an assessment is not available, a component-by-component approach may be employed. There are several commonly used approaches. Selection among the approaches involves consideration of the similarity of the mixture components with regard to their toxicological activity. There are a few groups of toxicologically similar chemicals for which the Agency recommends the use of relative potency factors (RPFs) or toxicity equivalence factors (TEFs). These factors have been developed by EPA and other organizations for two classes of compounds: PAHs and dioxins/furans. The World Health Organization (WHO) has developed TEFs for polychlorinated biphenyls (PCBs) as an extension of the factors for dioxins/furans (see Exhibit 12-14).

- **Polycyclic Aromatic Hydrocarbons (PAHs).** EPA has not developed IURs or CSFs for carcinogenic PAHs other than benzo(a)pyrene. EPA recommends use of a RPF based on the potency of each compound relative to that of benzo(a)pyrene.<sup>13</sup> Although several references may be found in the literature with proposed RPFs for PAHs, EPA recommends the following RPF values for seven PAHs, which are classified as B2, probable human carcinogens:<sup>(g)</sup>

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<sup>g</sup>CalEPA has developed IURs based on RPFs for several additional PAHs that have been classified as probably or possibly human carcinogens (e.g., IARC).

PAH	RPF
Benzo(a)pyrene	1.0
Benzo(a)anthracene	0.1
Benzo(b)fluoranthene	0.1
Benzo(k)fluoranthene	0.01
Chrysene	0.001
Dibenz(a,h)anthracene	1.0
Indeno(1,2,3-c,d)pyrene	0.1

Thus, for these seven PAHs, the IUR for benzo(a)pyrene is multiplied by the applicable RPF to derive the IUR.

- Dioxins, Furans, and PCBs.** For carcinogenic dioxins and furans, the TEF approach has an underlying assumption of additivity across mixture components. EPA currently recommends TEFs for specific congeners, rather than isomeric groups (see Exhibit 12-13). TEFs were determined by inspection of the available congener-specific data and an assignment of an “order of magnitude” estimate of relative toxicity when compared to 2,3,7,8-TCDD. The cancer potency of certain dioxin and furan congeners is estimated relative to 2,3,7,8-TCDD based on other toxicity information that is available for the congeners. Scientific judgment and expert opinion formed the basis for these TEF values. External review of the toxicity and pharmacokinetic data utilized in setting these TEF values supported the basic approach as a “reasonable estimate” of the relative toxicity of polychlorinated dibenzo-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs).<sup>14</sup> TEF values developed by scientific groups over the past 15 years are provided in Exhibit 12-13. The most recent consensus of the scientific community (including representation by EPA scientists) is represented by the WHO 1997 values.

TEFs based on the relative cancer potencies are used to adjust the exposure concentrations of mixture components, which are subsequently summed into a single exposure concentration for the mixture. That exposure concentration based on TEFs is then used, along with the 2,3,7,8-TCDD IUR or noncancer reference value, to estimate cancer risks or other health hazards for the mixture.

<b>Exhibit 12-14. Toxicity Equivalence Factors for Dioxins, Furans and PCBs</b>				
<b>Congener</b>	<b>EPA (1987)<sup>15</sup></b>	<b>NATO (1989)<sup>16</sup></b>	<b>WHO (1994)<sup>17</sup></b>	<b>WHO (1997)<sup>18</sup></b>
<b>TCDDs</b>				
2,3,7,8-TCDD	1	1		1
1,2,3,7,8-PeCDD	0.5	0.5		1
1,2,3,4,5,8-HxCDD	0.04	0.1		0.1
1,2,3,7,8,9-HxCDD	0.04	0.1		0.1
1,2,3,6,7,8-HxCDD	0.04	0.1		0.1
1,2,3,4,6,7,8-HpCDD	0.001	0.1		0.01
1,2,3,4,6,7,8,9-OCDD	0	0.001		0.0001
<b>TCDFs</b>				
2,3,7,8-TCDF	0.1	0.1		0.1
1,2,3,7,8-PeCDF	0.1	0.05		0.05
2,3,4,7,8-HxCDF	0.1	0.5		0.5
1,2,3,4,7,8-HxCDF	0.01	0.1		0.1
1,2,3,7,8,9-HxCDF	0.01	0.1		0.1
1,2,3,6,7,8-HxCDF	0.01	0.1		0.1
2,3,4,6,7,8-HxCDF	0.01	0.1		0.1
1,2,3,4,6,7,8-HpCDF	0.001	0.01		0.01
1,2,3,4,7,8,9-HpCDF	0.001	0.01		0.01
1,2,3,4,6,7,8,9-OCDF	0	0.001		0.0001
<b>PCBs</b>				
<b>IUPAC # Structure</b>				
77	3,3',4,4'-TCB		0.0005	0.0001
81	3,4,4',5-TCB		–	0.0001
105	2,3,3',4,4'-PeCB		0.0001	0.0001
114	2,3,4,4',5-PeCB		0.0005	0.0005
118	2,3',4,4',5-PeCB		0.0001	0.0001
123	2',3,4,4',5-PeCB		0.0001	0.0001
126	3,3',4,4',5-PeCB		0.1	0.1
156	2,3,3',4,4',5-HxCB		0.0005	0.0005
157	2,3,3',4,4',5'-HxCB		0.0005	0.0005
167	2,3',4,4',5,5'-HxCB		0.00001	0.00001
169	3,3',4,4',5,5'-HxCB		0.01	0.01
170	2,2',3,3',4,4',5-HpCB		0.0001	–
180	2,2',3,4,4',5,5'-HpCB		0.00001	–
189	2,3,3',4,4',5,5'-HpCB		0.0001	0.0001
Source: EPA's dioxin reassessment activities <sup>19</sup>				

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19. For more information on EPA's dioxin reassessment activities, see: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55264&CFID=12120688&CFTOKEN=95507561>.