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Risk Assessment Guidance for Superfund
Volume I: Human Health Evaluation Manual
(Part F, Supplemental Guidance for Inhalation Risk Assessment)

Final

Office of Superfund Remediation and Technology Innovation
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LIST OF ACRONYMS

µg	Microgram
µm	Micrometer
ADAF	Age Dependent Adjustment Factor
AT	Averaging Time
ATSDR	Agency for Toxic Substances and Disease Registry
BMCL	Benchmark Concentration, Lower confidence limit
BMD	Benchmark Dose
BW	Body Weight
CA	Contaminant Concentration in Air
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CSF	Cancer Slope Factor
DAF	Dosimetric Adjustment Factor
ED	Exposure Duration
EC	Exposure Concentration
EF	Exposure Frequency
EPA	Environmental Protection Agency
ER	Extra-respiratory
ET	Exposure Time
ETh	Extrathoracic
F_r	Fractional Deposition in region r
F_{total}	Total particle deposition in respiratory tract
$H_{b/g\text{-}animal}$	Animal Blood:Gas Partition Coefficient
$H_{b/g\text{-}human}$	Human Blood:Gas Partition Coefficient
HEAST	Health Effects Assessment Summary Table
HEC	Human Equivalent Concentration
HI	Hazard Index
HQ	Hazard Quotient
ICRP	International Commission for Radiological Protection
IR	Inhalation Rate
IRIS	Integrated Risk Information System
IUR	Inhalation Unit Risk
kg	Kilogram
LEC_{10}	Lower limit on Effective Concentration, using a 10 percent response level
LOAEL	Lowest Observable Adverse Effect Level
ME	Microenvironment
MF	Modifying Factor
mg	Milligram
MOA	Mode of Action
MRL	Minimal Risk Level
MW	Molecular Weight
NCEA	National Center for Environmental Assessment
NOAEL	No Observable Adverse Effect Level
ORD	Office of Research and Development
OSRTI	Office of Superfund Remediation and Technology Innovation

LIST OF ACRONYMS (CONT.)

OSWER	Office of Solid Waste and Emergency Response
PBPK	Physiologically Based Pharmacokinetic
POD	Point of Departure
ppm	Parts Per Million
PPRTV	Provisional Peer Reviewed Toxicity Value
PRG	Preliminary Remediation Goal
PU	Pulmonary
Q-alv	Alveolar ventilation rate
QSAR	Quantitative Structure-Activity Relationship
RAGS	Risk Assessment Guidance for Superfund
RBC	Risk-Based Concentration
RfC	Reference Concentration
RfD	Reference Dose
RGDR	Regional Gas Dose Ratio
RDDR	Regional Deposited Dose Ratio
RME	Reasonable Maximum Exposure
SA	Surface Area
SSL	Soil Screening Level
STSC	Superfund Health Risk Technical Support Center
TB	Tracheobronchial
TOT	Total Respiratory System
UF	Uncertainty Factor
V_e	Minute Volume

1. INTRODUCTION

The Environmental Protection Agency's (EPA's) Superfund Program has updated its approach for determining risk from inhaled chemicals to be consistent with the inhalation dosimetry methodology described in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (USEPA, 1994; hereafter, the *Inhalation Dosimetry Methodology*).[1] This document provides Superfund site risk assessors with guidance that should help more consistently address the *Inhalation Dosimetry Methodology*.

This document outlines recommended processes consisting of a series of steps as well as recommended equations for EPA Regions to consider when estimating inhalation exposure and risk at Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) sites. This guidance is intended to provide a recommended methodology for consistently addressing the inhalation pathway in risk assessments for Superfund sites.

Some of the statutory provisions described in this document contain legally binding requirements. However, this document does not substitute for those provisions or regulations, nor is it a regulation itself. Thus, it cannot impose legally binding requirements on EPA, States, or the regulated community, and may not apply to a particular situation based upon the circumstances. Any decisions regarding a particular remedy selection decision will be made based on the statute and regulations, and EPA decisionmakers retain the discretion to adopt approaches on a case-by-case basis that differ from this guidance where appropriate. EPA may change this guidance in the future.

1.1 Background

EPA's *Risk Assessment Guidance for Superfund (RAGS), Part A* (USEPA, 1989; hereafter, *RAGS, Part A*) outlined a previously recommended approach for conducting site-specific baseline risk assessments for inhaled contaminants.[2] According to the original RAGS approach, the inhalation exposure estimate was typically derived in terms of a chronic, daily "air intake" (mg/kg-day) using the following general approach. The intake of the chemical was estimated as a function of the concentration of the chemical in air (CA), inhalation rate (IR), body weight (BW), and the exposure scenario. Age-specific values for BW and IR were used when evaluating childhood exposures. Table 1 presents the *RAGS, Part A* equation for calculating intake for inhalation exposure. Inhalation toxicity values were "converted" into similar units for the risk quantification step. Cancer risk was estimated by multiplying the chronic daily intake of the chemical from the air by the "inhalation cancer slope factor" (CSF_i); the Hazard Quotient (HQ) for non-cancer effects was estimated by dividing the intake of the chemical by an "inhalation reference dose" (RfD_i).[3]

The approach outlined in *RAGS, Part A* was developed before EPA issued the *Inhalation Dosimetry Methodology*, which describes the Agency's refined recommended approach for interpreting

[1] The *Inhalation Dosimetry Methodology* can be found at the following web address: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993.

[2] See sections 6.6.3, 7.2.3, 7.3.3, and 8.2 of *RAGS, Part A*.

[3] EPA defines an HQ in *RAGS, Part A* as: "The ratio of a single substance exposure level over a specified time period (e.g., subchronic) to a reference dose (RfD) for that substance derived from a similar exposure period" (USEPA, 1989).

inhalation toxicity studies in laboratory animals or studies of occupational exposures of humans to airborne chemicals. Under the *Inhalation Dosimetry Methodology*, the experimental exposures are typically extrapolated to a Human Equivalent Concentration (HEC), and a reference concentration (RfC) is typically calculated by dividing the HEC by uncertainty factors (UFs). As described in the Agency's *Guidelines for Cancer Risk Assessment* (USEPA, 2005a), the HEC developed in accordance with the *Inhalation Dosimetry Methodology* typically is also used in developing an inhalation unit risk (IUR) for cancer risk assessment (which may also be called an inhalation cancer slope factor).[4] The procedure that was used to calculate the published RfC or IUR is described in the Integrated Risk Information System (IRIS) profile or other toxicological reference document for a chemical.

TABLE 1
RAGS, PART A EQUATION DESCRIBING THE ESTIMATION OF INHALATION EXPOSURE

Equation	Location in RAGS, Part A
Intake (mg/kg-d) = CA x (IR/BW) x (ET x EF x ED)/AT	Exhibit 6-16, Page 6-44
Key: CA (mg/m^3) = contaminant concentration in air; IR (m^3/hr) = inhalation rate; BW (kg) = body weight; ET (hours/day) = exposure time; EF (days/year) = exposure frequency; ED (years) = exposure duration; and AT (days) = averaging time (period over which exposure is averaged).	

The Superfund Program has updated its inhalation risk paradigm to be compatible with the *Inhalation Dosimetry Methodology*, which represents the Agency's current methodology for inhalation dosimetry and derivation of inhalation toxicity values.[5] This document recommends that when estimating risk via inhalation, risk assessors should use the concentration of the chemical in air as the exposure metric (e.g., mg/m^3), rather than inhalation intake of a contaminant in air based on IR and BW (e.g., mg/kg-day).

1.2 Purpose and Scope

The intake equation described above (*RAGS, Part A*, Exhibit 6-16) is not consistent with the principles of EPA's *Inhalation Dosimetry Methodology* because the amount of the chemical that reaches the target site is not a simple function of IR and BW. Instead, the interaction of the inhaled contaminant with the respiratory tract is affected by factors such as species-specific relationships of exposure concentrations (ECs) to deposited/delivered doses and physiochemical characteristics of the inhaled contaminant. The *Inhalation Dosimetry Methodology* also considers the target site where the toxic effect occurs (e.g., the respiratory tract or a location in the body remote from the portal-of-entry) when applying dosimetric adjustments to experimental concentrations (USEPA, 1994). Therefore, this *RAGS, Part A* equation is not recommended for estimating exposures to inhaled contaminants.

[4] The phrase "inhalation cancer slope factor," as used in this guidance, refers generally to the risk per a measure of inhalation exposure. Inhalation exposure in cancer bioassays or occupational studies from which slope factors may be derived is most commonly expressed as an exposure concentration (e.g., µg agent/m^3 air). Please note that this differs from past use of the phrase "inhalation cancer slope factor" or "CSF_i" by the Superfund program to refer to a cancer slope expressed as an "inhalation intake" (e.g., *RAGS, Part A* (USEPA, 1989)).

[5] For additional information about the Superfund program's adoption of the *Inhalation Dosimetry Methodology*, please refer to the summary of a 2003 Superfund workshop on inhalation risk assessment: http://www.epa.gov/oswer/riskassessment/pdf/finalinhalationriskworkshop.pdf.

The purpose of this document is to provide a recommended approach for developing the information necessary to assist risk assessment and risk management decision-making at waste sites involving potential risks from inhalation exposures.[6, 7] This includes providing equations that may be used in conducting baseline risk assessments and in calculating risk-based concentrations (RBCs). It is intended that *RAGS, Part F* will replace those portions of *RAGS, Part A*, which addressed inhalation risk.

1.3 Effects on Other Office of Superfund Remediation and Technology Innovation Guidance

EPA recommends that the intake equation presented in *RAGS, Part A* (USEPA, 1989, Exhibit 6-16) should no longer be used when evaluating risk from the inhalation pathway. Implementation of a risk assessment approach consistent with the *Inhalation Dosimetry Methodology* will also affect the following guidance documents: *RAGS, Part B*, Section 3.3: Volatilization and Particulate Emission Factors (USEPA, 1991); and the Office of Solid Waste and Emergency Response's (OSWER's) *Draft Guidance for Evaluating the Vapor Intrusion to Indoor Air Pathway from Groundwater and Soils* (USEPA, 2002a; hereafter the *Vapor Intrusion Guidance*). EPA no longer recommends using the equations in Section 3.3 of *RAGS, Part B* nor the inhalation toxicity values generated using simple route-to-route extrapolation, such as those presented in the 2002 draft *Vapor Intrusion Guidance* and related documents.[8]

This guidance does not affect the equations pertaining to risk from inhaled chemicals in the *Soil Screening Guidance* (USEPA, 1996), Section 2.4, or the *Supplemental Guidance for Developing Soil Screening Levels for Superfund Sites* (USEPA, 2002b), Sections 4.2.3, 5.3.2 and Appendix B, other than to clarify that the IURs and RfCs used in the equations are based on continuous exposure (24 hours per day). If the exposure scenario of interest is less than 24 hours per day, the scenario-specific exposure time (ET) in hours per day should be used in the equations and the averaging time should be in units of hours (see Equations 6 and 8 in this document). *RAGS, Part D* (USEPA, 2001) is also not affected by *RAGS, Part F*, as it includes sufficient flexibility to accommodate the revisions described in this guidance. In addition, the screening values presented on the "Regional Screening Levels for Chemical Contaminants at Superfund Sites" screening level/preliminary remediation goal table are consistent with *RAGS, Part F* (USEPA, 2008a).[9] Readers can contact EPA headquarters with questions about the compatibility of specific Superfund documents with *RAGS, Part F*.

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[6] Note that the assessment of risk from inhaled nanoparticles is outside the scope of this document.

[7] If a site contains asbestos contamination, risk assessors should contact EPA's Technical Review Workgroup for Metals and Asbestos for assistance.

[8] Related documents include the *Johnson and Ettinger (1991) Model for Subsurface Vapor Intrusion into Buildings* spreadsheet models (http://www.epa.gov/oswer/riskassessment/airmodel/johnson_ettinger.htm) and the accompanying *User's Guide for Evaluating Subsurface Vapor Intrusion into Buildings* (USEPA, 2004a).

[9] This table can be found on EPA Regions 3, 6, and 9 websites (http://www.epa.gov/reg3hwmd/risk/human/rb-concentration_table/index.htm; http://www.epa.gov/earth1r6/6pd/rcra_c/pd-n/screen.htm; and http://www.epa.gov/region09/waste/sfund/prg/index.html).

2. BACKGROUND ON DERIVATION OF INHALATION TOXICITY VALUES

For all exposure routes, there are generally two approaches for deriving toxicity values. One involves the derivation of a reference value (e.g., RfC or RfD), while the other involves derivation of a predictive cancer risk estimate (e.g., an oral or inhalation CSF, such as an IUR). For the inhalation route, both approaches rely on EPA's *Inhalation Dosimetry Methodology* for the extrapolation of experimental concentrations to HECs. This extrapolation is described in Section 2.1 and its subsections. The approaches for deriving a toxicity value from the HEC are described in Sections 2.2 and 2.3 and differ depending on the type of toxicity value (e.g., RfC, IUR). This information is provided for background purposes only. **The procedures outlined in Section 2 are typically performed by IRIS chemical managers or by inhalation toxicologists at the National Center for Environmental Assessment's (NCEA's) Superfund Health Risk Technical Support Center (STSC) rather than as part of a baseline risk assessment.**

2.1 Application of Inhalation Dosimetry

The *Inhalation Dosimetry Methodology* recognizes a hierarchy of approaches that can be used for determining the HEC that is used to derive the RfC or IUR. Generally, the preferred approach is to use physiologically-based pharmacokinetic (PBPK) models.[10] With sufficient data, a PBPK model is capable of calculating the amount of the chemical that reaches the target organ in an animal from any exposure scenario and then estimating what human exposure would result in this same amount of chemical reaching the target organ (i.e., the HEC). PBPK models can also be used to derive continuous ECs from human and animal studies with less-than-continuous exposures. Because constructing a valid PBPK model is an information-intensive process that typically requires substantial chemical-specific data, this approach has rarely been used (USEPA, 2004b); an example can be found in the IRIS file for vinyl chloride (USEPA, 2000a). In cases where a complete PBPK model is not available, an intermediate model relying on certain chemical-specific data may be used (USEPA, 1994).[11]

If the database to support the preferred approach is inadequate, an alternative approach, called the Default Chemical Category-Specific Method can be used. This method incorporates the use of limited or categorical chemical-specific and physiological information. The default method is discussed below, followed by the procedures outlined in the *Inhalation Dosimetry Methodology* for deriving the RfC and IUR as they apply to the interpretation of animal and human data.

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[10] EPA defines PBPK models in the IRIS glossary as a model that 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 (USEPA, 2008b). For further information about PBPK modeling, please refer to *Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment* (USEPA, 2006a).

[11] The *Inhalation Dosimetry Methodology* recognizes the existence of alternate approaches in addition to the two presented in this guidance. The PBPK approach is generally preferred. In the absence of such a model, alternate models may be more optimal than the default approach when default assumptions or parameters can be replaced by more detailed, biologically-motivated descriptions or actual data, respectively. For instance, a model may be considered more optimal if it incorporates chemical or species-specific information or if it accounts for mechanistic determinants. See Table 3-6 in the *Inhalation Dosimetry Methodology* for more details on the hierarchy of approaches (EPA, 1994, page 3-40).

2.1.1 Default Approach - Extrapolation from Experimental Animal Data

The default method involves a two-step procedure that uses limited or categorical chemical-specific and physiological information to calculate the HEC. First, the chosen point of departure (POD) from the experimental data for a chemical is adjusted to derive a concentration intended to represent an equivalent dose under conditions of continuous exposure (7 days a week, 24 hours a day).[12] In the second step, this concentration is then multiplied by a Dosimetric Adjustment Factor (DAF) to generate the HEC. Further details on each step are outlined below.

2.1.1.1 Duration Adjustment to Continuous Exposure

Most of the inhalation studies of laboratory animals used to derive RfCs and IURs involve an exposure regimen of four to six hours per day, five to seven days per week, for 13 weeks or more (equivalent to 10 percent or more of the lifetime of the animal). The POD concentration from an animal study is mathematically adjusted to reflect an equivalent dose under conditions of continuous exposure.[13] Adjustment of duration to a continuous exposure scenario is regularly applied as a default procedure to studies with repeated exposures but not to single-exposure inhalation toxicity studies in animals (USEPA, 1994). Operationally, this is accomplished by applying a *c* x *t* product (where "*c*" is concentration, and "*t*" is duration of exposure) for both the number of hours in a daily exposure period and the number of days per week that the exposure is experienced. For example, if exposure in a particular study was 6 hours per day, 5 days per week, the experimental exposure is multiplied by 6/24 x 5/7 to calculate an equivalent continuous exposure. The general equation provided in the *Inhalation Dosimetry Methodology* (USEPA, 1994, Equation 4-2) for calculating duration-adjusted exposure levels in mg/m^3 for experimental animals is presented below.

$NOAEL_{[ADJ]}$ = E x D x W **(Equation 1)**

Where:

$NOAEL_{[ADJ]}$ (mg/m^3) = the NOAEL or analogous exposure level obtained with an alternate approach (e.g., LOAEL, LEC_{10}), adjusted for duration of experimental regimen;
E (mg/m^3) = the NOAEL or analogous exposure level observed in the experimental study;
D (h/h) = number of hours exposed/24 hours; and
W (days/days) = number of days of exposure/7days.

Using the example above, the assumption is that the product of *c* x *t*, not concentration alone, is associated with the toxicity observed. This is roughly equivalent to implying that if an effect occurs from a chemical at an exposure of 6 hours per day at 40 parts per million (ppm), that same effect will

[12] Examples of PODs include the no-observed-adverse-effect level (NOAEL); the lowest-observed-adverse-effect level (LOAEL); Benchmark Concentration, Lower confidence limit (BMCL); and the Lower limit on an Effective Concentration using a 10 percent response level (LEC_{10}). For definitions of the various PODs, please refer to the IRIS glossary (http://www.epa.gov/ncea/iris/help_gloss.htm).

[13] Continuous exposure refers to 24 hours per day, 7 days per week.

occur at an exposure of 24 hours per day at 10 ppm.[14] Note that this adjustment always produces a lower concentration value than that administered to experimental animals. Thus, as stated in *A Review of the Reference Dose and Reference Concentration Processes* (hereafter, the *RfD/RfC Review*), application of this procedure results in an automatic margin of protectiveness for chemicals for which concentration alone may be the more appropriate dose metric, and it reflects the maximum dose for chemicals for which total or cumulative dose is the appropriate measure (USEPA, 2002c). If a different procedure is used to calculate the continuous exposure, it should be fully discussed in the relevant technical support document for the chemical (e.g., IRIS profile, Provisional Peer Reviewed Toxicity Values (PPRTVs) Assessment). For additional discussion, including the uncertainties associated with this approach, see Section 4.3.2 of the *Inhalation Dosimetry Methodology* and Section 4.4.2.1 of the *RfD/RfC Review* (USEPA, 2002c).

2.1.1.2 Dosimetric Adjustment to Human Equivalent Concentration

Typically, the adjusted POD concentration from the animal study is next converted to an HEC using the following equation (USEPA, 1994, Equation 4-3):

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times DAF$ **(Equation 2)**

Where:

$NOAEL_{[HEC]}$ (mg/m^3) = the NOAEL or analogous exposure level obtained with an alternate approach, dosimetrically adjusted to an HEC;

$NOAEL_{[ADJ]}$ (mg/m^3) = the NOAEL or analogous exposure level obtained with an alternate approach, adjusted for duration of experimental regimen; and

DAF = Dosimetric Adjustment Factor for the specific site of effects (e.g., respiratory tract region or extra-respiratory).

The DAF is typically based on ratios of animal and human physiologic parameters. The specific DAF used depends on the nature of the contaminant (e.g., particle or gas) and the target site where the toxic effect occurs (e.g., respiratory tract or a location in the body remote from the portal-of-entry). For example, the DAF can be based on either the Regional Gas Dose Ratio (RGDR), for gases with respiratory effects, or the Regional Deposited Dose Ratio (RDDR) for particles.

Table 2 provides information on the site of effects for the different chemical types. It also lists the physiologic parameters considered when calculating the DAF for specific regions of the body.[15] In addition, the table provides references to the equations from the *Inhalation Dosimetry Methodology* used in deriving the DAFs. Figure 1 provides a schematic of the human respiratory tract, illustrating each of the different regions.

[14] This assumption is based on Haber's Law, which states that "the incidence and/or severity of an adverse health effect depends on the total exposure to a potentially toxic substance. Total exposure (*K*) is the concentration of the substance (*c*) times the duration time of exposure (*t*), (i.e., $c \times t = K$)" (Gaylor, 2000).

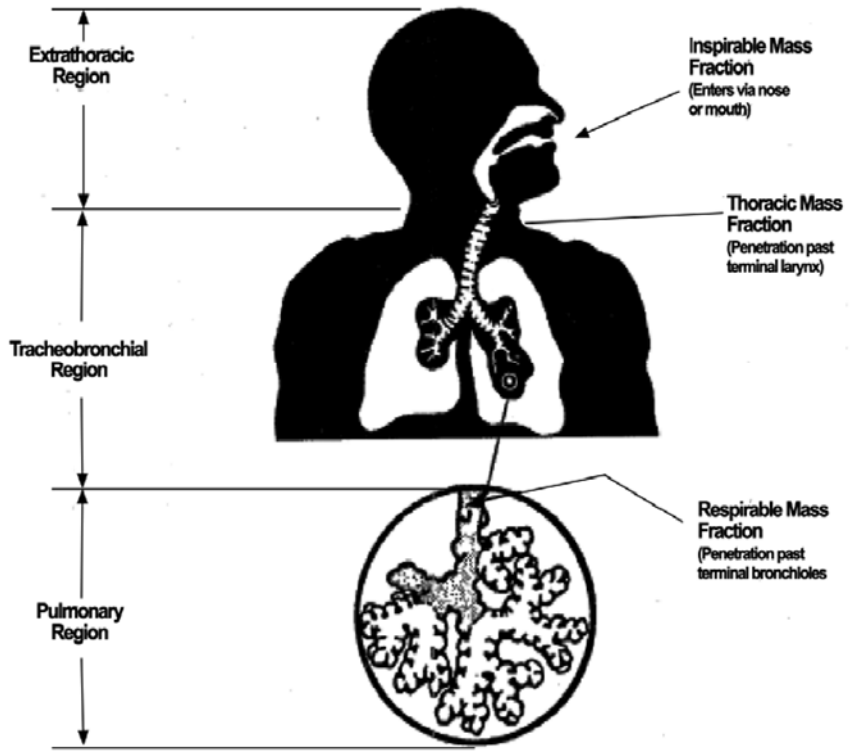
[15] The three main regions of the respiratory tract include the following: 1) Extrathoracic (includes nose, mouth, nasopharynx, oropharynx, laryngopharynx, and larynx); 2) Tracheobronchial (includes trachea, bronchi, and bronchioles); and 3) Pulmonary (includes respiratory bronchioles, alveolar ducts, alveolar sacs and the alveoli).

TABLE 2
CONTAMINANT PROPERTIES AND DOSIMETRIC ADJUSTMENT FACTORS[a]

Chemical Type	Site of Effects	Parameters Considered in Derivation of DAF for Regions of the Body[b]	DAF Equation Numbers in Inhalation Dosimetry Methodology[c]
Category 1 Gases (e.g., acrolein, hydrogen fluoride, chlorine)	Respiratory	-Minute volume (ETh, TB) -Surface area (ETh, TB, PU) -Mass transport coefficient (TB, PU) -Fraction of inhaled chemical penetrating the respiratory region (PU) -Alveolar ventilation rate (PU)	4-18 (ETh), 4-21 & 4-22 (TB), 4-28 (PU)
Category 2 Gases (e.g., acetonitrile, xylene, propanol, isoamyl alcohol)	Respiratory and Remote	-Mass transport coefficients (ETh, TB) -Blood:gas partition coefficient (ET, TB, ER) -Cardiac output (ETh, TB, ER) -Alveolar ventilation rate (PU) -Surface Area (PU) -Minute volume (ER)	4-18 (ETh), 4-21 & 4-22 (TB), 4-28 (PU), 4-48 (ER)[d,e]
Category 3 Gases (e.g., benzene, styrene)	Remote	Blood:gas partition coefficient (ER)	4-48[d]
Particles	Respiratory and Remote	-Minute volume (TOT, ER) -Surface area (TOT) -Fractional deposition of particle (TOT, ER) -Body weight (ER) -Inhaled concentration (ER)	4-14 (TOT), 4-15 (ER)

[a] Due to the complexities inherent in evaluating the health effects associated with exposure to gases, no definitive or comprehensive list of Category 1, 2, or 3 gases is available. Risk assessors should consult with an inhalation toxicologist in order to classify a specific gas as Category 1, 2, or 3, since there is overlap between the sites of effects and the parameters considered in deriving the DAF for different regions of the respiratory tract.
[b] Additional discussion of the terms used in this table can be found in the *Inhalation Dosimetry Methodology*.
[c] The *Inhalation Dosimetry Methodology* provides equations for deriving DAFs for the different contaminant categories. The equations listed in this table are the default equations for each specific region in the body.
[d] This refers to Equation 4-48 that is found on page 4-60 of the *Inhalation Dosimetry Methodology*.
[e] The equations presented for Category 2 gases in the *Inhalation Dosimetry Methodology* contain errors. Therefore, this table refers to the equations for Category 1 and 3 gases, which are expected to cover respiratory and remote effects from Category 2 gases.
Acronyms: ETh = Extrathoracic; TB = Tracheobronchial; PU = Pulmonary; ER = Extra-respiratory; TOT = Total respiratory system.

FIGURE 1
HUMAN RESPIRATORY TRACT



Source: EPA (1994), Figure 3-1, Page 3-5.

Category 1 gases are highly water-soluble and/or are rapidly irreversibly reactive in the respiratory tract (e.g., acrolein, hydrogen fluoride, chlorine). They do not significantly accumulate in the blood, and therefore their effects are usually exclusively respiratory (USEPA, 1994). The DAF for Category 1 gases consists of an RGDR and is based on the animal to human ratio of the minute volume (V_e) divided by the surface area (SA) of the region of the respiratory tract where the effect occurs.[16] See Appendix A, Sections 1, 2, and 3 of this guidance for examples of specific Category 1 DAF equations.

[16] For the purposes of this document, the V_e is defined as the total ventilation per minute and equals the product of the tidal volume (the air volume entering or leaving the lungs with a single breath) and the respiratory frequency.

Category 3 gases are relatively water-insoluble and are unreactive in the respiratory tract (e.g., benzene, styrene). Their toxicity is generally at sites remote to the respiratory tract (USEPA, 1994). The DAF for Category 3 gases is based on the ratio of the animal blood:gas partition coefficient ($H_{b/g\text{-}animal}$) and the human blood:gas partition coefficient ($H_{b/g\text{-}human}$). See Appendix A, Section 4 of this guidance for an example of a Category 3 DAF equation.

Category 2 gases are moderately water-soluble and may be rapidly reversibly reactive or moderately to slowly irreversibly reactive in respiratory tract tissue (e.g., acetonitrile, xylene, propanol, isoamyl alcohol). These gases have potential for significant accumulation in the blood, so they can exhibit both respiratory and remote toxicity (USEPA, 1994). The DAF for respiratory effects of Category 2 gases consists of an RGDR and is based on the animal to human ratio of the V_e and the SA of the region of the respiratory tract where the effect occurs, as for Category 1 gases. The DAF for extra-respiratory (ER) effects of a Category 2 gas is based on the ratio of the $H_{b/g\text{-}animal}$ and the $H_{b/g\text{-}human}$, as for Category 3 gases.

Particles also vary by solubility and reactivity. However, the default equations used to estimate the predicted regional deposition fractions for particles are based on non-soluble, non-hygroscopic particles (USEPA, 1994, Section 4.3.5.3). The DAF for a particle causing an effect in the respiratory tract is the $RDDR_r$. The $RDDR_r$ is based on the animal to human ratio of the V_e and the fractional deposition of the particle in that region (F_r), divided by the SA_r of the region where the effect occurs. This derivation, from the *Inhalation Dosimetry Methodology,* conservatively assumes that 100 percent of the deposited dose remains in the respiratory tract; clearance mechanisms are not considered. The DAF for a particle causing an ER effect, the $RDDR_{ER}$, is based on the animal to human ratio of the V_e and the total deposition of the particle in the entire respiratory tract (F_{total}), divided by BW (USEPA, 1994). The $RDDR_{ER}$ assumes that 100 percent of the deposited dose in the entire respiratory tract is available for uptake into the systemic circulation. See Appendix A, Section 5 for examples of specific particle DAF equations.

2.1.2 Default Approach - Extrapolation from Human Occupational Data

When human data are available to derive an RfC, duration adjustments are often required to account for differences in exposure scenarios (e.g., extrapolation from an 8 hour/day occupational exposure to a continuous chronic exposure). The default approach recommended by the *Inhalation Dosimetry Methodology* for adjusting the POD concentration (e.g., the no observable adverse effect level (NOAEL)) obtained from human study data is provided below in Equation 3 (USEPA, 1994, Equation 4-49).[17,18]

[17] If sufficient data are available, a PBPK model or intermediate approach using chemical-specific information may be employed in preference to the default method for extrapolating human occupational data to an HEC.

[18] EPA's IRIS glossary defines an adverse effect as the following: "A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge" (USEPA, 2008b).

$NOAEL_{[HEC]}$ = NOAEL x (VEho/VEh) x 5 days/7 days **(Equation 3)**

Where: $NOAEL_{[HEC]}$ (mg/m^3) = the NOAEL or analogous exposure level obtained with an alternate approach, dosimetrically adjusted to an ambient HEC;
NOAEL (mg/m^3) = occupational exposure level (time-weighted average over an 8-hour exposure period);
VEho = human occupational default minute volume over 8 hours (10 m^3); and
VEh = human ambient default minute volume over 24 hours (20 m^3).

2.2 Derivation of the Inhalation Unit Risk

The default approach for determining predictive cancer risk recommended by EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005a; hereafter, *Cancer Guidelines*) is a linear extrapolation from exposures observed in the animal or human occupational study.[19] This approach involves drawing a straight line from the POD to the origin. The default linear extrapolation approach is generally considered to be conservatively protective of public health, including sensitive sub-populations (USEPA, 2005a). The slope of this line is commonly called the slope factor, and when the units are risk per $\mu g/m^3$, it is also called the IUR. EPA defines an IUR in the IRIS glossary as "the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air" (USEPA, 2008b). Equation 4 below presents a linear extrapolation from a POD of 10 percent response (LEC_{10}).[20]

$IUR = 0.1/LEC_{10[HEC]}$ **(Equation 4)**

Where: IUR $(\mu g/m^3)^{-1}$ = Inhalation Unit Risk; and
$LEC_{10[HEC]}$ ($\mu g/m^3$) = the lowest effective concentration using a 10 percent response level, dosimetrically adjusted to an HEC.

2.3 Derivation of the Reference Concentration

EPA defines an RfC in the IRIS glossary as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime" (USEPA, 2008b). The RfC is derived after a review of the health effects database for a chemical and identification of the most sensitive and relevant endpoint along with the principal study or studies demonstrating that endpoint. EPA Chemical Managers use UFs to account for recognized

[19] According to the *Cancer Guidelines*, "[a] nonlinear approach should be selected when there are sufficient data to ascertain the mode of action [MOA] and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses" (USEPA, 2005a, page 3-22). In addition, [l]inear extrapolation should be used when there are MOA data to indicate that the dose-response curve is expected to have a linear component below the POD" (USEPA, 2005a, page 3-21). This information will appear on the IRIS profile or other toxicological information source for a chemical. Chemicals with a mutagenic MOA are thought to pose a higher risk during early life. Procedures for assessing cancer risk from these chemicals are outlined in Section 5.1.

[20] The POD used in Equation 4 is an LEC_{10}, which is the lower 95 percent confidence limit on the concentration corresponding to a 10 percent response rate (i.e., the EC_{10}). Other PODs may be substituted for this value, which could be associated with alternative response levels (e.g., 1 percent, 5 percent).

uncertainties in the extrapolations from the experimental data conditions to an estimate appropriate to the assumed human scenario (USEPA, 1994). See Table 3 for a description of the standard UFs. The formula used for deriving the RfC from the HEC is provided below.

$RfC = NOAEL_{[HEC]}/(UF)$[1] **(Equation 5)**

Where: RfC (mg/m^3) = Reference Concentration
$NOAEL_{[HEC]}$ (mg/m^3) = The NOAEL or analogous exposure level obtained with an alternate approach, dosimetrically adjusted to an HEC; and
UF = Uncertainty factor(s) applied to account for the extrapolations required from the characteristics of the experimental regimen.

[1] Some toxicological information sources for RfCs will incorporate an additional factor to account for deficiencies in the available data set, called a modifying factor (MF). In 2002, however, EPA published the *RfD/RfC Review,* which recommended that the use of MFs be discontinued because their purpose is "sufficiently subsumed in the general database UF" (USEPA, 2002c, page xviii). Therefore, RfCs published subsequent to this document will not include MFs.

TABLE 3
THE USE OF UNCERTAINTY FACTORS IN DERIVING AN INHALATION REFERENCE CONCENTRATION

Standard UFs	Processes Considered in the UF Purview
H = Human to sensitive human: Extrapolation of valid experimental results from studies using prolonged exposure to average healthy humans. Intended to account for the variation in sensitivity among the members of the human population.	-Pharmacokinetics/Pharmacodynamics -Sensitivity[2] -Differences in body weight (age, obesity) -Concomitant exposures -Activity pattern -Does not account for idiosyncrasies
A = Animal to human: 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.	-Pharmacokinetics/Pharmacodynamics -Relevance of laboratory animal model -Species sensitivity
S = Subchronic to chronic: 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.	-Accumulation/Cumulative damage -Pharmacokinetics/ Pharmacodynamics -Severity of effect -Recovery -Duration of study -Consistency of effect with duration
L = LOAEL to NOAEL: Derivation from a LOAEL instead of a NOAEL. Intended to account for the uncertainty in extrapolating from LOAELs to NOAELs.	-Severity -Pharmacokinetics/Pharmacodynamics -Slope of dose-response curve -Trend, consistency of effect -Relationship of endpoints -Functional vs. histopathological evidence -Exposure uncertainties
D = Incomplete to complete data: 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.[1]	-Quality of critical study -Data gaps -Power of critical study/supporting studies -Exposure uncertainties

[1] The *RfD/RfC Review* indicates that this UF accounts for the potential for deriving an underprotective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity or if the existing data suggest that a lower reference value might result if additional data were available (considering both the lacking and available data for particular organ systems as well as life stage) (USEPA, 2002c).

[2] The *RfD/RfC Review* also stresses that susceptible populations and life stages are accounted for with this UF (USEPA, 2002c).

Source: USEPA, 1994, Table 4-9, page 4-77.

3. CHARACTERIZING EXPOSURE

3.1 Introduction

This section describes an approach for characterizing exposure in a baseline risk assessment that is consistent with the *Inhalation Dosimetry Methodology*. The approach involves the estimation of exposure concentrations (ECs) for each receptor exposed to contaminants via inhalation in the risk assessment. ECs are time-weighted average concentrations derived from measured or modeled contaminant concentrations in air at a site, adjusted based on the characteristics of the exposure scenario being evaluated.[21,22]

Equations for estimating ECs are provided below. This document does not provide default input values for the exposure parameters referenced in these equations. EPA recommends the use of site-specific exposure values consistent with the exposure pathways and receptors at a site wherever practicable and appropriate. If a risk assessor opts to rely on default exposure input values, current Superfund-supported values may be found at the exposure assessment portion of the Superfund website: (http://www.epa.gov/oswer/riskassessment/superfund_hh_exposure.htm).

3.2 Estimating Exposure Concentrations for Assessing Cancer Risks

The estimation of an EC when assessing cancer risks characterized by an IUR involves the CA measured at an exposure point at a site as well as scenario-specific parameters, such as the exposure duration and frequency.[23] The EC typically takes the form of a CA that is time-weighted over the duration of exposure and incorporates information on activity patterns for the specific site or the use of professional judgment. The equation for estimating an EC for use with an IUR is presented below.

[21] The default method for deriving inhalation toxicity values also involves calculating time-weighted ECs, as discussed in Sections 2.1.1.1 and 2.1.2.

[22] The ECs in this document are in units of $\mu g/m^3$. Inhalation toxicity values presented on IRIS are typically expressed in units of $\mu g/m^3$ or mg/m^3, which are mass units. Some regulatory contexts require the use of volumetric units such as ppm. The conversion from mass units to volumetric units depends on the molecular weight (MW) of the material as well as the ambient temperature and atmospheric pressure. To convert from ppm to mg/m^3, the following equation can be used: $\frac{ppm \times MW}{V} = mg/m^3$; where MW is the molecular weight of the gas and V is the volume of 1 gram molecular weight of the airborne contaminant. This is derived by the formula V = RT/P; where R is the ideal gas constant, T is the temperature in Kelvin (K = 273.16 + T°C) and P is the pressure in mm Hg. The value of R is 62.4 when T is in Kelvin, (K = 273.16 + T°C), the pressure is expressed in units of mm Hg and the volume is in liters. The value of R differs if the temperature is expressed degrees Fahrenheit (°F) or if other units of pressure are used (e.g., atmospheres, kilopascals).

[23] ECs are typically based on either estimated (i.e., modeled) or measured contaminant concentrations in air.

EC = (CA x ET x EF x ED)/AT **(Equation 6)**

Where: EC ($\mu g/m^3$) = exposure concentration;
CA ($\mu g/m^3$) = contaminant concentration in air;
ET (hours/day) = exposure time;
EF (days/year) = exposure frequency;
ED (years) = exposure duration; and
AT (lifetime in years x 365 days/year x 24 hours/day) = averaging time

3.3 Estimating Exposure Concentrations for Calculating Hazard Quotients

When estimating ECs for non-cancer or cancer hazards characterized by an HQ, risk assessors should match each exposure scenario at a site to the appropriate EC equation, based on the scenario duration and frequency of exposure.[24] Figure 2 presents a flowchart to assist risk assessors with this process and provides recommended equations that can be used to estimate the EC for each type of scenario.[25] As shown in Figure 2, the recommended process for estimating ECs to be used in calculating an HQ involves the following three steps: 1) assess the duration of the exposure scenario; 2) assess the exposure pattern of the exposure scenario; and 3) estimate the scenario-specific EC.

3.3.1 Step 1: Assess Duration

The first step in the recommended process of estimating an EC for use in calculating an HQ involves assessing the duration of the exposure scenario at a site. Step 1 in Figure 2 indicates that the risk assessor first should decide whether the duration of the exposure scenario is generally acute, subchronic, or chronic. Toxicologists have long been aware that effects from a single or short-term exposure can differ markedly from effects resulting from repeated exposures. The response by the exposed person depends upon factors such as whether the chemical accumulates in the body, whether it overwhelms the body's mechanisms of detoxification or elimination, or whether it produces irreversible effects (Eaton & Klaassen, 2001). Therefore, ideally, the chemical-specific elements of metabolism and kinetics, reversibility of effects, and recovery time should be considered as part of this recommended process when defining the duration of a site-specific exposure scenario.

[24] Traditionally, the HQ approach was limited to non-cancer hazard assessment. However, the HQ approach may also be appropriate for carcinogens with a non-linear mode of action. The 2005 *Cancer Guidelines* state the following on this subject: "For cases where the tumors arise through a nonlinear mode of action, an oral reference dose or an inhalation reference concentration, or both, should be developed in accordance with EPA's established practice for developing such values … this approach expands the past focus of such reference values (previously reserved for effects other than cancer) to include carcinogenic effects determined to have a nonlinear mode of action" (USEPA, 2005a; page 3-24).

[25] Figure 2 was developed for the evaluation of inhalation exposures. While the concepts presented in this flowchart may be useful for assessing other exposure routes (e.g., oral or dermal), these other routes are beyond the scope of this document, and therefore, are not explicitly considered. Caution should be used when using Figure 2 to evaluate other exposure routes, as considerations beyond those outlined in the flowchart may apply (e.g., time to reach steady state for dermal exposures).

To the extent possible, exposure durations (EDs) evaluated in a site-specific risk assessment should be consistent with the ED represented by the toxicity value. However, frequencies or durations of human exposures often are not as clearly defined as those in animal studies with controlled exposures, particularly for intermittent exposures. For example, the emission of some volatile chemicals into the ambient air may vary with temperature and season, providing fluctuating exposures for humans living near the source. Therefore, risk assessors should use best professional judgment to determine if the ED in a given scenario is reasonably similar to the duration associated with the toxicity value. Risk assessors should describe the uncertainties associated with their choice of toxicity value in the risk characterization section of the risk assessment (see Section 9.2.2 of this document). For situations where duration-appropriate toxicity values are not available, please follow the procedures outlined in Section 4.2 and Appendix C of this document.

The specific definition for each exposure duration category may vary depending on the source of the toxicity value being used. For Tier 1 toxicity values obtained from EPA's IRIS database, acute exposures are defined as lasting 24 hours or less; subchronic exposures are defined as repeated exposures by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10 percent of the human lifespan; and chronic exposures are defined as repeated exposures for more than approximately 10 percent of the human lifespan (USEPA, 2008b).[26, 27]

After deciding which duration the exposure scenario most closely matches, risk assessors should then proceed to Step 2, following the path of the selected duration. Note that if an acute duration is selected, risk assessors should proceed directly to Step 3 to estimate an acute EC for each acute exposure period.

3.3.2 Step 2: Assess Exposure Pattern

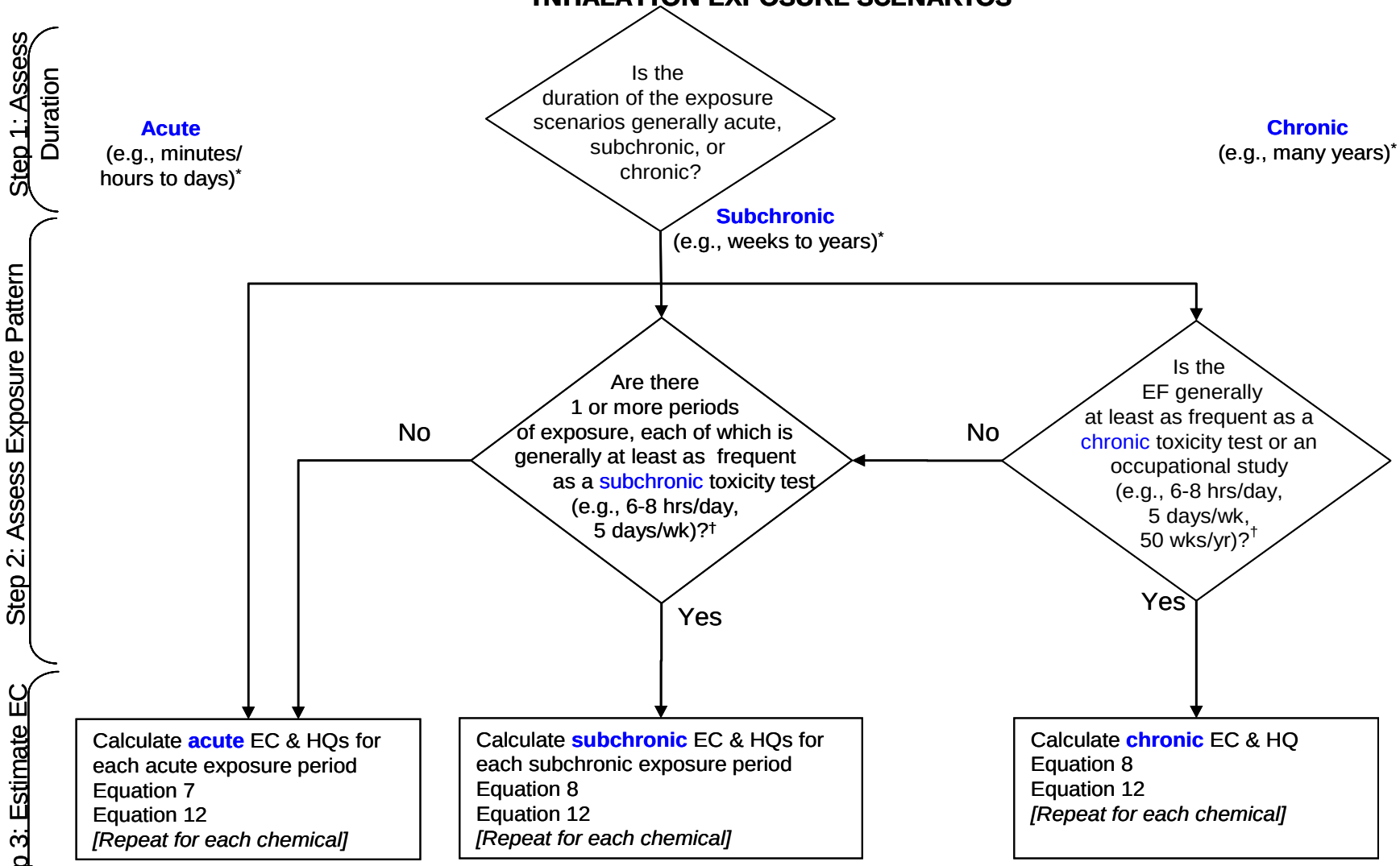
Step 2 of the recommended process for estimating an EC for use in a hazard quotient involves assessing the exposure pattern for each exposure scenario at a site. This entails comparing the exposure time and frequency at a site to that of a typical subchronic or chronic toxicity test.[28]

[26] Note that other sources of toxicity values may define exposures differently. For example, the Agency for Toxic Substances and Disease Registry (ATSDR) (which publishes Minimal Risk Levels (MRLs)) defines acute exposures as occurring from one to 14 days, intermediate exposures as greater than 14 to 364 days, and chronic exposures as 365 days or longer. However, the toxicity values are based on the same underlying toxicological concepts described in this section.

[27] Exposures with a duration lasting between 24 hours and 30 days should be treated as subchronic for the purposes of this document.

[28] Exposure regimens vary from study to study. Risk assessors should use best professional judgment to determine if the exposure pattern in a given scenario is reasonably similar to a typical regimen for a subchronic or chronic study.

FIGURE 2
RECOMMENDED PROCEDURE FOR DERIVING EXPOSURE CONCENTRATIONS AND HAZARD QUOTIENTS FOR INHALATION EXPOSURE SCENARIOS



* The specific definition for each duration category may vary depending on the source of the toxicity value being used. For Tier 1 toxicity values obtained from IRIS:
acute exposures are defined as those lasting 24 hours or less;
subchronic exposures are defined as repeated exposures for more than 30 days, up to approximately 10 percent of the life span in humans; and
chronic exposures are defined as repeated exposures for more than approximately 10 percent of the life span in humans (EPA, 2008b).
For the purposes of this document, short-term exposures, defined by the IRIS glossary as repeated exposures for more than 24 hours, up to 30 days, should be treated as subchronic.

† Exposure regimens vary from study to study. Risk assessors should use best professional judgment to determine if the exposure pattern in a given scenario is reasonably similar to a typical regimen for a chronic or subchronic study.

For exposure scenarios with a subchronic duration, risk assessors should follow the center path on the flowchart. Step 2 in this path asks whether there are one or more periods of exposure, each of which is generally as frequent as a subchronic toxicity test (e.g., 6-8 hours per day, 5 days per week). If the exposure scenario matches this description, risk assessors should proceed to Step 3 and estimate a subchronic EC for each subchronic exposure period. However, if the exposure pattern contains periods that are significantly shorter and/or involve significantly less frequent exposures than indicated in the flow chart, risk assessors should derive acute ECs for each of these exposure periods. If it is difficult to determine whether a specific exposure scenario is best modeled as a subchronic exposure or as a series of independent acute exposures, due to uncertainty in the time required to return to baseline following exposure, risk assessors may want to derive ECs using both approaches.

If the exposure scenario has a chronic duration, risk assessors should follow the right hand path on the flowchart. Step 2 in this path asks whether the exposure frequency (EF) is generally as frequent as a chronic animal toxicity test or a human occupational study (e.g., 6-8 hours per day, 5 days per week, for 50 weeks per year). If the exposure scenario matches this description, risk assessors should proceed to Step 3 and estimate a single chronic EC. However, if the scenario differs significantly from this pattern, risk assessors should proceed to the second question under the subchronic duration path and proceed as outlined above.

3.3.3 Step 3: Estimate Exposure Concentration

Step 3 of the recommended process involves estimating the EC for the specific exposure scenario based on the decisions made in Steps 1 and 2. For acute exposures, the EC is equal to the CA. Risk assessors can estimate an acute EC for each acute exposure period at a site using Equation 7. For longer-term exposures, risk assessors should take into consideration the exposure time, frequency, and duration for each receptor being evaluated as well as the period over which the exposure is averaged (i.e., the averaging time (AT)) to arrive at a time-weighted EC. If there are one or more exposure periods that are generally as frequent as a subchronic toxicity test, risk assessors should use Equation 8 to estimate a subchronic EC for each of these exposure periods. (Exposure periods with significantly less frequency should be treated as acute exposures.) If the exposure pattern is generally as frequent as a chronic toxicity test of an occupational study, risk assessors should use Equation 8 to estimate a single chronic EC for the duration of the exposure.

Acute Exposures

EC = CA **(Equation 7)**

Where: EC ($\mu g/m^3$) = exposure concentration;
CA ($\mu g/m^3$) = contaminant concentration in air;

Chronic or Subchronic Exposures

EC = (CA x ET x EF x ED)/AT **(Equation 8)**

Where:
EC ($\mu g/m^3$) = exposure concentration;
CA ($\mu g/m^3$) = contaminant concentration in air;
ET (hours/day) = exposure time;
EF (days/year) = exposure frequency;
ED (years) = exposure duration; and
AT (ED in years x 365 days/year x 24 hours/day) = averaging time

Note: If the duration of the exposure period is less than one year, the units in the above equation can be changed to the following: EF (days/week); ED (weeks/exposure period); and AT (hours/exposure period).

It is important to use the EC equation that most closely matches the exposure pattern and duration at a site. For instance, if the exposure pattern at a site consists of a series of short (e.g., 4-hour) periods of high exposure separated by several days of no exposure, the approach outlined above recommends estimating an acute EC for each acute exposure period. If the chronic EC equation (Equation 8) were to be used instead, the result would be an average EC value that may lead to an underestimate of risk since the inhaled concentrations could be higher than acute toxicity values during periods of exposure.

3.4 Estimating Exposure Concentrations in Multiple Microenvironments

When detailed information on the activity patterns of a receptor at a site is available, risk assessors can use these data to estimate the EC for either non-carcinogenic or carcinogenic effects. The activity pattern data describe how much time a receptor spends, on average, in different microenvironments (MEs), each of which may have a different contaminant concentration level.[29] By combining data on the contaminant concentration level in each ME and the activity pattern data, the risk assessor can calculate a time-weighted average EC for a receptor. Because activity patterns (and hence, MEs) can vary over a receptor's lifetime, EPA recommends that risk assessors pursuing the ME approach first calculate a time-weighted average EC for each exposure period characterized by a specific activity pattern (e.g., separate ECs for a school-aged child resident and a working adult resident). These exposure period-specific ECs can then be combined into a longer term or lifetime average EC by weighting the EC by the duration of each exposure period. The following sections further explain these two steps.

3.4.1 Using Microenvironments to Estimate an Average Exposure Concentration for a Specific Exposure Period

The ME approach can be used to estimate an average EC for a particular exposure period during which a receptor has a specified activity pattern. As a simplified example, a residential receptor may

[29] EPA defines a microenvironment in *Air Quality Criteria for Particulate Matter: Volume II* as a defined space that can be treated as a well-characterized, relatively homogeneous location with respect to pollutant concentration for a specified time period (e.g., rooms in homes, restaurants, schools, offices, inside vehicles, or outdoors) (USEPA, 2004b).

be exposed to a higher concentration of a contaminant in air in the bathroom for 30 minutes per day while showering, and exposed to a lower concentration in the rest of the house for the remaining 23.5 hours per day. In this case, risk assessors can use the CA value experienced in each ME weighted by the amount of time spent in each ME to estimate an average EC for the period of residency in that house using Equation 9.[30] This approach may also be used to address exposures to contaminants in outdoor and indoor environments at sites where both indoor and outdoor samples have been collected or where the vapor intrusion pathway has been characterized.

$$EC_j = \sum_{i=1}^{n} \left(CA_i \times ET_i \times EF_i\right) \times ED_j / AT_j \qquad \textbf{(Equation 9)}$$

Where:
EC_j ($\mu g/m^3$) = average exposure concentration for exposure period j;
CA_i ($\mu g/m^3$) = contaminant concentration in air in ME i;
ET_i (hours/day) = exposure time spent in ME i;
EF_i (days/year) = exposure frequency for ME i;
ED_j (years) = exposure duration for exposure period j; and
AT_j (hours) = averaging time = ED_j x 24 hours/day x 365 days/year.

3.4.2 Estimating an Average Exposure Concentration Across Multiple Exposure Periods

To derive an average EC for a receptor over multiple exposure periods, the average EC from each period (as calculated above in Equation 9) can be weighted by the fraction of the total exposure time that each period represents, using Equation 10. For example, when estimating cancer risks, the risk assessor may calculate a lifetime average EC where the weights of the individual exposure periods are the duration of the period, ED_j, divided by the total lifetime of the receptor. Alternatively, when estimating an HQ, risk assessors can use Equation 10 to calculate less-than-lifetime average ECs across multiple exposure periods. In that case, the AT will equal the sum of the individual EDs for all of the exposure periods.

$$EC_{LT} = \sum_{i=1}^{n} \left(EC_j \times ED_j\right) / AT \qquad \textbf{(Equation 10)}$$

Where:
EC_{LT} ($\mu g/m^3$) = long-term average exposure concentration;
EC_j ($\mu g/m^3$) = average exposure concentration of a contaminant in air for exposure period j;
ED_j (years) = duration of exposure period j; and
AT (years)[1] = averaging time.

[1] When evaluating cancer risk, the AT is equal to lifetime in years. When evaluating non-cancer hazard, the AT is equal to the sum of the EDs for each exposure period.

[30] If one or more MEs involve acute exposures, risk assessors should conduct a supplemental analysis comparing the CA for each of those MEs to a corresponding acute toxicity value to ensure that receptors are protected from potential acute health effects.

4. SELECTING APPROPRIATE TOXICITY VALUES

After characterizing the exposure scenarios and estimating ECs for each receptor at a site, the risk assessor should select appropriate inhalation toxicity values for each inhaled contaminant. For estimating cancer risks, this typically involves identifying and evaluating available published cancer potency estimates. For estimating HQs, this typically involves identifying and evaluating reference values that match the characterization of the exposure scenario from Figure 2 (i.e., acute, subchronic, or chronic reference values).

This section provides guidance for the selection of toxicity values appropriate for assessing risk under inhalation exposure scenarios. It describes sources for the most current inhalation data and provides guidance for proceeding when published inhalation toxicity data are not available.

4.1 Sources for Inhalation Toxicity Data

The OSWER Directive, *Human Health Toxicity Values in Superfund Risk Assessment* (USEPA, 2003), provides a recommended hierarchy of toxicological data sources to guide risk assessors when selecting appropriate toxicity values. This document sets out a recommended three-tiered framework for selecting human toxicity values. Tier 1 consists of EPA's IRIS, Tier 2 consists of EPA's PPRTVs, and Tier 3 includes other toxicity values as recommended by NCEA, such as the California EPA toxicity values, the Agency for Toxic Substances and Disease Registry's (ATSDR's) Minimal Risk Levels (MRLs), and Health Effects Assessment Summary Table (HEAST) toxicity values. Priority in Tier 3 should be given to sources that are the most current and those that are peer reviewed. Consultation with the Superfund Headquarters office is recommended regarding the use of Tier 3 values for Superfund response decisions when the contaminant appears to be a risk driver for the site.

The most up-to-date information on Superfund-supported cancer potency estimates and chronic and subchronic cancer and non-cancer reference values for inhaled contaminants are available on the Superfund risk assessment website (www.epa.gov/oswer/riskassessment/superfund_toxicity.htm). Superfund-recommended sources for acute non-cancer toxicity values can be found at www.epa.gov/oswer/riskassessment/superfund_acute.htm.[31]

In situations where the desired reference value (e.g., acute, subchronic, chronic) is not available, risk assessors may use a reference value based on the next longer duration of exposure as a conservative estimate that would be protective for a shorter-term ED (USEPA, 2002c). For example, if a risk assessor determines that an ED at a site is subchronic, but no subchronic toxicity value is available, a chronic RfC can be used to assess hazard.

EPA recommends that toxicity values published in Superfund-supported sources should generally be used in the risk equations presented in this guidance, without modification. This includes IURs on IRIS that were calculated from oral values using a default ventilation rate and BW (see Appendix B for a list of these chemicals). It is not generally appropriate to make adjustments to these values

[31] In selecting an acute toxicity value, risk assessors should consider the duration associated with their estimate of exposure (e.g., a 1-hour versus a 24-hour air sample). Use of a toxicity value specified for a longer duration than that of the exposure estimate may overestimate hazard, while the use of a shorter duration acute reference value may underestimate hazard.

based on IR and BW using the intake equation, because the amount of the chemical that reaches the target site through the inhalation pathway is not a simple function of these parameters (see Section 1.2). Use of the toxicity values listed in Appendix B should be noted in the uncertainty section of the risk assessment (see Section 9).

4.2 Recommended Procedures for Assessing Risk in the Absence of Inhalation Toxicity Values

The following section provides guidance on recommended procedures for situations where inhalation toxicity values are not available in any of the toxicity data sources described in Section 4.1.

If RfC and IUR values are not available for an inhaled contaminant, risk assessors should first contact NCEA's STSC for guidance.[32] Risk assessors working on Superfund sites can contact STSC to determine whether a provisional peer-reviewed toxicity value (PPRTV) exists for a contaminant; if not, the risk assessor, in cooperation with the appropriate EPA Regional office may request that STSC develop a PPRTV document or that STSC develop an inhalation toxicity value as a "consult". The latter would be specific to the site in question only. Additional information on STSC's current process for developing alternative toxicity values is described in Appendix C.

If STSC indicates that no quantitative toxicity information for the inhalation route is available, the risk assessor should conduct a qualitative evaluation of this exposure route. The risk assessor should discuss in the uncertainty section of the risk assessment report the implications of not quantitatively assessing risks due to inhalation exposures to chemicals lacking inhalation toxicity data. See the section on Risk Characterization (Section 9) in this guidance for more information.

Performing simple route-to-route extrapolation without the assistance of STSC is generally not appropriate because hazard may be misrepresented when data from one route are substituted for another without any consideration of the pharmacokinetic differences between the routes (USEPA, 1998). The following circumstances, outlined in the *Inhalation Dosimetry Methodology* (page 4-6), are specific examples of situations when route-to-route extrapolation from oral toxicity values might not be appropriate, even for use during screening:

- When groups of chemicals are expected to have different toxicity by the two routes – for example, 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 was not adequately studied in the oral studies; and
- When short-term inhalation studies, dermal irritation, in vitro studies, or characteristics of the chemical indicate the potential for portal-of-entry effects at the respiratory tract, but studies themselves are not adequate for inhalation toxicity value development.

[32] All contact with STSC should be performed by an EPA regional risk assessor. States and other entities should first contact their EPA regional risk assessor with questions on inhalation toxicity values. Regional risk assessors can then contact STSC on their behalf.

The *Cancer Guidelines* (USEPA, 2005a) includes the following statement regarding route-to-route extrapolation:

> "When a qualitative extrapolation can be supported, quantitative extrapolation may still be problematic due to the absence of adequate data. The differences in biological processes among routes of exposure (oral, inhalation, dermal) can be great because of, for example, first-pass effects and different results from different exposure patterns. There is no generally applicable method for accounting for these differences in uptake processes in a quantitative route-to-route extrapolation of dose-response data in the absence of good data on the agent of interest. Therefore, route-to-route extrapolation of dose data relies on a case-by-case analysis of available data" (page 3-10).

5. ESTIMATING RISKS

This section provides updated equations recommended for estimating excess cancer risks and HQs from inhaled contaminants of concern at Superfund sites. Please see Section 8.2.1 of *RAGS, Part A* for further information about how to interpret calculated excess cancer risks and HQs.

5.1 Cancer Risks Characterized by an Inhalation Unit Risk

The excess cancer risk for a receptor exposed via the inhalation pathway can be estimated with the following equation:

Risk = IUR x EC **(Equation 11)**

Where: IUR $(\mu g/m^3)^{-1}$ = Inhalation Unit Risk; and
EC $(\mu g/m^3)$ = exposure concentration (See Equation 6).

When estimated ECs are above the POD used for the low dose extrapolation described in Section 2.3, a linear concentration-response relationship may not hold.[33] In such situations, the risk assessor should not use toxicity values developed through low dose extrapolation techniques. Instead, the risk assessor may report semi-quantitative risk estimates (e.g., risks are greater than 10^{-2}) or estimate risk using the original model underlying the toxicity value, which can be found in the technical support document for the value (e.g., IRIS profile, PPRTV Assessment).

When estimating cancer risks for children, risk assessors should be aware of chemicals that pose a higher risk of cancer when exposure occurs during early life. If evidence exists suggesting differences in risk across age groups for a chemical, this typically will be considered in the derivation of the toxicity value and described in the chemical's technical support document.

[33] Reviews of chemical-specific IRIS files indicate that the risk level corresponding to the concentration level above which the IUR should not be used often falls at or near 10^{-2}. However, this risk level varies by chemical and, therefore, risk assessors should refer to the toxicity value's technical support document for information on the concentration range for which the IUR was intended to be used.

Chemicals that have been determined to cause cancer by a mutagenic mode of action (MOA) are thought to pose a higher risk during early life. An EPA-recommended procedure exists for assessing risks from these chemicals. Figure 3 summarizes the recommendations of the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (USEPA, 2005b; hereafter *Supplemental Cancer Guidelines*) on how to adjust childhood risk calculations to account for chemicals with a mutagenic MOA for carcinogenicity. Please refer to the *Supplemental Cancer Guidelines* (USEPA, 2005b) for a list of chemicals with a mutagenic MOA that were used in the development of that document.

In addition, EPA's website for the "Handbook for Implementing the Supplemental Cancer Guidance at Waste and Cleanup Sites" contains an up-to-date list of chemicals that EPA has determined to have a mutagenic MOA (http://www.epa.gov/oswer/riskassessment/sghandbook/index.htm). As chemicals receive new assessments for mutagenicity, this information will appear in the IRIS profile or PPRTV assessment.

FIGURE 3
GUIDANCE ON ASSESSING RISK FROM EARLY-LIFE EXPOSURES FOR CHEMICALS ACTING BY A MUTAGENIC MODE OF ACTION FOR CARCINOGENICITY

If a chemical has been determined to cause cancer by a mutagenic MOA, it is possible that exposures to that chemical in early-life may result in higher lifetime cancer risks than a comparable duration adult exposure.

In risk assessments of exposure to chemicals for which a mutagenic MOA for carcinogenicity has been determined by EPA and a linear low-dose extrapolation performed, one of the following generally pertains:

1) If chemical-specific data on susceptibility from early-life exposures were available for derivation of CSFs, those slope factors are used for risk characterization, and Age Dependent Adjustment Factors (ADAFs) are not applied.
2) If chemical-specific data on susceptibility from early-life exposures were not available, the ADAFs are applied in calculating or estimating risks associated with early-life exposures (USEPA, 2005c).

If the latter case applies, the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (USEPA, 2005b) recommends the following default ADAFs be applied in risk assessments:

- 10-fold adjustment for exposures during the first 2 years of life;
- 3-fold adjustment for exposures from ages 2 to <16 years of age; and
- No adjustment for exposures after turning 16 years of age.

In such cases, Equation 11 can be altered to include the ADAFs in the following way:

$$Risk = (IUR \times EC_{<2} \times ADAF_{<2}) + (IUR \times EC_{2\text{-}16} \times ADAF_{2\text{-}16}) + (IUR \times EC_{>16})$$

Sources: USEPA, 2005b and USEPA, 2005c.
Note: All communications and factsheets pertaining to the implementation of the 2005 *Cancer Guidelines* can be found at www.epa.gov/osa/spc/cancer_guidelines.htm.

5.2 Hazard Quotients

The HQ for the inhalation pathway can be calculated with the following general equation:

HQ = EC/(Toxicity Value[1] x 1000 µg/mg) **(Equation 12)**

Where: HQ (unitless) = Hazard Quotient;
EC ($\mu g/m^3$) = exposure concentration (See Equations 7 or 8);
Toxicity Value (mg/m^3) = Inhalation toxicity value (e.g., RfC) that is appropriate for the exposure scenario (acute, subchronic, or chronic).

[1] Risk assessors should refer to the flowchart (Figure 2) to select an appropriate inhalation toxicity value for the exposure scenario at a site in order to calculate the HQ.

6. EXAMPLE EXPOSURE SCENARIOS

This section of the guidance includes examples of the types of exposure scenarios risk assessors may encounter when evaluating inhalation exposures at waste sites. Each scenario includes sample values for exposure parameters and reviews the process of estimating the EC and risks for cancer and other health effects. These examples are provided for illustrative purposes only and are not representative of every exposure scenario that could be encountered at a site. Furthermore, risk assessors should use site-specific values for exposure parameters if practicable when estimating ECs and risk levels or HQs. This would typically require some information on activity patterns for the specific site or the use of professional judgment. If default values are to be used for certain exposure parameters, please consult the Superfund website for up-to-date information on Superfund-recommended default exposure parameters.[34]

6.1 Residential Receptor

An example of a residential scenario could consist of inhalation exposure for up to 24 hours per day, up to 350 days per year for 6 to 30 years. When estimating cancer risk for this type of scenario, Equation 6 is recommended to calculate an EC and Equation 11 is recommended to estimate risk. For estimating hazard quotients for cancer or non-cancer effects, this scenario can be evaluated using the steps outlined in Figure 2. The duration of this scenario ranges from 6 to 30 years, which can be considered chronic (because it consists of repeated exposures for approximately 10 percent of a receptor's lifespan). The frequency of this scenario is generally as frequent as a chronic toxicity test and therefore Equation 8 is recommended to derive a chronic EC and Equation 12 with a chronic toxicity value is recommended to calculate an HQ. If information about multiple MEs is available, risk assessors should proceed according to Section 3.4 to estimate ECs to use in estimating cancer risks or HQs.

When assessing the risk under the residential scenario for children, the risk assessor should keep in mind that exposure parameters, specifically those related to activity patterns (e.g., exposure time, frequency, and duration) may be different for children and adults at the same site. For example, due

[34] http://www.epa.gov/oswer/riskassessment/superfund_hh_exposure.htm.

to outdoor play patterns, children may spend more time near the source of contamination than adults, and thus would have higher exposure time and/or exposure frequency values than adults living in the same location.[35] For indoor vapor intrusion from the subsurface, very young children might be more highly exposed due to substantial time spent indoors.

Beyond the consideration of activity patterns, MEs, and chemicals with a mutagenic MOA for carcinogenicity (as described in Section 5.1), no additional adjustments to account for specific child receptors should be made to the default values. Appendix A of this document is intended to illustrate that the use of default values sufficiently covers age-related variation in DAF or HEC values derived using the EPA *Inhalation Dosimetry Methodology's* default approach.

6.2 Commercial-Industrial/Occupational Receptor

An example of a commercial-industrial or occupational inhalation exposure scenario could be characterized by full-time workers (e.g., 8 hours per day, 5 days per week) in an indoor setting, such as an office building, exposed via vapor intrusion of subsurface contamination on a daily basis for 5 to 25 years. When estimating cancer risk for this type of scenario, Equation 6 is recommended to calculate an EC and Equation 11 is recommended to estimate risk. Following the flowchart in Figure 2, the duration and exposure pattern of this scenario would typically be considered chronic. Therefore, Equation 8 is recommended to derive a chronic EC and Equation 12 is recommended (with a chronic RfC) when calculating an HQ for cancer or non-cancer effects. If information about multiple MEs is available, risk assessors should proceed according to Section 3.4 when deriving ECs to use in estimating cancer risks or HQs. Exposure parameters should be adjusted to consider the exposure time, frequency and duration for this scenario, which may differ from a residential scenario. Risk assessors should also use appropriate exposure parameters for outdoor workers who, similar to children, may spend more time near a source of contamination than indoor workers.

6.3 Construction Worker

One example of a construction worker scenario could involve a long-term project (1-2 years) with workers exposed regularly to contaminant vapors and fugitive dust (8 hours per day, 5 days per week). When estimating cancer risk for this type of scenario, Equations 6 and 11 are recommended to calculate an EC and the risk estimate, respectively. Following the flowchart in Figure 2, the duration of this exposure scenario would typically be considered subchronic. In addition, this exposure is generally as frequent as a subchronic toxicity test. Therefore, Equation 8 is recommended to derive a subchronic EC, and Equation 12 is recommended for use with a subchronic toxicity value to calculate the HQ. If information about multiple MEs is available, risk assessors should proceed according to Section 3.4 when deriving ECs to use in estimating cancer risks or HQs.

6.4 Trespasser/Recreational Receptor

An example trespasser/recreational scenario could consist of an exposure of 1 to 2 hours per day, for 100 days per year or less. When estimating cancer risk for this type of scenario, Equations 6 and 11

[35] For additional information about early-lifestage age groups to consider when assessing children's exposure to environmental contaminants, please consult EPA's *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (EPA, 2005d).

are recommended to calculate an EC and the risk estimate, respectively. Following the steps in Figure 2 for cancer or non-cancer effects characterized by an RfC, each exposure period should be assessed separately because this exposure lasts only one to two hours each day for an average of two days per week. Therefore, Equation 7 is recommended to derive acute ECs for each exposure period. In addition, Equation 12 is recommended for use with an acute toxicity value to calculate HQs for each exposure period.

7. TARGET CONCENTRATIONS FOR SCREENING ANALYSIS OF INHALATION PATHWAYS

For purposes of this guidance, risk-based screening levels are values that may be compared to the contaminant concentration in air to help risk assessors identify potential contaminants of concern. Screening levels can also be calculated for comparison with samples from source media at a site, such as soil. Screening levels are generally not appropriate for use as clean-up levels; they are intended to aid in initial evaluation of contaminants and exposure pathways of concern prior to proceeding with a baseline risk assessment.[36] If contaminant concentrations in air exceed the risk-based screening levels appropriate for the receptor population of interest, risk assessors should gather site-specific information to determine the need for any remedial action. The following sections outline a recommended approach for calculating screening levels in air as well as source media.

7.1 Target Contaminant Concentrations in Air

The equations recommended for estimating ECs and risk (Equations 6 through 12) can be used to calculate target contaminant concentrations in air by following the four steps outlined below in Table 4.[37]

If air samples from a site are found to be below the target concentration, the risk assessor can generally conclude that this pathway does not pose an unacceptable level of risk from the contaminant. If the concentrations are found to exceed the screening levels, the risk assessor should evaluate the inhalation pathway further by gathering additional site-specific data on contaminant levels, site conditions, and receptor characteristics.

7.2 Screening Levels for Other Media

Inhalation risk-based screening levels may also be calculated for media other than air, including soils, tap water, soil gas, and ground water. The soil gas and ground water values may be derived specifically to address concerns about vapor intrusion from subsurface contamination into indoor spaces.

[36] EPA regions, states, or other agencies may support unique screening levels for specific purposes that may differ from the method presented in this document. Generally, when using screening levels it is important that risk assessors understand the target risks, toxicity, and exposure assumptions as well as migration-attenuation assumptions on which they are based, and to apply them for their intended use.

[37] Target contaminant concentrations in air calculated according to the procedure outlined in this document are generally protective for direct inhalation exposures. This process should not be used to calculate concentrations in air to be protective of indirect exposures (e.g., ingestion of crops contaminated through air delivery or vapor phase transfer, ingestion of livestock or fish contaminated indirectly through air deposition or vapor phase transfer).

TABLE 4 RECOMMENDED PROCEDURE FOR CALCULATING RISK-BASED SCREENING CONCENTRATIONS FOR CONTAMINANTS IN AIR		
	Cancer Risk-Based	**Hazard-Based**[1]
Step 1: Select Target Levels	Select target cancer risk (e.g., 1×10^{-6}).	Select target HQ (e.g., 1).
Step 2: Identify Toxicity Value[2]	Identify inhalation cancer potency value (e.g., IUR). If none exists, proceed with hazard-based screening level calculation.	Identify inhalation reference value (e.g., RfC) to match exposure scenario (acute, subchronic, or chronic). If none exist, proceed with cancer screening level calculation.
Step 3: Calculate CA	Using target cancer risk from Step 1 along with the receptor- and scenario-specific exposure parameter values, calculate CA; the following equation is recommended: CA = (AT x Target Risk)/(IUR x ET x EF x ED)	Using target HQ from Step 1 along with the receptor- and scenario-specific exposure parameter values, calculate CA; the following equation is recommended: CA = (AT x Target HQ x RfC x 1000 µg/mg)/(ET x EF x ED)
Step 4: Select Screening Concentration	Select minimum of predicted cancer risk- and hazard-based values as screening concentrations.[3] Repeat for each receptor/scenario combination of interest.	

[1] Hazard-based screening concentrations are typically derived from reference values such as RfCs. These values may be available for non-cancer effects but may include cancer, if a nonlinear MOA is thought to operate for a chemical.
[2] If no inhalation toxicity value is available for a chemical, contact STSC for further direction on how to proceed.
[3] Screening levels estimated from the equations presented in Step 3 could yield concentrations that exceed the maximum possible vapor concentration for a chemical. In such cases, it may be useful to calculate the maximum possible vapor concentration of the pure contaminant at the temperature of interest, using the following formula: $C_{max} = S \times H \times 10^3$ L/m^3, where S = solubility at 25° C (or temperature of interest) and H (unitless) = Henry's Law Constant at 25° C (or temperature of interest). This equation is based on an established relationship (see, for example, Schwartzenbach et al. 1993), that allows the Henry's Law Constant to be estimated as the ratio of a compound's vapor pressure and aqueous solubility for compounds that are slightly to moderately soluble in water. When the dimensionless Henry's Law constant, H, is used, the relationship described above can be used to calculate the vapor concentration of a saturated solution of a given compound, assuming equilibrium between the vapor and aqueous phases.

7.2.1 Soil Screening Levels

When evaluating risk in a source medium, such as soil, it is typically possible to calculate screening levels for that medium that are expected to be protective of inhalation exposures based on the expected transfer of a contaminant from the source medium to the air. Soil Screening Levels (SSLs) can be described as "risk-based soil concentrations derived for individual chemicals of concern from standardized sets of equations. These equations combine EPA chemical toxicity data with parameters defined by assumed future land uses and exposure scenarios, including receptor characteristics and potential exposure pathways" (USEPA, 2002b). These SSLs may be used for screening analyses and may serve as the basis for the development of Preliminary Remediation Goals (PRGs). Refer to the *Soil Screening Guidance* (USEPA, 1996) and the *Supplemental Guidance for Developing Soil Screening Levels for Superfund Sites* (USEPA, 2002b) for recommended equations that can be used to calculate SSLs for volatilization of chemicals from soil to air and for particulate emissions.

7.2.2 Tap Water Screening Values

Contaminated tap water may pose risk by the inhalation route if the contaminants present are volatile. Screening levels can be calculated for tap water that account for inhalation exposures resulting from the household use of water (e.g., showering, laundering, dishwashing). Risk assessors should consult their local EPA regional risk assessor for direction on how to calculate appropriate screening levels for tap water.

7.2.3 Soil Gas or Ground Water Screening Values for Vapor Intrusion

If there is concern at a site about the possibility of migration of vapor-forming chemicals from contaminated soil gas or ground water into the indoor air of overlying buildings ("vapor intrusion"), screening values can be calculated for these media. Risk assessors should first follow the procedure outlined in Section 7.1 and Table 4 to calculate a risk-based target concentration for the contaminant in air.

For the calculation of a soil gas screening-level concentration, the target air concentration is then divided by an assumed screening-level attenuation factor. The attenuation factor (the ratio of indoor air divided by subsurface source concentration) represents the factor by which subsurface vapor concentrations migrating into indoor air spaces are reduced due to a variety of attenuating mechanisms.

For the calculation of a ground water screening-level concentration, the target air concentration is divided by an assumed screening-level attenuation factor, and the resulting soil gas concentration is converted to a corresponding ground water concentration, assuming equilibrium between the aqueous and vapor phases at the water table.

Risk assessors should consult their local EPA regional risk assessor for direction on how to calculate appropriate screening levels for soil gas and ground water when vapor intrusion is an issue at a site.

8. DEVELOPING AGGREGATE AND CUMULATIVE RISK ESTIMATES

EPA's current approach to estimating cumulative risk or hazard at a site from multiple chemicals, set forth in *RAGS, Part A* (USEPA, 1989), is not affected by the *Inhalation Dosimetry Methodology* and therefore is not being updated at this time. In addition, the aggregation of risks and hazards across multiple exposure routes should remain unchanged. The recommended approaches for aggregating risk and hazard estimates are outlined below.

8.1 Estimating Cumulative Risks and Hazards Across Multiple Chemicals

The recommended method for estimating cumulative risk and hazard at a site from exposure to multiple chemicals is described in *RAGS, Part A*, Section 8.2.2. This method is based on the default approaches described in *Guidelines for the Health Risk Assessment of Chemical Mixtures* (USEPA, 1986). Additional information on this method was subsequently published in the *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 2000b). The recommended methods to use with quantitative cancer risk estimates as well as with HQs are outlined below.

8.1.1 Cancer Risks

When evaluating predicted cancer risks from multiple contaminants, risk assessors should estimate the cancer risk for each substance and then sum these risks. This yields an estimate of total cancer risk, which represents the cumulative predicted cancer risk for the chemicals at a site.

Risk assessors should note, however, that this recommended method assumes "independence of action by the compounds involved (i.e., that there are no synergistic or antagonistic chemical interactions and that all chemicals produce the same effect, i.e., cancer)" (USEPA, 1989). In addition, this simple additive approach is generally most appropriate for total cancer risks less than 0.1. If these assumptions are incorrect, over- or under-estimation of actual multiple-substance risk could result (USEPA, 1989).

8.1.2 Hazard Quotients

When the evaluation involves multiple chemicals assessed via HQs, risk assessors typically first calculate the HQ for each substance, and then sum the individual HQ values. This generally yields an estimated hazard index (HI) for the multiple chemicals assessed via a hazard-based approach. Separate HIs should be calculated for each type of exposure period (i.e., chronic, subchronic, acute). If an HI is greater than 1, it is generally appropriate to derive separate HIs for each target organ of concern (for more information, see *RAGS, Part A*, page 8-14).[38] When multiple acute exposures are present at a site, risk assessors should evaluate each acute exposure event separately. Hazards from multiple chemicals generally should be summed only when the exposures to these chemicals occur simultaneously.[39]

8.2 Aggregating Risk and Hazard Quotients Across Exposure Routes

Guidance for combining the multi-chemical risk estimates and hazard quotients across exposure pathways is described in *RAGS, Part A*, Section 8.3 (USEPA, 1989). In order to determine whether risks or HIs should be combined across exposure pathways, risk assessors should first identify reasonable exposure pathway combinations. Then, risk assessors should examine whether it is likely that the same individuals would consistently face the reasonable maximum exposure (RME) by more than one pathway.

[38] This recommended method assumes that "the dose for each individual component is at a level at which effects are not expected to occur, be observable, or be of concern; however, when the doses are combined, effects of concern may be expected or observed in response to the higher dose level of the mixture" (EPA, 2000b, page 12). Another assumption of the HI approach is that the compounds induce the same effect by the same mechanism of action. Therefore, "application of the HI equation to a number of compounds that are not expected to induce the same type of effects or that do not act by the same mechanism, although appropriate as a screening-level approach, could overestimate the potential for effects" (EPA, 1989, page 8-14). This is generally less of a concern if one to two substances are responsible for driving the HI above 1.

[39] In cases where a single chemical is present at a site and receptors are exposed through a series of acute exposure events, the highest single EC should be compared to an acute reference value of the appropriate duration to assess hazard.

The recommended approach for estimating excess cancer risk from exposure via multiple routes is to first estimate cancer risk from each exposure pathway and then sum across the multiple routes.[40]

For the effects assessed via a reference value, risk assessors should calculate the HI for each exposure pathway and sum across the multiple routes. Separate total HIs should be calculated for each type of exposure period (i.e., chronic, subchronic or acute). If the HI exceeds one, there may be concern for potential adverse effects and risk assessors should consider deriving separate HIs for each target organ of concern.

9. RISK CHARACTERIZATION

Risk characterization is the final, summarizing step in conducting a risk assessment. Generally, the purpose of the risk characterization section of a report is to:[41]

- Describe the key findings of the risk assessment in a transparent manner, including identifying hazard, characterizing the dose-response relationship, and describing receptor exposures;
- Identify and describe the scientific and policy assumptions used in the assessment;
- Characterize uncertainties in results; and
- Provide an overall conclusion about the risks present at a site (USEPA, 2000c).

A well-crafted risk characterization section puts risk calculations into context for risk managers so that they may effectively weigh and interpret risk assessment results (i.e., it is the interface between risk assessment and risk management). A few of the key issues and uncertainties involved in calculating risks from inhalation exposures are outlined below.

9.1 Highly Exposed or Susceptible Populations and Life Stages

EPA recommends that the risk characterization portion of the risk assessment explain any particular susceptibilities to inhaled toxicants or potential for increased inhalation exposures among the various receptor groups at a site.[42] We discuss below two possible examples, children and worker receptors, though this discussion could apply to other receptor characteristics as well (e.g., age, disease, gender, genetic characteristics).

9.1.1 Children

One population group that could potentially be more highly exposed to inhalation exposures at a site is children. As discussed in Section 6.2, exposure parameters related to activity patterns (e.g., exposure time, frequency, and duration) and MEs, may vary across age groups. For example, due to outdoor play patterns, children may spend more time near the source of contamination than adults,

[40] Note that this approach is generally most appropriate for total cancer risks of less than 0.1 (EPA, 1989).

[41] For specific information on the format of risk characterizations, refer to *Elements to Consider when Drafting EPA Risk Characterizations* (EPA, 1995c).

[42] EPA's IRIS glossary defines susceptibility as the following: "Increased likelihood of an adverse effect, often discussed in terms of relationship to a factor that can be used to describe a human subpopulation (e.g., life stage, demographic feature, or genetic characteristic)" (EPA, 2008b).

and thus would have higher exposure time and/or exposure frequency values than adults living in the same location. Therefore, it is important to carefully describe site-specific exposures to children, and assumptions made in risk calculations.[43]

If chemical-specific data on susceptibility to the toxic effects from early life exposures are available, these data are considered when developing toxicity values that specifically address differential toxicity to the young (e.g., vinyl chloride) (USEPA, 2005c). Toxicity values derived using the default approach from the *Inhalation Dosimetry Methodology* are developed for the human population as a whole, including sensitive subgroups. Therefore, as described in Section 6 of Appendix A, no quantitative adjustment of toxicity values derived using the default approach in the *Inhalation Dosimetry Methodology* is recommended for specific age groups to account for different ventilation rates or body weights of specific age groups.

When evaluating risk to carcinogenic chemicals with a demonstrated mutagenic MOA but which lack chemical-specific information on susceptibility from early life exposures, EPA recommends a quantitative adjustment of the toxicity value to account for early life susceptibility, as described in the *Supplemental Cancer Guidelines* (see USEPA, 2005b & 2005c; and Section 5.1 of this guidance for further information).

9.1.2 Workers

Workers could have increased exposure under certain occupational scenarios. Some outdoor workers might spend more time near a source of contamination in the course of their job and this should be reflected in adjustments to the exposure parameters (e.g., ET, Exposure Frequency (EF), and ED) describing the worker exposure scenario. Toxicity values derived using the *Inhalation Dosimetry Methodology* are developed for the human population as a whole, including sensitive populations and life stages. In the default *Inhalation Dosimetry Methodology* approach, typical variation in IRs between periods of high activity and rest is considered. However, if workers have especially high levels of exertion with correspondingly high ventilation rates, these workers could be at the upper end of the risk range, particularly if they are exposed to Category 1 gases, which have direct effects in the respiratory tract. This implication should be recognized in the risk characterization section.

9.2 Uncertainties in Inhalation Risk Assessment

This guidance recommends including an assessment of the key uncertainties that may significantly impact risk estimates for inhaled chemicals. This should ensure transparency, clarity, reasonableness and consistency in risk assessments, as recommended by EPA's *Policy for Risk Characterization* (USEPA, 1995a). Other sources of uncertainty may be present and other EPA documents provide guidance on characterizing uncertainty in risk the assessment process (USEPA, 1992, 1995a, 1995b, 1995c, 1997a, 1997b). Key uncertainties related to inhalation risk assessment, which is the focus of this section, include the development of ECs, choice of toxicity value, lack of quantitative toxicity information via inhalation, and the approach to estimating and aggregating risks. According to EPA's *Guidance for Risk Characterization*, the discussion of uncertainty "should reflect the type and complexity of the risk assessment, with the level of effort for analysis and discussion of uncertainty

[43] For additional information on children's health risk assessment, please consult *A Framework for Assessing Health Risks of Environmental Exposures to Children* (EPA, 2006b).

corresponding to the level of effort for the assessment" (USEPA, 1995b). Therefore, risk assessors should provide a qualitative and/or quantitative evaluation of key uncertainties pertaining to inhalation risk, and their impact on the outcome of the assessment, consistent with the level of effort of the specific risk assessment.

9.2.1 Development of Exposure Concentrations

As described in Section 3 of this guidance, with the exception of acute exposures, time-weighted averages are typically used to represent intermittent or variable inhalation exposures to receptors at a site. This recommended approach is consistent with the duration adjustment approach (based on Haber's Law) that is generally used in deriving the toxicity values (see Section 2.1.1.1 for further information). As mentioned in Section 3, when evaluating situations in which the exposure is long-term, yet there are short periods of significantly higher exposure, those periods should also be assessed using appropriate short-term toxicity values. This ensures that periods of much higher exposure can be appropriately assessed and not "diluted out" in the assessment of longer-term exposure.

When information on multiple MEs exists at a site, risk assessors may choose to estimate ECs as outlined in Section 3.4. However, this typically requires sufficient time-activity information of receptors at a site to accurately determine the time spent in each ME. Incomplete or low quality data on time-activity pattern may introduce uncertainty into the estimation of the ECs for MEs. Risk assessors should describe the quality and completeness of these data.

The recommended method for determining the CA at a site can potentially introduce uncertainty into the EC calculations. For instance, if contaminant concentrations in air are measured, risk assessors should consider uncertainties related to how well the set of air samples available at a site represents the duration and time period being assessed as well as measurement uncertainty related to the methods and equipment used. In addition, risk assessors should describe any potential confounding of indoor air samples by other sources of contaminants (e.g., household products). If contaminant concentrations in air are modeled, (e.g., by EPA's spreadsheet models for vapor intrusion) risk assessors should address model-related uncertainties and their potential impact on the estimate of contaminant concentrations in air. Considerations of particle size at the site versus particle size used to derive the toxicity value are also important.

9.2.2 Toxicity Assessment

Section 4.1 of this document indicates that some IURs on IRIS were developed through extrapolation from oral CSFs (see Appendix B of this document). The use of toxicity values derived through simple route-to-route extrapolation introduces additional uncertainty into risk calculations. Therefore, risk assessors should indicate when extrapolated IURs are used and should characterize the potential impact of the uncertainty associated with using these values, if known.

Section 4.2 and Appendix C of this guidance recommends contacting STSC to help identify appropriate toxicity values for conducting a risk assessment at Superfund sites in the absence of published inhalation toxicity values. If STSC is unable to recommend a toxicity value, risk assessors should acknowledge the resulting uncertainty in risk associated with the chemical(s) lacking inhalation toxicity data. If STSC provides risk assessors with a toxicity value based on a PBPK

model, model uncertainty should be discussed. In addition, if STSC provides risk assessors with one or more structurally analogous chemicals, risk assessors can use toxicity data for these chemicals to help characterize the potential magnitude of the inhalation risk associated with the chemical(s) lacking data. In this case, risk assessors should acknowledge the uncertainty associated with relying on toxicity data for analogous chemicals to characterize risk at the site.

Risk assessors should also acknowledge chemicals that lack duration-appropriate toxicity values and discuss the potential impacts of substituting alternative toxicity values for HQ calculations. For instance, if the ED is determined to be subchronic but no subchronic inhalation RfC or analogous toxicity value is available for that chemical, the risk assessor should address the uncertainty associated with calculating an HQ using a toxicity value for a different duration, such as chronic, or the impact of not quantifying those risks. In addition, if risk assessors use an acute toxicity value that does not match the duration of the acute exposure being assessed, the possibility of under or overestimating hazard should be discussed.

When conducting a screening-level risk assessment using screening values such as those described in Section 7, it is important to further evaluate and clearly describe the quality and uncertainties associated with the inhalation toxicity values used in the risk assessment if measured sample contaminant concentrations at a site exceed these screening values.

9.2.3 Estimating Cancer Risks

For high exposures, for example those within the range of epidemiological studies (usually those predicted to have risks greater than 10^{-2}), the IUR derived from the linear extrapolation below the range of observation is generally not appropriate for use (see Section 5.1 of this document for further information).[44] Risk assessors should provide specific information in the risk characterization describing how these high exposures were addressed in the risk assessment. For instance, if a risk assessor chose to provide a semi-quantitative approach (e.g., indicating that risks are above 10^{-2}), this should be indicated, along with a description of the uncertainties involved in not fully quantifying risk associated with exposure to this chemical. If a risk assessor chose to use the original model in the IRIS file or other technical background document, the risk characterization section should include a description of any uncertainties in the model used and could contain examples of the risks estimated.

9.2.4 Estimating Risk and Hazard from Multiple Chemicals and Exposure Pathways

Risk assessors should also describe uncertainties involved in aggregating risk and hazard across multiple chemicals and exposure pathways. For instance, the approaches described in Section 8 of this document are associated with several assumptions (e.g., independence of action and doses for individual compounds at levels not expected to be of concern). If these assumptions are not met, aggregation may not be appropriate. This should be fully described in the risk characterization section and any uncertainties involved in the lack of quantitative information should be indicated.

[44] Also refer to Section 8.2.1 of *RAGS, Part A* for further discussion of this topic (EPA, 1989, page 8-6).

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APPENDICES

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APPENDIX A

APPENDIX A

ANALYSIS OF DEFAULT APPROACH FOR HEC DERIVATION AS COMPARED TO POPULATION- AND LIFESTAGE-SPECIFIC CALCULATIONS

NOTE: The Agency's inhalation dosimetry methodology (USEPA, 1994; hereafter, "the *Inhalation Dosimetry Methodology"*) is a technical report that describes the derivation of human equivalent concentrations (HECs) from animal (or human) studies, as well as the other steps involved in developing a chronic Reference Concentration (RfC). This appendix is included to illustrate the HEC derivation using the *Inhalation Dosimetry Methodology*'s default approach (with the recommended default values for humans), and to also illustrate the impact of substituting alternate age- and activity-specific human values into the default calculations. The default approach is employed for chemicals for which more chemical-specific dosimetric and pharmacokinetic data are not available, thus precluding the use of more advanced models for deriving the HEC. The calculations in this appendix do not represent a refined or optimal model for assessing intra-human variability (e.g., age- and activity-specific risks), and are not intended to imply that risk assessors should deviate from the *Inhalation Dosimetry Methodology* by substituting alternate values into the default calculations. Age-specific data are limited. Because of these limitations, the calculations made for different ages and exposure groups in this appendix are not recommended for use in quantitative risk assessment (i.e., they are only for the purpose of illustration), but may be useful in discussions of uncertainty and variability associated with the default approach.

It is also noted that, as of this writing, the Agency is involved in a routine reevaluation of scientific advancements in the field, with consideration of the need for improvement to the *Inhalation Dosimetry Methodology*. Any revisions will consider current understanding of inhalation dosimetry and differences across and within species, as well as the Agency's risk assessment needs. In order to transparently and quantitatively address children's inhalation dosimetry and risk assessment, this guidance document will be updated (on-line) when Agency methodology updates are available that are specific to early life. Until that time, the 1994 *Inhalation Dosimetry Methodology* is the appropriate Agency methodology.

INTRODUCTION

This appendix consists of examples and discussions illustrating the current default chemical category-specific approach to inhalation dosimetry for the various categories of gases and particles as described in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (USEPA, 1994; hereafter, the *Inhalation Dosimetry Methodology*). This default inhalation dosimetry approach is used to convert toxicological and epidemiological study data to an HEC that can then be used to derive chronic RfCs for the human population (inclusive of susceptible populations and life stages, such as children) and also in the development of Inhalation Unit Risks (IURs) (USEPA, 2005). The default approach does not rely on age- or activity-specific values for physiological parameters when calculating HECs; however the default approach has been designed by EPA to derive reference values that are protective across the entire population.

The appendix includes six sections. Sections 1 through 3 address Category 1 gases. These sections provide example calculations for Category 1 highly reactive, high water solubility gases that are typically absorbed in the upper airways, exhibiting adverse effects in the extrathoracic (ETh), tracheobronchial (TB), and pulmonary (PU) regions of the respiratory tract, respectively. These examples include comparisons of HEC calculations based on default parameters with those derived using age- and activity-specific parameters for the respiratory region affected. Section 4 addresses Category 3 low reactivity, limited water solubility gases that exhibit systemic effects outside the respiratory tract. Section 5 addresses changes in particle deposition in the respiratory tract across age groups. The conclusions are summarized in Section 6.

When reviewing the examples, please note the following:

- An RfC derived using the *Inhalation Dosimetry Methodology* is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (USEPA, 2008).

- All examples in this appendix are based on the *Inhalation Dosimetry Methodology*. EPA is committed to periodically reviewing and updating the *Inhalation Dosimetry Methodology* to ensure that it reflects the current state of the science and that it yields toxicity values that sufficiently cover potential age- and activity-related variation in inhalation exposure. A review and update is currently underway.

- The examples in this appendix are all based on calculating HECs from a point of departure (POD) for non-cancer effects (e.g., a No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL), or Benchmark Concentration, Lower confidence limit (BMCL)). These calculations could also be performed in an identical manner for carcinogens using a POD for cancer risk estimate derivation (e.g., a Lower limit on the Effective Concentration (LEC) value).

- The default animal and human values for minute volume (V_e) and surface area (SA) used in these examples were obtained from *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (USEPA, 1994).[45] The age- and activity-specific V_e values were obtained from the International Commission on Radiological Protection (ICRP) Publication 66, *Human Respiratory Tract Model for Radiological Protection* (ICRP, 1994).[46] Age-specific SA values used in Examples 1 and 2 were calculated using scaled estimates for the mass and thickness of respiratory region-specific target tissue from ICRP (1994); Values for Example 3 were calculated from an allometric scaling equation presented in a publication by Zeltner et al. (1987). EPA's Office of Research and Development (ORD) selected these data following review of the available physiological data for the age groups indicated in the examples.

- Chemical-specific data from the Integrated Risk Information System (IRIS) file for acrolein were used in the ETh example (Example 1). However, the other two examples, which focus on effects in the TB and PU regions, respectively, use hypothetical data for the POD because there are currently no chemicals on IRIS exhibiting Critical Effects (for RfC derivation) in those regions.[47] The conclusions of these two examples are unaffected by the use of hypothetical data because the results are driven by the values of parameters that are not chemical-specific (i.e., SA and V_e).

[45] The minute volume is the total ventilation per minute and equals the product of the tidal volume (the air volume entering or leaving the lungs with a single breath) and the respiratory frequency.

[46] For further information on inhalation rates in humans under different scenarios, refer to Chapter 5 of EPA's *Exposure Factors Handbook* (EPA, 1997).

[47] Hypothetical examples for the TB and PU regions were included in this appendix because currently no RfCs for gases on IRIS are calculated based on animal studies showing health effects occurring in these regions of the respiratory system

1. EXAMPLE 1: CATEGORY 1 GAS, EXTRATHORACIC EFFECTS, ACROLEIN

The Dosimetric Adjustment Factor (DAF) for a Category 1 gases, the Regional Gas Dose Ratio (RGDR), is based on the animal to human ratio of the V_e divided by the SA of the region of the respiratory tract where the effect occurs. For acrolein, the effect occurs in the ETh region. The DAF is typically calculated using the following equation (USEPA, 1994, Equation 4-18):

$$RGDR_{ETh} = \frac{\left(\frac{V_e}{SA_{ETh}}\right)_{animal}}{\left(\frac{V_e}{SA_{ETh}}\right)_{human}} = \frac{\frac{0.14\,L/min}{15\,cm^2}}{\frac{13.8\,L/min}{200\,cm^2}} = 0.14 \qquad \textbf{(Equation A-1)}$$

The default *Inhalation Dosimetry Methodology*-recommended values for the V_e and SA_{ETh} of the Wistar rat (the animal in the principal study for acrolein) are 0.14 L/min (0.20 m^3/day) and 15 cm^2, respectively (USEPA, 1994). EPA's default human values are 13.8 L/min (20 m^3/day) for V_e and 200 cm^2 for SA_{ETh} (USEPA, 1994). The RGDR for the ETh region ($RGDR_{ETh}$) was calculated using these values for the rat and the human as shown in Equation A-1. In the laboratory animal study on acrolein, the LOAEL adjusted for continuous exposure ($LOAEL_{[ADJ]}$) of 0.16 mg/m^3 (USEPA, 2003) is used as the point of departure. The $LOAEL_{[HEC]}$ is the $LOAEL_{[ADJ]}$ multiplied by the $RGDR_{ETh}$.

To illustrate any potential age- or activity-related variation in the $LOAEL_{[HEC]}$ that might result from using human parameter values other than the defaults, scaled estimates for the mass and thickness of ETh target tissue from ICRP (1994) at different ages are used to calculate the SA_{ETh} values in Table A-1. Age- and activity-related V_e reported in ICRP (1994) are based on daily time-budgeted reference values. Table A-1 shows little variation in the resultant $LOAEL_{[HEC]}$ across the groups in this example. The default procedure produces the lowest $LOAEL_{[HEC]}$ value in Table A-1 and is, therefore, sufficient to cover all of these groups.

TABLE A-1 COMPARISON OF THE HEC-DEFAULT (EPA, 1994) WITH EXAMPLE $LOAEL_{[HEC]}$ VALUES FOR HUMANS OF DIFFERENT AGES AND ACTIVITY PATTERNS FOR THE EXTRATHORACIC REGION					
	Total $V_{e\ (human)}$ (L/min)[a]	**$SA_{ETh\ (human)}$ (cm^2)[b]**	**$(V_e/SA_{ETh})_{human}$ (L/min-cm^2)**	**$RGDR_{ETh}$**	**$LOAEL_{[HEC]}$ (mg/m^3)**
Outdoor Worker, Male	17.5	470	0.037	0.25	0.04
Sedentary Worker, Male	15.4	470	0.033	0.28	0.04
Sedentary Worker, Female	12.6	407	0.031	0.30	0.05
15 Year-Old Male	14.0	439	0.032	0.29	0.05
15 Year-Old Female	10.9	397	0.027	0.35	0.06
10 Year-Old	10.6	293	0.036	0.26	0.04
5 Year-Old	6.1	198	0.031	0.30	0.05
1 Year-Old	3.6	97.1	0.037	0.25	0.04
3 Month-Old	2.0	65.8	0.030	0.31	0.05
HEC - Default	13.8	200	0.069	0.14	0.02

[a] These values are from the ICRP publication, Tables 8, 27, B.16a, B.16b and B.17 (ICRP, 1994).
[b] These values are from the ICRP publication, Tables 1 and 5 (ICRP, 1994).

2. EXAMPLE 2: CATEGORY 1 GAS, TRACHEOBRONCHIAL EFFECTS, HYPOTHETICAL CHEMICAL

The DAF for a Category 1 gas or vapor exhibiting effects in the TB region is based on the animal to human ratio of the V_e divided by the SA of the TB region for each species. The DAF is typically calculated using the following equation:

$$RGDR_{TB} = \frac{\left(\frac{V_e}{SA_{TB}}\right)_{animal}}{\left(\frac{V_e}{SA_{TB}}\right)_{human}} = \frac{\frac{0.14\ L/min}{22.5\ cm^2}}{\frac{13.8\ L/min}{3200\ cm^2}} = 1.4 \qquad \textbf{(Equation A-2)}^{48}$$

This example assumes that the hypothetical chemical has been tested on Wistar rats and therefore utilizes the EPA animal default values for that strain. The V_e value used is 0.14 L/min (0.20 m^3/day) and the default SA_{TB} is 22.5 cm^2 (USEPA, 1994). EPA's default human values are 13.8 L/min (20 m^3/day) for V_e and 3200 cm^2 for SA_{TB} (USEPA, 1994). The RGDR for the TB region ($RGDR_{TB}$) is calculated using these values for the rat and the human, as shown in Equation A-2. The example also assumes a NOAEL adjusted for continuous exposure ($NOAEL_{[ADJ]}$) of 0.16 mg/m^3 as the point of departure. The $NOAEL_{[HEC]}$ is the $NOAEL_{[ADJ]}$ multiplied by the $RGDR_{TB}$.

Table A-2 shows little variation across age and activity groups in the $NOAEL_{[HEC]}$. The variation from the default (less than a factor of 2) is less than the default value of 10 used for the uncertainty factor for intraspecies variability when deriving the RfC. Application of the normal procedure for

[48] This equation is the reduced, default version of Equation 4-19 of the *Inhalation Dosimetry Methodology*. Equation 4-19 is reduced to this form consistent with the derivation of the reduced form of the RGDR equation of extrathoracic effects described in section 4.3.6.1 and Appendix I of the *Inhalation Dosimetry Methodology*.

determining the RfC will accommodate the observed variation. In addition, RfCs and IURs are developed for chronic exposure and will generally involve an exposure for multiple years.

TABLE A-2
COMPARISON OF THE HEC-DEFAULT (EPA, 1994) WITH EXAMPLE $LOAEL_{[HEC]}$ VALUES FOR HUMANS OF DIFFERENT AGES AND ACTIVITY PATTERNS FOR THE TRACHEOBRONCHIAL REGION

	Total $V_{e\ (human)}$ (L/min)[a]	$SA_{TB\ (human)}$ (cm^2)[b]	$(V_e/SA_{TB})_{human}$ (L/min-cm^2)	$RGDR_{TB}$	$NOAEL_{[HEC]}$ (mg/m^3)
Outdoor Worker M	17.5	2660	0.0066	0.94	0.15
Sedentary Worker M	15.4	2660	0.0058	1.1	0.18
Sedentary Worker F	12.6	2640	0.0048	1.3	0.21
15 year M	14.0	2520	0.0056	1.1	0.18
15 year F	10.9	2250	0.0048	1.3	0.21
10 Year	10.6	1830	0.0058	1.1	0.18
5 Year	6.1	1340	0.0046	1.4	0.22
1 Year	3.6	857	0.0042	1.5	0.24
3 Months	2.0	712	0.0028	2.2	0.35
HEC-default	13.8	3200	0.0043	1.4	0.22

[a] These values are from the ICRP publication, Tables 8, 27, B.16a, B.16b and B.17 (ICRP, 1994).
[b] These values are from the ICRP publication, Tables 1 and 5 (ICRP, 1994).

3. EXAMPLE 3: CATEGORY 1 GAS, PULMONARY EFFECTS, HYPOTHETICAL CHEMICAL

The DAF for a Category 1 gas or vapor with an effect in the PU region is based on the animal to human ratio of the alveolar ventilation rate (Q-alv) divided by the SA of the PU region (SA_{PU}) for each species. The Q-alv is approximately equal to the V_e multiplied by 0.7. This adjustment accounts for the anatomic/physiologic deadspace in the PU region, making the Q-alv equivalent to the amount of inspired air available for gas exchange (West, 2000). The DAF for this region of the respiratory tract is typically calculated using the following equation:

$$RGDR_{PU} = \frac{\left(\frac{Q-alv}{SA_{PU}}\right)_{animal}}{\left(\frac{Q-alv}{SA_{PU}}\right)_{human}} = \frac{\frac{0.1\,L/min}{0.34\,m^2}}{\frac{9.7\,L/min}{54\,m^2}} = 1.6 \qquad \textbf{(Equation A-3)}^{49}$$

This example assumes that the hypothetical chemical has been tested on Wistar rats and therefore utilizes the EPA animal default values for that strain. The V_e valued used is 0.14 L/min (0.20 m^3/day), which when multiplied by 0.7, yields a Q-alv of 0.1 L/min. The example uses the EPA default rat SA_{PU} of 0.34 m^2 (USEPA, 1994). EPA's default human values are 13.8 L/min (20

[49] This equation is the reduced, default version of Equation 4-23 of the *Inhalation Dosimetry Methodology*. Equation 4-23 is reduced to this form consistent with the derivation of the reduced form of the RGDR equation of extrathoracic effects described in section 4.3.6.1 and Appendix I of the *Inhalation Dosimetry Methodology*.

m^3/day) for V_e (which yields a Q-alv of 9.7 L/min) and 54 m^2 for SA_{PU} (USEPA, 1994). The RGDR for the PU region ($RGDR_{PU}$) is calculated using these values for the rat and the human, as shown in Equation A-3. The example also assumes a $NOAEL_{[ADJ]}$ of 0.16 mg/m^3 as the point of departure. The $NOAEL_{[HEC]}$ is the $NOAEL_{[ADJ]}$ multiplied by the $RGDR_{PU}$.

Table A-3 below provides the Q-alv values for humans based on the daily time-budgeted V_e for different ages and activity levels from the ICRP publication (1994). SA data for the PU region in the ICRP publication are estimated using an allometric scaling model fitted to data from a morphometric analysis of SA_{PU} in a sample of seven children (ranging in age from 26 days to 5 years) and eight adults (Zeltner et al., 1987). ORD selected the Zeltner analysis for this example because these SA_{PU} data are based on empirical morphometric measurements of human lungs as opposed to scaled estimates determined from lung models (such as those done by Yu and Xu, 1987 or Yu and Yoon, 1991). In addition, the children and adult SA_{PU} values calculated in the Zeltner analysis are supported by several independent studies that measured SA_{PU} in children (Langston et al., 1984) or in adults using similar morphometric techniques (Crapo et al., 1982 & 1983; Stone et al., 1992; Mercer et al., 1994).

Table A-3 shows little variation in the resultant $NOAEL_{[HEC]}$ across the groups in this example. The default procedure produces the lowest $NOAEL_{[HEC]}$ value in Table A-3 and is, therefore, sufficient to cover all of these groups.

TABLE A-3

COMPARISON OF THE HEC-DEFAULT (EPA, 1994) WITH EXAMPLE $LOAEL_{[HEC]}$ VALUES FOR HUMANS OF DIFFERENT AGES AND ACTIVITY PATTERNS FOR THE PULMONARY REGION

	Total V_e (L/min)[a]	$Q\text{-}alv_{(human)}$ (L/min)[b]	$SA_{PU\ (human)}$ (m^2)	$(Q\text{-}alv/SA_{PU})_{human}$ (L/min-m^2)	$RGDR_{PU}$	$NOAEL_{HEC}$ (mg/m^3)
Outdoor Worker, Male	17.5	12	139	0.088	3.3	0.53
Sedentary Worker, Male	15.4	11	139	0.078	3.7	0.59
Sedentary Worker, Female	12.6	8.8	114	0.077	3.8	0.61
15 Year-Old Male	14.0	9.8	108	0.091	3.2	0.51
15 Year-Old Female	10.9	7.6	100	0.076	3.8	0.61
10 Year-Old	10.6	7.4	62.0	0.12	2.4	0.38
5 Year-Old	6.1	4.3	37.3	0.11	2.6	0.42
1 Year-Old	3.6	2.5	18.5	0.14	2.1	0.34
3 Month-Old	2.0	1.4	11.0	0.13	2.2	0.35
HEC-Default	13.8	9.7	54.0	0.18	1.6	0.26

[a] These values are from the ICRP publication, Tables 8, 27, B.16a, B.16b and B.17 (ICRP, 1994).
[b] These values are from Zeltner et al. (1987).

4. CATEGORY 3 GASES

The DAF for a Category 3 gas or vapor is based on the ratio of the animal blood:gas partition coefficient to the human blood:gas partition coefficient and is typically calculated using the following equation:

$$DAF = \frac{(H_{b/g})_{animal}}{(H_{b/g})_{human}} \qquad \textbf{(Equation A-4)}$$

The blood:gas partition coefficient is primarily determined by the solubility of the gas in an aqueous medium as well as the protein and lipid content of the blood. There is little reason to suspect that the blood:gas partition coefficient for a non-metabolized chemical will vary greatly across the human population. The limited data available indicate no difference in the blood:gas partition coefficient with age for methylene chloride in mice (Thomas et al., 1996), and for sevoflurane, isoflurane, and halothane in humans (Malviya and Lerman, 1990). Two studies examining the solubility of volatile anesthetics (isoflurane, enflurane, halothane, and methoxyflurane) in the blood and body tissues found higher blood:gas partition coefficients in adults compared with children (Lerman, et al., 1984 & 1986). Any variability in the blood:gas partition coefficient with age is expected to be less than the default value of 10 used for the uncertainty factor for intraspecies variability when deriving the RfC. Any variability in the blood:gas partition coefficient with age is also not expected to cause a large overestimate or underestimate in the calculated cancer risk.

Because of the limited data available, the *Inhalation Dosimetry Methodology* makes the science policy decision to use a value of one for the ratio of the partition coefficients when the animal to human ratio exceeds one or when the animal or human value is unknown. At this time, all chemicals on IRIS for which both human and animal data are available have an animal to human ratio of partition coefficient greater than 1.[50] Therefore, the default assumption of one is a conservative approach that is not likely to underestimate the chemical-specific DAF.

5. PARTICLE DEPOSITION ACROSS AGE GROUPS

The DAF for a particle causing an effect in the respiratory tract, the Regional Dose Deposition Ratio ($RDDR_r$), is based on the animal to human ratio of the V_e and the fractional deposition of the particle in that region (F_r), divided by the surface area of the region where the effect occurs (SA_r) (USEPA, 1994). Inherent in this derivation is the assumption that 100 percent of the deposited dose remains in the respiratory tract and any clearance mechanisms are not considered. The $RDDR_r$ is typically calculated using the following equation:

$$RDDR_r = \frac{\left(\frac{V_e}{SA_r} \times F_r\right)_{animal}}{\left(\frac{V_e}{SA_r} \times F_r\right)_{human}} \qquad \textbf{(Equation A-5)}$$

[50] While 1,4-dioxane has not yet been evaluated on IRIS, it provides an exception to this statement, in that the blood:gas partition coefficient is 2750 for mice, 1850 for rats, and 3650 for humans, yielding an animal to human ratio of 0.75 for mice and 0.51 for rats (Reitz et al., 1990).

The DAF for a particle causing an extra-respiratory (ER) effect, the $RDDR_{ER}$, is based on the animal to human ratio of the V_e and the total deposition of the particle in the entire respiratory tract (F_{total}), divided by body weight (BW) (USEPA, 1994). The $RDDR_{ER}$ assumes that 100 percent of the deposited dose in the entire respiratory tract is available for uptake into the systemic circulation. The following general equation can be used to estimate the $RDDR_{ER}$:

$$RDDR_{ER} = \frac{\left(\frac{V_e}{BW} \times F_{total}\right)_{animal}}{\left(\frac{V_e}{BW} \times F_{total}\right)_{human}} \qquad \textbf{(Equation A-6)}$$

The information on particle deposition in various age groups is quite limited. A discussion of the current state of the science can be found in the *Air Quality Criteria for Particulate Matter Volume II*, Section 6.2.3.2 (USEPA, 2004; hereafter, *PM Criteria Document*).

Experimental and modeling results are summarized in Table A-4. The results for experimental studies are mixed, some suggesting higher deposition in children and others finding no difference across age groups. Bennett and Zeman (1998) and Schiller-Scotland et al. (1994) found no difference between total deposition of particles in the respiratory tract of children (aged 7 to14 and 6 to12, respectively) and adults for 1 to 2 micrometer particles. Schiller-Scotland et al. did find two- to three-fold higher total particulate deposition in 6 to 12 year olds for particles of 2 to 3 micrometers in size. In addition, Bennett et al. (1997) found that deposition in the ETh region was 50 percent greater in children than adults. The *PM Criteria Document* concludes that "these...studies ...do not provide unequivocal evidence for significant differences in deposition between adults and children" (USEPA, 2004, page 6-29). The document notes, however, that children may have higher activity levels and higher associated minute ventilation per lung size, potentially causing a greater size-specific dose of particles to the lung.

Modeled results suggest a higher deposition of particles in the TB region of children when compared to adults, depending on the particle size (Xu and Yu (1986); Hofmann et al. (1989); Musante and Martonen (1999); Phalen and Oldham (2001); Asgharian et al. (2004); Jarabek et al. (2005); Ginsberg et al. (2005)). Mixed results again are found in modeling studies for total deposition and deposition in other respiratory regions. In general, where differences are observed in either experimental or modeled studies, variability in deposition between age groups has been reported to be most often in the range of 1- to 3-fold greater for children than for adults, but ranging from equivalency or less up to 7-fold greater.[51]

[51] A modeling analysis examining deposition fraction per unit area at various airway generations of the lung as a function of age for various particle sizes (ranging from 0.01 to 10 μm) reported comparisons between a 3-month old and 21-year old that ranged from equivalency up to a 14-fold difference in this metric for some specific airway generations (Asgharian et al., 2004).

TABLE A-4
PARTICLE DEPOSITION ACROSS AGE GROUPS

Study	Particle Size	Results
Experimental Studies		
Becquemin et al. (1991)	Various	Nasal deposition higher in adults (up to 1.8-fold higher at rest and up to 3.4-fold higher during exercise) than children – meaning that thoracic airways of children are less protected than those of adults.
Bennett et al. (1997)	4.5 µm	-ETh deposition of particles 50 percent greater in children (higher for younger ages). -No significant difference in total respiratory tract deposition.
Bennett and Zeman (1998)	1-2 µm	No difference between 7-14 year olds and adults in total deposition of particles in the respiratory tract.
Schiller-Scotland et al. (1994)	1-2 µm	No difference between 6-12 year olds and adults in total deposition of particles in the respiratory tract.
	2-3 µm	Two- to three-fold higher total deposition of particles in 6-12 year olds versus adults.
Modeled Studies		
Asgharian et al. (2004)	0.01-10 µm	-Up to 1.2-fold higher total deposition in 3 month olds compared to adults in the TB region. -Up to 1.5-fold higher total deposition in 8 year olds compared to adults in the alveolar region. Total deposition higher in adults than 3 and 23 month olds (up to 2-fold). -Estimates of deposition fraction per unit area at various airway generations of the lung and various particle sizes highest for 3 month olds compared to adults (up to 14-fold). Higher deposition also seen for 23 month olds (up to 5-fold) and 8 year olds (up to 3-fold) compared with adults. No difference in deposition in 14 year olds compared to adults.
Cheng et al. (1995)	0.0046-0.2 µm	Nasal casts of children's airways found increased deposition efficiency for ultrafine particles with decreasing age, suggesting that young children may receive a higher dose of ultrafine particles to the upper airways.
Ginsberg et al. (2005)	0.001-10 µm	-Higher deposition in 3 month olds compared with adults for coarse and fine particles in the upper TB (up to 2-fold) and PU (up to 4-fold) regions. -Higher deposition in adults in the lower TB region.
Hoffmann et al. (1989)	1-2 µm	-1.5- to 2-fold higher total deposition in the TB region for particles in resting 8 year olds versus adults. -40-50 percent lower total deposition of particles in 8 year olds under conditions of exercise.
Jarabek et al. (2005)	0.3-6 µm	-Retained mass in the TB region normalized to regional SA was compared across age groups. -Up to 2-fold lower deposition in 3 month olds compared to adults. -Up to 2-fold higher deposition in 3 year olds and 14 year olds compared to adults.
Musante and Martonen (1999)	0.25-5 µm	-Total deposition was generally higher in children (ages 7, 22, 48, and 98 months) than adults (e.g., total lung deposition in 48-month olds was 38 percent higher than adults for 1µm particles). -TB deposition monotonically decreased as a function of age (i.e., younger children had increased TB deposition). -PU deposition greatest in the 48 and 98-month children.
Musante and Martonen (2000)	2 µm	3-fold higher deposition of particles in the PU region for 7 month olds versus adults.
Oldham et al. (1997)	Various	Airway models of trachea and bronchial airways showed total deposition in children (ages 4 and 7) greater than adult (up to approximately 7-fold higher for 4 year olds compared to adults for 4.5 µm particles).
Phalen and Oldham (2001)	0.1-10 µm	-No difference in total deposition of particles in 2 year olds versus adults. -Somewhat higher (13-81 percent; depending on particle size) deposition of particles in the TB region. -Lower deposition of particles in the PU region.
Xu and Yu (1986)	Various	Increased total deposition (up to 1.5-fold higher) in children aged 6 months, 2 years, and 8 years compared with adults for particles of varying sizes.

6. CONCLUSIONS

The examples and discussions included in this appendix suggest that the *Inhalation Dosimetry Methodology's* default approaches for derivation of the HEC for Category 1 gases with effects in the ETh, TB, and PU regions and for Category 3 gases typically are sufficient to cover variation across human age- and activity-level groups. The process for deriving an RfC from the HEC includes applying an uncertainty factor (UF) to account for within-species variability, adding further protection. When deriving an IUR for a carcinogen, UFs are not used. However the procedures for estimating an IUR incorporate conservative assumptions that would likely accommodate the degree of variation observed in these examples.

Experimental and modeling results for particles suggest the potential for small differences in deposition of particles in the respiratory tract as a function of age. The assumption that 100 percent of the deposited dose is available for uptake into the systemic circulation (for remote acting toxicants), or for activity in the respiratory tract (for local toxicity) is likely to result in an overestimation of dose to the target tissue. Any small variation in deposition among age groups should be considered against the potential magnitude of such overestimation. These differences in calculated deposition are small relative to the default 10-fold UF that accounts for intra-species variability in the derivation of the RfC. In addition, RfCs and IURs are developed for chronic exposure and will generally involve an exposure for multiple years. No additional correction of the toxicity values for these age groups is needed when the RfC or IUR is used in a risk assessment. Calculations in these examples are based on empirical data from sources listed and referenced in ICRP Publication 66 (ICRP, 1994). While ORD selected the ICRP values as the best estimates for these examples, other published values for V_e and SA exist. The use of alternate values may change the $LOAEL_{[HEC]}$ calculated for the various populations and life stages and may show more or less variability in results across the age and activity groups. In addition, the examples for the TB and PU regions are based on a hypothetical chemical, since currently no RfCs for gases on IRIS are calculated based on animal studies showing health effects occurring in these regions of the respiratory system. Given the parameter values used in the default method for calculating the HEC, it is likely that the process would yield results sufficient to cover populations and life stages with varying activities and physiologic characteristics.

Note that the available data, albeit limited, generally support these conclusions. As recommended by the Reference Dose (RfD)/RfC Technical Panel (USEPA, 2002), EPA has been exploring issues involving dose to the young from inhalation exposures, both theoretically and experimentally as well as further considering the existing animal-to-human extrapolation procedures described in current methodologies (e.g., USEPA, 1994). This is especially important because of the significant developmental changes that occur in the lung from birth well into adolescence (Pinkerton and Joad, 2000). The review and updating of these methodologies will be based on the best available science.

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APPENDIX B

APPENDIX B

CHEMICALS ON IRIS WITH EXTRAPOLATED INHALATION UNIT RISKS

Table B-1 contains chemicals on the Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) with Inhalation Unit Risk (IUR) values calculated by extrapolation using the default ventilation rate and body weight from the oral Cancer Slope Factor (CSF). These chemicals cause tumors remote from the respiratory tract. Also listed is the year EPA verified the cancer assessment. The list was compiled in September 2008.

EPA recommends that extrapolated IURs should be used with risk Equations 6 and 11 in the main document without additional modification for calculation of cancer risk by the inhalation route of exposure. It is generally not appropriate to make adjustments based on ventilation rate and body weight using the intake equation, because the amount of the chemical that reaches the target site of the chemical through the inhalation pathway is not a simple function of the inhalation rate and body weight. Risk assessors should outline the uncertainties involved in using extrapolated IURs in the risk characterization section of the risk assessment.

TABLE B-1 CHEMICALS WITH EXTRAPOLATED INHALATION UNIT RISKS ON IRIS	
Chemical	**Year of Verification**
Acrylamide[1]	1988
Aldrin	1987
Aramite	1991
Azobenzene	1988
Bromoform	1989
Chlordane	1997
Chloroform[1]	1987
DDT	1987
1,2-Dichloroethane	1986
Dieldrin	1987
1,2-Diphenylhydrazine	1986
Heptachlor	1987
Heptachlor epoxide	1987
Hexachlorobenzene	1989
Hexachlorobutadiene[1]	1986
Alpha-hexachlorocyclohexane	1986
Beta-hexachlorocyclohexane	1986
Technical-hexachlorocyclohexane	1986
Hexachlorodibenzo-p-dioxin mixture	1987
Hexachloroethane	1986
N-nitroso-di-n-butylamine	1986
N-nitrosodiethylamine	1986
N-nitrosodimethylamine	1986
N-nitrosopyrrolidine	1986
Polychlorinated biphenyls	1996
1,1,2,2-Tetrachloroethane	1986
1,1,1,2-Tetrachloroethane	1988
Toxaphene	1987
1,1,2-Trichloroethane	1986
2,4,6-Trichlorophenol	1989
[1] Note that this chemical's IUR is currently under review.	

APPENDIX C

APPENDIX C

STSC's PROCESS FOR DERIVING ALTERNATIVE INHALATION TOXICITY VALUES

If Reference Concentration (RfC) and/or Inhalation Unit Risk (IUR) values for an inhaled contaminant are not available from the sources in the Environmental Protection Agency's (EPA's) Office of Solid Waste and Emergency Response (OSWER) hierarchy, risk assessors should first contact the National Center for Environmental Assessment's (NCEA's) Superfund Health Risk Technical Support Center (STSC) for guidance.[52] Risk assessors working on Superfund sites can contact STSC to determine whether a provisional peer-reviewed toxicity value (PPRTV) exists for a contaminant; if not, the risk assessor, in cooperation with the appropriate EPA Regional office may request that STSC develop a PPRTV document or that STSC develop an inhalation toxicity value as a "consult." The latter would be specific to the site in question only.

As a first choice, if human or whole animal studies exist providing a suitable No Observable Adverse Effect Level (NOAEL)/Lowest Observable Adverse Effect Level (LOAEL) or Point of Departure (POD) from a Benchmark Dose (BMD) analysis, this data normally will be used by STSC to develop an inhalation toxicity value. If, in addition, a suitable human inhalation physiologically based pharmacokinetic (PBPK) model exists that can be utilized to refine the dose metric to the target organ, then this information generally will be included in developing an inhalation toxicity value.

If no appropriate whole animal or human studies exist, but an appropriate peer reviewed human inhalation PBPK model exists that has been validated by experimental results, then STSC usually will attempt to derive an inhalation toxicity value from this model. If none exists, but a suitable PBPK animal inhalation models exists, STSC may attempt developing a human model and deriving an inhalation value.

PBPK modeling quantitatively describes the absorption/metabolism/distribution and elimination of the chemical from a point of entry (oral, inhalation, dermal) to the target organ(s). In some cases, an oral PBPK model can be extrapolated to the inhalation pathway, but care must be taken to consider direct pulmonary effects that may not be evident by oral dosing.

As a next approach, STSC typically will evaluate development of an inhalation toxicity value using a suitable surrogate chemical based on a quantitative structure-activity relationship (QSAR) model with structural selection criteria and solubility/toxicity considerations. STSC may evaluate possible surrogate chemicals based on several available structural models and provide a comparison. Selection of the appropriate surrogate may depend on the weight of evidence of these models.

[52] All contact with STSC should be performed by an EPA regional risk assessor. States and other entities should first contact their EPA regional risk assessor with questions on inhalation toxicity values. Regional risk assessors can then contact STSC on their behalf.

If STSC uses any of the methods for developing toxicity values other than from human or whole animal data, the value normally will be presented as a "screening" value with the caveat that it should not be used as a risk driver for a site without consultation with the STSC. The uncertainties associated with using toxicity values derived through PBPK modeling or QSAR, or with using a surrogate value should be described in the risk characterization portion of the risk assessment (see Section 9). Risk assessors are discouraged from performing simplistic route-to-route extrapolations from oral data using default assumptions about Inhalation Rate (IR) and body weight (BW).[53]

[53] If STSC indicates that no quantitative toxicity information for the inhalation route is available, the risk assessor should conduct a qualitative evaluation of this exposure route. The risk assessor should discuss in the uncertainty section of the risk assessment report the implications of not quantitatively assessing risks due to inhalation exposures to chemicals lacking inhalation toxicity data. See the section on Risk Characterization (Section 9) in the main text of this guidance for more information.