RG-442
Revised September 2015

# TCEQ Guidelines to Develop Toxicity Factors

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Toxicology Division
TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

# TCEQ Guidelines to Develop Toxicity Factors

Prepared by
Toxicology Division, Office of the Executive Director

RG-442
Revised September 2015


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# Document Description and Intended Use

This document is an update of and replacement for the previous TCEQ Regulatory Guidance-442 (RG-442), *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors*. It is a technical guide written and used by the Texas Commission on Environmental Quality (TCEQ) to develop the following health- and welfare-based inhalation toxicity values, and health-based oral toxicity values:

- acute and chronic inhalation Effects Screening Levels (ESLs),
- acute and chronic inhalation Reference Values (ReVs),
- chronic inhalation Unit Risk Factor (URF) values,
- chronic oral reference dose (RfD) and slope factor (SFo) values.

Although this document is primarily written as guidance for the TCEQ staff, it also documents (largely by reference) the processes used to develop different toxicity values for any interested person with training in inhalation and oral toxicology and risk assessment. If members of the general public are interested in learning more about risk assessments, the United States Environmental Protection Agency (USEPA) has the following Web page available that provides basic information about environmental risk assessments:

www.epa.gov/risk_assessment/index.htm.

Inhalation ESLs are chemical-specific air concentrations set to protect human health and welfare. ESLs are used in the air permitting program. Short-term ESLs are based on data concerning acute health effects, the potential for odors to be a nuisance, and effects on vegetation, while long-term ESLs are based on data concerning chronic health and vegetation effects. Welfare-based ESLs (odor and vegetation) are set based on effect threshold concentrations. Health-based ESLs, however, are calculated from ReV and URF toxicity factors. ReVs and URFs are based on the most sensitive adverse health effect relevant to humans. Derivation of a ReV or URF begins with a toxicity assessment involving hazard identification and dose-response assessment based on the chemical's mode of action. The resulting ReV and URF values are then used to calculate ESLs that correspond to no significant risk levels. Air Monitoring Comparison Values (AMCVs) are used to evaluate ambient air monitoring data and are based on specific health-based ReV and health- and welfare-based ESL values.

Chronic RfDs are chemical-specific oral doses set to protect human health for exposure via ingestion and are based on data concerning chronic noncancer health effects. A SFo represents the carcinogenic potency of a chemical and is based on data concerning chronic cancer effects. RfD and SFo values are based on the most sensitive adverse health effect relevant to humans from oral exposure. Derivation of RfD and SFo values begins with a toxicity assessment involving hazard identification and dose-response assessment based on the chemical's mode of action. ReV, URF, RfD, and SFo values are used to calculate health-protective cleanup levels for the TCEQ's remediation program.

This guide is presented in seven chapters. In Chapter 1, several fundamental topics are addressed including legal authority and regulatory use, consideration of cumulative risk, problem formulation, and public participation opportunities. Chapter 1 also provides an introduction to the different toxicity values and their use in calculating health-based inhalation ESLs, introduces and explains the use of AMCVs, and the use of toxicity factors in remediation projects. Chapter 2 describes how welfare-based ESLs are determined (i.e., odor- and vegetation-based values). Chapter 3 discusses common procedures used to develop both acute and chronic toxicity values for the inhalation routes and chronic toxicity factors for the oral routes of exposure. Chapter 4 addresses the procedures that are unique to the derivation of acute inhalation ReVs, and Chapter 5 addresses the procedures that are unique to the derivation of chronic toxicity factors. Chapter 6 provides procedures for the treatment of chemical groups and mixtures and Chapter 7 discusses procedures for using epidemiology studies to develop toxicity factors.

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# Acronyms and Abbreviations

| Acronyms and Abbreviations | Definition |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ADAF | age-dependent default adjustment factors |
| ADI | acceptable daily intake |
| AEGL | Acute Exposure Guideline Level |
| AIHA | American Industrial Hygiene Association |
| AMCV | Air Monitoring Comparison Value |
| AMCV Odor | $^{acute}ESL_{odor}$ |
| AMCV short-term vegetation | $^{acute}ESL_{veg}$ |
| AMCV long-term vegetation | $^{chronic}ESL_{veg}$ |
| AMCV short-term health | Acute ReV or $^{acute}ESL_{generic}$ or interim ESL |
| AMCV long-term health | lowest value of the chronic ReV [threshold(c)], chronic ReV [threshold(nc)], $^{chronic}ESL_{nonthreshold(c)}$, or $^{chronic}ESL_{nonthreshold(nc)}$, or interim ESL |
| APWL | Air Pollutant Watch List |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BMC | benchmark concentration |
| BMCL | benchmark concentration lower confidence limit |
| BMD | benchmark dose |
| BMDL | benchmark dose lower confidence limit |
| BMDS | benchmark dose software |
| BMR | benchmark response |
| C | concentration |
| Cal EPA | California Environmental Protection Agency |
| CFR | Code of Federal Regulations |

| Acronyms and Abbreviations | Definition |
|---|---|
| CNS | central nervous system |
| COT | Committee on Toxicology |
| CSAF | chemical-specific adjustment factor |
| D | exposure duration, hour per day |
| da | dalton |
| DF | deposition fraction in the target region of the respiratory tract |
| DAF | dosimetric adjustment factor |
| DOE | Department of Energy |
| DSD | development support document |
| E | exposure level or concentration |
| EC | effective concentration |
| ET | extrathoracic |
| ERPG | Emergency Response Planning Guideline |
| ESL | Effects Screening Level |
| $^{acute}ESL$ | acute health-based Effects Screening Level for chemicals meeting minimum database requirements |
| $^{acute}ESL_{generic}$ | acute health-based Effects Screening Level for chemicals not meeting minimum database requirements |
| $^{acute}ESL_{odor}$ | acute odor-based Effects Screening Level |
| $^{acute}ESL_{veg}$ | acute vegetation-based Effects Screening Level |
| $^{chronic}ESL_{nonthreshold(c)}$ | chronic health-based Effects Screening Level for nonthreshold dose response cancer effect |
| $^{chronic}ESL_{nonthreshold(nc)}$ | chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects |
| $^{chronic}ESL_{threshold(c)}$ | chronic health-based Effects Screening Level for threshold dose response cancer effects |
| $^{chronic}ESL_{threshold(nc)}$ | chronic health-based Effects Screening Level for threshold dose response noncancer effects |
| $^{chronic}ESL_{veg}$ | chronic vegetation-based Effects Screening Level |
| F | exposure frequency, days per week |
| FAQ | Frequently Asked Question |

| Acronyms and Abbreviations | Definition |
|---|---|
| FDA | Food and Drug administration |
| FEL | frank effect level |
| FEV | Forced Expiratory Volume |
| GHS | Globally Harmonized System |
| GLC | ground-level concentration |
| $GLC_{max}$ | maximum ground-level concentration |
| h | hour |
| $H_{b/g}$ | blood:gas partition coefficient |
| HEAST | Health Effects Assessment Summary Tables |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| HQ | hazard quotient |
| IARC | International Agency for Research on Cancer |
| ICRP | International Commission on Radiological Protection |
| IDLH | Immediately Dangerous to Life or Health |
| IPCS | International Programme on Chemical Safety |
| IRIS | Integrated Risk Information System |
| K | constant level or severity of response |
| $LC_{50}$ | concentration producing lethality in 50% of experimental |
| $LC_{Lo}$ | lowest concentration producing lethality |
| $LD_{50}$ | dose producing lethality in 50% of experimental animals |
| LEC | lowest effective concentration |
| LLNA | local lymph node assay |
| LOAEL | lowest-observed-adverse-effect-level |
| LTD | limited toxicity data |
| m | meter |
| MAK | Federal Republic of Germany Maximum Concentration Values in the Workplace |
| MERA | Modeling and Effects Review Applicability |
| MF | modifying factor |
| MLA | Mouse Lymphoma Assay |

| Acronyms and Abbreviations | Definition |
|---|---|
| MW | molecular weight |
| µg | microgram |
| min | minute |
| MPPD | Multiple-Path Particle Dosimetry Model |
| MOA | mode of action |
| MRL | Minimal Risk Level |
| NAAQS | National Ambient Air Quality Standards |
| NAC | National Advisory Committee |
| NATA | National-Scale Air Toxics Assessment |
| NCEA | National Center for Environmental Assessment |
| NF | normalizing factor |
| NIOSH | National Institute for Occupational Safety and Health |
| N-L Ratio | NOAEL-to $LC_{50}$ Ratio |
| NLM | National Library of Medicine |
| NOAEL | no-observed-adverse-effect-level |
| NOEL | no-observed-effect-level |
| NRC | National Research Council |
| NTIS | National Technical Information Service |
| NTP | National Toxicology Program |
| OECD | Organisation for Economic Co-operation and Development |
| OEHHA | Office of Environmental Health Hazard Assessment |
| OEL | Occupational Exposure Limit |
| OPPTS | Office of Prevention, Pesticides and Toxic Substances |
| OSHA | Occupational Safety and Health Administration |
| PAH | polycyclic aromatic hydrocarbon |
| PBPK | physiologically-based pharmacokinetic model |
| PCBs | polychlorinated biphenyls |
| PEL | Permissible Exposure Limit |
| PM | particulate matter |
| POD | point of departure |
| $POD_{ADJ}$ | point of departure adjusted for exposure duration |

| Acronyms and Abbreviations | Definition |
|---|---|
| $POD_{HEC}$ | point of departure adjusted for human equivalent concentration |
| POE | portal of entry |
| PU | pulmonary |
| ppbv | parts per billion by volume |
| ppm | parts per million |
| QSAR | quantitative structure-activity relationship |
| RDDR | regional deposited dose ratio |
| REL | Reference Exposure Level (Cal EPA OEHHA) |
| REL | Recommended Exposure Limit (NIOSH) |
| ReV | Reference Value |
| RfC | Reference Concentration |
| RfD | Reference dose |
| $RGD_A$ | regional gas dose in animal |
| $RGD_H$ | regional gas dose in human |
| RGDR | regional gas dose ratio |
| RIVM | Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment) |
| $R_{GM}$ | geometric mean ratio |
| RPF | relative potency factor |
| RTECS | Registry of Toxic Effects of Chemical Substances |
| SAR | structure activity relationship |
| SCAPA | Subcommittee on Consequence Assessment and Protective |
| SFo | Oral Slope Factor |
| STEL | Short-term Exposure Level |
| T | time or exposure duration |
| TB | tracheobronchial |
| TC | toxicity category |
| TCEQ | Texas Commission on Environmental Quality |
| 2,3,7,8-TCDD | 2,3,7,8-tetrachlorodibenzo-p-dioxin |
| TEEL | Temporary Emergency Exposure Limit |
| TEF | toxicity equivalency factor |

| Acronyms and Abbreviations | Definition |
|---|---|
| TH | thoracic |
| THSC | Texas Health and Safety Code |
| TLV | Threshold Limit Value |
| TD | Toxicology Division |
| TOC | threshold of concern |
| TOXLINE | Toxicology Literature Online |
| TRRP | Texas Risk Reduction Program |
| TWA | Time-Weighted Average |
| TWA-TLV | Time-Weighted Average Threshold Limit Value |
| UF | uncertainty factor |
| $UF_H$ | interindividual or intraspecies human uncertainty factor |
| $UF_A$ | interspecies animal to human uncertainty factor |
| $UF_{Sub}$ | subchronic to chronic exposure uncertainty factor |
| $UF_L$ | LOAEL to NOAEL uncertainty factor |
| $UF_D$ | incomplete database uncertainty factor |
| UN | United Nations |
| URF | Unit Risk Factor |
| USEPA | United States Environmental Protection Agency |
| $V_E$ | minute volume |
| $VE_{ho}$ | default occupational ventilation rate for an eight-hour day |
| $VE_h$ | default non-occupational ventilation rate for a 24-h day |
| WEEL | Workplace Environmental Exposure Level |
| WHO | World Health Organization |
| WOE | weight of evidence |

# Chapter 1 Introduction to Inhalation and Oral Toxicity Factors

## 1.1 Legal Authority and Regulatory Use

### *1.1.1 Inhalation Toxicity Factors*

The Texas Clean Air Act (Chapter 382 of the Texas Health and Safety Code (THSC)) authorizes the Texas Commission on Environmental Quality (TCEQ) to prevent and remedy conditions of air pollution. Section 382.003 of the THSC defines air pollution as:

> *the presence in the atmosphere of one or more air contaminants or combination of air contaminants in such concentration and of such duration that:*
> *(a) are or may tend to be injurious to or to adversely affect human health or welfare, animal life, vegetation, or property; or*
> *(b) interfere with the normal use and enjoyment of animal life, vegetation, or property.*

Sections 382.0518 and 382.085 of the THSC specifically mandate the TCEQ to conduct air permit reviews of all new and modified facilities to ensure that the operation of a proposed facility will not cause or contribute to a condition of air pollution. Air permit reviews typically involve evaluations of best available control technology and predicted air concentrations related to proposed emissions from the new or modified facility. In the review of proposed emissions, federal/state standards and chemical-specific Effects Screening Levels (ESLs) are used, respectively, for criteria and non-criteria pollutants. Because of the comprehensiveness of the language in the THSC, ESLs are developed for as many air contaminants as possible, even for chemicals with limited toxicity data. Health-based ESLs are calculated from reference value (ReV) and unit risk factor (URF) toxicity factors. Welfare-based ESLs, however, are set based on odor and vegetation effect threshold concentrations.

Air contaminants may cause both direct and indirect effects. Direct effects are those that result from direct inhalation and dermal exposures to chemicals in air. Deposition of contaminants on soil and water—and subsequent uptake by plants and animals—may cause indirect effects in humans who consume those plants and animals. However, the THSC authorizes the prevention and remedy of air pollution based on effects and interference from contaminants present in the atmosphere, i.e., direct effects. Therefore, during the air permitting process, the TCEQ does not set air emission limits to restrict, or perform analysis to determine, the impacts emissions may have, by themselves or in combination with other contaminants or pathways, after being deposited on land or water or incorporated into the food chain. However, indirect effects are assessed during cleanup

efforts under the Risk Reduction and Texas Risk Reduction Program (TRRP) Rules, described below.

The TCEQ also relies upon this authority to evaluate air monitoring data. Texas has the largest ambient air toxics monitoring network in the country. Air toxics are defined here as including volatile organic compounds (VOCs), semivolatile organic compounds (SVOCs), carbonyls, and metals. As of March 2011, TCEQ receives and analyzes monitoring data for more than 120 air toxics at approximately 90 different locations throughout the state. An Air Monitoring Comparison Value (AMCV) is used to evaluate measured air toxics concentrations for their potential to cause health and welfare effects, as well as to help the agency prioritize its resources in the areas of permitting, compliance, and enforcement. Health-based AMCVs are based on ReV and URF toxicity factors whereas welfare-based AMCVs are equal to welfare-based ESLs.

### *1.1.2 Oral Toxicity Factors*

The 2007 TRRP rule (30 Texas Administrative Code (TAC) §350) and the dated 1993 Risk Reduction Rule (Subchapters A and S of 30 TAC §335) require the calculation of health-protective cleanup levels for the TCEQ's remediation program. Oral reference dose (RfD) and slope factor (SFo) values as well as inhalation ReV and URF values are used, in accordance with rule requirements and guidance, to calculate media (e.g., soil and groundwater) cleanup levels that are health-protective of long-term exposure to contaminants. Under TCEQ's most current remediation rule (TRRP), the need for the TCEQ to develop chronic toxicity factors is consistent with §350.73.

### *1.1.3 Outline*

With this legal authority as the starting point, the subsequent sections of this chapter will introduce the following basic concepts:

- development of inhalation ReV and URF or oral RfD and SFo values based on the chemical's critical dose-response data with extrapolation to lower exposures informed by the mode of action (MOA),
- discuss consideration of cumulative risk and risk management objectives for toxicity values used in air permitting, review of ambient air monitoring data, and remediation projects,
- describe calculation of a health-based ESL from ReV and URF values,
- describe the use of AMCVs for review of ambient air monitoring data and discuss the relationship between AMCVs and ESLs,
- describe the use of oral toxicity factors (e.g., RfD and SFo values) in remediation projects.

Chapter 1 ends with sections describing the use of ReV, URF, RfD, SFo, ESL, and AMCV values in various TCEQ program areas, instances when chemicals are exempt from ESL development, the completion of individual Development Support Documents (DSDs), the selection of chemicals for toxicity factor development, and opportunities for public participation in the toxicity factor development process. Although welfare-based

ESLs will be referred to in this chapter, development of welfare-based ESLs for odor and vegetation effects will be discussed in detail in Chapter 2.

## 1.2 Definition of ReV, URF, RfD, and SFo Values

Acute and chronic ReV and chronic URF toxicity factors are the health-based values used in the evaluation of ambient air monitoring data and in the calculation of health-based ESLs. Chronic ReVs and URFs are used in the inhalation component for calculations of environmental media (e.g., soil) cleanup levels for remediation (e.g., TRRP). RfD and SFo toxicity factors are chronic health-based values used in the oral exposure component for calculations of media cleanup levels. This section introduces several toxicological concepts necessary for derivation of ReV, URF, RfD, and SFo values. Subsequent chapters discuss the development of these toxicity factors in detail. The method by which ReVs and URFs are used in the calculation of health-based ESLs is described in Section 1.5.2. Section 1.6 describes how they are used to calculate health-based AMCVs.

Derivation of ReV, URF, RfD, and SFo values begins with a toxicity assessment involving hazard identification and dose-response assessment based on critical dose-response data, as well as extrapolation to lower exposures based on the chemical's MOA. For each hazard (i.e., critical adverse health effect) this assessment determines whether the dose-response relationship is (or is presumed to be) nonthreshold (typically a linear low-dose extrapolation) or threshold (typically a nonlinear low-dose extrapolation) in the low-dose region, depending on the MOA. The low-dose region is generally defined as the dose range below the experimental doses. Nonlinear dose response, linear dose response, and threshold are defined as follows:

> **Nonlinear Dose-Response:** A pattern of frequency or severity of biological response that does not vary directly with the dose of an agent. Noncarcinogenic effects typically exhibit nonlinear dose-response relationships. In addition, when MOA information indicates that carcinogenic effects may not follow a linear pattern below the dose range of the observed data, nonlinear methods for determining risk at low dose may be justified. If a chemical's dose-response relationship is nonlinear such that it has an effects threshold, there exists a concentration and resulting dose of that chemical below which exposure is not expected to cause adverse effects.
>
> **Linear Dose-Response**: A pattern of frequency or severity of biological response that varies directly with dose of an agent. In the absence of data to the contrary, carcinogenic effects are typically assumed to exhibit a linear dose-response relationship in the extrapolated low-dose range below the observed data. Thus, if a chemical's dose-response relationship is assumed to be linear, it is presumed to be nonthreshold, meaning that any dose, no matter how small, increases the probability of causing an effect.
>
> **Threshold**: The dose or exposure below which no deleterious effect is expected to occur. In addition to noncancer effects, this may also apply to cancer effects for some chemicals (e.g., formaldehyde-induced respiratory tract cancers, dioxin).

Acute and chronic inhalation ReV and chronic oral RfD values are derived for human health hazards associated with threshold dose-response relationships. Chronic inhalation URF and oral SFo values are derived for hazards associated with nonthreshold dose-response relationships. In other words, the derivation of a ReV, URF, RfD, or SFo is dependent on whether the adverse effect is associated with (or assumed to have) a nonthreshold or threshold dose-response relationship, not with the classification of the effect as carcinogenic or noncarcinogenic.

### *1.2.1 ReV and RfD Values for Threshold Dose-Response Effects*

For adverse human health effects determined to be associated with threshold dose-response relationships in the low-dose region, the TCEQ adopts or derives acute and chronic ReVs to evaluate inhalation exposure and chronic RfDs for oral exposure. The determination of threshold dose-response relationships in the low-dose region is based on data or science policy default assumptions. Typically, the effects associated with such threshold dose-response relationships are noncarcinogenic. However, some carcinogenic effects, such as formaldehyde-induced respiratory tract cancers (TCEQ 2008) and possibly cancers from other chemicals (e.g., dioxins), are understood to exhibit a nonlinear or threshold dose-response. The TCEQ derives or adopts inhalation ReVs and oral RfDs for both noncarcinogenic and carcinogenic effects which are associated with threshold dose-response relationships based on their MOAs (Chapter 3, Chapter 4, Chapter 5, and Chapter 6).

Acute ReVs are health-based exposure concentrations used in assessing health risks of short-term chemical exposures. They are typically derived from acute or subacute human or animal studies, or from short-term reproductive/developmental toxicity studies conducted on animals. Occasionally, information is available from epidemiology or occupational studies. Acute ReVs are typically derived for a 1-hour (h) exposure duration, although those based on reproductive/ developmental effects may be derived for exposure durations other than 1 h. If other short-term exposure durations are needed to evaluate air monitoring data, then acute ReVs may be developed using other averaging times; however, the appropriateness of such a ReV will need to be evaluated using the guidelines in Chapter 4.

Chronic inhalation ReV and oral RfD values are health-based exposure concentrations and oral doses, respectively, used in assessing health risks of long-term (i.e., lifetime) chemical exposures. Chronic toxicity factors are derived from chronic human epidemiology studies, chronic animal studies, or well-conducted subchronic human or animal studies. Chronic ReV and oral RfD values are derived for a lifetime exposure duration.

An inhalation ReV or oral RfD is defined as an estimate of an inhalation exposure concentration or oral exposure dose, respectively, for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse effects. ReV and RfD values are based on the most sensitive adverse health effect relevant to humans reported in the scientific literature. ReV and RfD values are derived by adjusting an appropriate point of departure (POD, see Section 3.6.2 Definitions of PODs) with uncertainty factors (UFs) to reflect data limitations and to

derive a value that is below levels where health effects would be expected to occur. Examples of PODs include the benchmark concentration lower confidence limit (BMCL) and the no-observed-adverse-effect-level (NOAEL).

ReV and RfD values are designed to protect the most sensitive individuals in a population, such as children, pregnant women, and the elderly, in part by inclusion of uncertainty factors (UFs). However, ReVs may not protect individuals who exhibit rare or idiosyncratic responses which cannot be predicted based on typical animal toxicity studies or human health effects studies. While the default UF for intrahuman variability is generally considered protective, the true range of variability among the population for a response to a given chemical is often unknown. The TCEQ attempts to identify specific sensitive subgroups for each substance from the available scientific literature, but may not identify all conditions that result in adverse health effects following exposure to chemicals. However, UFs account for differences between study animal species and humans, variability within the human species, and uncertainties related to the applicability and completeness of the available data. Since UFs are incorporated to address data gaps, variability, and other uncertainties, exceeding the ReV or RfD does not necessarily indicate that an adverse health effect would occur. In addition, if a useable study in a population known to be sensitive through data and/or mode-of-action or other chemical-specific information is available, dose-response data from that study will be used to derive the ReV and RfD.

### 1.2.2 URF and SFo Values for Nonthreshold Dose-Response Effects

For chronic adverse effects determined to be associated with nonthreshold dose-response relationships in the low-dose region, the TCEQ adopts or derives inhalation URF and oral SFo values. This determination is based on data or science policy default assumptions. Typically, the effects associated with nonthreshold dose-response relationships are carcinogenic and are from chronic exposures.

For adverse effects associated with a nonthreshold dose-response, it is assumed that an effects threshold does not exist. Therefore, a linear extrapolation from the POD to the origin of the dose-response curve is performed to estimate excess lifetime risk at lower doses. Excess risk is estimated risk above background morbidity or mortality rates. The slope of the line from this linear extrapolation is the URF or SFo. The URF is generally defined as the upper-bound excess risk estimated to result from continuous lifetime exposure to an agent at a concentration of 1 $\mu g/m^3$ in air (i.e., risk estimate per $\mu g/m^3$). The SFo is generally defined as the statistically-derived upper-bound excess risk estimated to result from continuous lifetime exposure to an agent at an oral dose of 1 mg/kd-day. However, the central estimate as opposed to the upper-bound estimate may be used in certain circumstances as discussed in Chapter 5. A biologically-based model, if available, may be used.

While guidance for developing URF and SFo values has been explicit for carcinogenic effects (USEPA 2005a), URF and SFo values could also be developed for chronic noncarcinogenic effects which exhibit a nonthreshold dose-response relationship.

### 1.2.3 Margin of Exposure Approach

On rare occasions, instead of developing a ReV, RfD, URF, or SFo, the TCEQ may use a margin of exposure approach to evaluate the health risk of a chemical concentration in air or other environmental media. In a margin of exposure evaluation, the POD is compared with the level of exposure observed in humans or surrogate species, and the distance between the two levels is assessed with respect to the safety of human health. For example, a margin of exposure approach has often been used for dioxins (USEPA 2004c, Aylward et al. 2008).

## 1.3 Consideration of Cumulative Risk

The term "cumulative" has been used to describe various combinations of exposure or risk. In its Framework for Cumulative Risk Assessment, USEPA (2003a) defined cumulative risk as "the combined risks from aggregate exposures to multiple agents or stressors", where aggregate exposure is the "combined exposure of an individual (or defined population) to a specific agent or stressor via relevant routes, pathways, and sources."

### 1.3.1 Cumulative Risk for Air Emissions

In 2001, House Bill 2912 (77th Texas Legislature) Section 1.12 amended Subchapter D, Chapter 5 of the Texas Water Code by adding Section 5.130 Consideration of Cumulative Risk which states:

> *The Commission shall:*
> *(1) develop and implement policies, by specific environmental media, to protect the public from cumulative risk in areas of concentrated operations; and*
> *(2) give priority to monitoring and enforcement in areas in which regulated facilities are concentrated.*

In this document which describes the development of ESL, ReV and URF toxicity factors for evaluation of pollutant concentrations in air, "cumulative" considerations are restricted to the air medium. Cumulative exposure is exposure to multiple airborne chemicals. Aggregate exposure, on the other hand, is exposure to a single airborne chemical multiple times or from multiple sources. Cumulative risk combines consideration for both cumulative and aggregate exposure.

In addition to the Texas Water Code amendment quoted above, empirical evidence supports consideration of cumulative risk. First, ambient air monitoring demonstrates the presence of multiple chemicals present in air at a single location and time. Second, monitoring data indicate that a single chemical can be detected intermittently over time. Third, multiple sources of the same chemical can contribute to the concentration of that chemical detected at a single location. Thus, exposure to chemicals in ambient air can be both cumulative across chemicals and aggregate across sources and time.

Risk management objectives should take into account the statutory requirement for consideration of cumulative risk as discussed in Section 1.3. However, other procedures

are used by the TCEQ to protect against cumulative risk, as discussed in the TCEQ FAQ sheet Cumulative Risk from Airborne Chemicals (tceq.com/assets/public/implementation/tox/faqs/cumulative%20risk%20assessment.pdf). These procedures include review of air data for multiple chemicals from TCEQ's extensive air monitoring network and designation of an Air Pollutant Watch List (APWL) in areas exceeding AMCVs (tceq.com/assets/public/implementation/tox/faqs/cumulative%20risk%20assessment.pdf).

The public and TCEQ benefit from the largest stationary air toxics monitoring network in the country. The TCEQ's extensive air monitoring network helps verify that its permitting process has been effective for multiple chemicals and emission sources even in the most industrialized areas of Texas. Many of these monitors are placed in areas with densely located sources, such as industrial areas, which represent a worst-case scenario of aggregate exposure—giving the agency high confidence that policies and practices that work in those areas will work equally well in less industrial areas.

Air monitors provide reliable data on aggregate and cumulative exposure as they measure the air concentrations of many chemicals due to emissions from all sources (such as industrial sites, mobile sources such as cars, and area sources such as gas stations). The vast majority of the monitors in the state show annual average concentrations for carcinogenic chemicals like benzene to be under their respective AMCVs. Because actual monitoring data are used to verify acceptable exposure levels and the AMCVs are inherently conservative and health-protective, the TCEQ is confident that the potential for additional impacts from individual sources in an area is minimal.

The TCEQ also uses cumulative risk assessments from other organizations, such as USEPA's National-Scale Air Toxics Assessment (NATA), to identify areas with computer-modeled concentrations above a level of concern. Although NATA is based on a theoretical model of reported emissions rather than actual monitored concentrations, the assessment helps the TCEQ identify other potential issues.

Finally, in the limited areas where actual monitored concentrations of chemicals indicate a potential concern, the TCEQ uses the APWL to focus agency resources and efforts to reduce ambient levels of chemicals of concern: the list considers all possible sources. More information can be found online at www.tceq.state.tx.us/goto/apwl.

### *1.3.2 Cumulative Risk and Hazard in Remediation Projects*

The TRRP rule (30 TAC §350) and the dated 1993 Risk Reduction Rule (Subchapters A and S of 30 TAC §335) consider and provide limits for cumulative risk and hazard. The details are addressed within the rules, specific to remediation risk assessment, and are irrelevant to the derivation of toxicity factors for use with remediation rules, and thus are beyond the scope of this document. Please refer to the rules for information regarding how cumulative risk and hazard are addressed in remediation programs.

# 1.4 General Risk Management Objectives

## *1.4.1 Health-Based Risk Management Objectives (No Significant Risk Levels)*

In order to ensure consistent protection of human health, ReV and RfD values are based on a defined risk management objective of no significant risk. The no significant risk level for an individual chemical with a threshold dose-response assessment is defined as the concentration associated with a hazard quotient (HQ) of 1 (Section 1.5.2.1). The no significant excess risk level for a carcinogenic chemical with a nonthreshold assessment is defined as the concentration associated with a theoretical excess lifetime cancer risk of one in 100,000 ($1 \times 10^{-5}$) (Section 1.5.2.2). This theoretical excess lifetime cancer risk level is consistent with the State of California's No Significant Risk Level (22 CCR §12703). These risk management goals were approved by the Commissioners and Executive Director of the TCEQ and are consistent with other TCEQ programs.

## *1.4.2 Air Permitting Risk Management Objectives*

ESLs are intended to be screening levels used in the TCEQ's air permitting process to help ensure that authorized emissions of air contaminants do not cause or contribute to a condition of air pollution. To help meet this objective, short-term and long-term ESLs are developed to evaluate short-term and long-term emissions, respectively. A short-term ESL is specifically defined as the lowest value of all acute health- and welfare-based ESLs (Section 1.5.3) so the short-term ESL for a given chemical protects against short-term health effects, nuisance odor conditions, and vegetation effects. They also consider that ambient exposure is dependent on meteorology and source emission patterns, and that peak exposure could potentially occur several times per day. A long-term ESL is specifically defined as the lowest value of all chronic health- and vegetation-based ESLs (Section 1.5.3), so the long-term ESL for a given chemical protects against chronic health effects and vegetation effects. Additional TCEQ guidance is available that describes how short-term and long-term ESLs, which are specific regulatory terms, are used in the air permitting process (TCEQ 1999, TCEQ 2009a).

During the air permit review process, emissions of one chemical from one site are evaluated, not emissions from multiple sites or multiple chemicals (i.e., chemicals are evaluated on a chemical-by-chemical basis). In consideration of cumulative and aggregate exposure, the TCEQ uses an HQ of 0.3 to calculate acute and chronic health-based ESLs for chemicals with a threshold dose-response assessment (Section 1.5.2.1). The HQ of 0.3 used for the calculation of health-based ESLs from derived referenced values (ReVs) is a policy decision made by the TCEQ. During the air permit review process, the predicted maximum ground level concentrations ($GLC_{max}$s) from the potential emissions are evaluated. The $GLC_{max}$s are predicted using the maximum allowable emission rates and worst-case meteorological conditions which may or may not actually occur. Typically, when evaluating the maximum GLC predicted to occur at a sensitive receptor, the concentration must be at or below the ESL. There is a lot of conservatism incorporated into the ESL (e.g., the ESL is 70% lower than the ReV) and layers of conservative assumptions are made in the worst-case modeling analysis itself. Thus, in the event that multiple facilities in an area emit the same chemicals, it is very

unlikely that the maximum concentrations of emissions from other facilities emitting the same chemicals would occur at the same place. It is also very unlikely that the maximum concentrations of emissions from multiple chemicals from a facility and other facilities (if any) would occur at the same time and place. The TCEQ uses an excess risk management goal of $1 \times 10^{-5}$ to calculate ESLs for individual chemicals (e.g., carcinogens) with a nonthreshold dose-response assessment (Section 1.5.2.2). Further adjustment of this no significant excess risk level is not necessary since few chemicals with a known or assumed nonthreshold dose-response assessment are routinely permitted in Texas for a given facility and the risk management goal of $1 \times 10^{-5}$ is ten times lower than the $1 \times 10^{-4}$ level, defined by USEPA as an acceptable level of risk (USEPA 2000d). Health-based ESLs developed in accordance with a HQ of 0.3 and an excess risk management goal of $1 \times 10^{-5}$ are intended to prevent adverse effects potentially associated with cumulative and aggregate exposures (Section 1.3). Air concentrations of chemicals collected in air monitoring samples represent emissions from multiple chemicals and from different facilities and sources (i.e., can be both cumulative across chemicals and aggregate across sources and time). As described in Section 1.3.1, exposure to chemicals in ambient air can be both cumulative across chemicals and aggregate across sources and time. Therefore, air monitoring data would indicate whether or not cumulative and/or aggregate exposure problems exist in an area of concern. Vegetation- and odor-based ESLs are not adjusted for cumulative risk but are near effect threshold levels.

### *1.4.3 Air Monitoring Risk Management Objectives*

For air monitoring, acute health-based ReVs are developed to evaluate short-term sampling results (e.g., grab samples, 1-h automated gas chromatograph data, and 24-h canister data,), and chronic health-based ReV and URF values are developed to evaluate long-term sampling results (e.g., annual average concentrations). The ReV is used for air monitoring whereas the corresponding health-based ESL, which is 70% lower than the ReV, is used in air permitting. The reasons are as follows:

- Air concentrations of chemicals collected in air monitoring samples represent emissions from multiple chemicals and from different sites and sources (i.e., are representative of both cumulative exposure across chemicals and aggregate exposure across sources and time). Thus, for review of air monitoring data, the health-based ReV is appropriate. The acute or chronic ReV, which corresponds to a HQ of 1, is used for chemicals with a threshold dose-response assessment.
- For review of air permit applications, site-wide modeled concentrations are evaluated one chemical at a time. The impacts from multiple chemicals or from different sites are not included. Therefore, for air permitting, an additional buffer which considers these impacts is applied to the acute or chronic ReV to calculate the acute and chronic ESLs, respectively (i.e., the final acute and chronic health-based ESLs are 70% lower than the respective acute and chronic ReV).
- For chemicals with cancer-based long-term values, the same level of conservatism is used in both air monitoring and air permitting. The no significant excess risk level of $1 \times 10^{-5}$ risk (one in 100,000) is ten times less than the upper end of USEPA's acceptable risk range ($1 \times 10^{-4}$) and is used to calculate cancer-based air concentrations from URFs.

- If the Guidelines have not yet been used to develop a health-based ReV for a chemical, the original short-term and long-term ESLs (i.e., interim ESLs) are used in both program areas (i.e., air monitoring and air permitting).
- Welfare-based ESLs (odor and vegetation) are set based on effect threshold concentrations so the same level or ESL is used in both air program areas (i.e., a higher value is not used in air monitoring).

### *1.4.4 Remediation Risk Management Objectives*

The TRRP rule (30 TAC §350) and the dated 1993 Risk Reduction Rule (Subchapters A and S of 30 TAC §335) provide the risk management objectives associated with calculation of environmental media (e.g., soil, groundwater) cleanup levels. These objectives are addressed within the rules, specific to remediation, and are not subject to this guidance. The only remediation risk management objective of any significance within the context of this guidance is that generic noncarcinogenic-based cleanup values are calculated at an HQ of 1. Therefore, the chronic ReV (HQ of 1), as opposed to the chronic ESL (HQ of 0.3), is the relevant noncarcinogenic air toxicity factor for use with remediation rules (e.g., TRRP). Please refer to the rules for information regarding risk management objectives (both individual chemical and cumulative) for remediation programs.

## 1.5 ESLs for Air Permitting

### *1.5.1 Problem Formulation*

ESLs are chemical-specific air concentrations set to protect human health and welfare. Exposure to an air concentration at or below the ESL is not likely to cause an adverse health effect in the general public, including sensitive subgroups such as children, the elderly, pregnant women, and people with preexisting health conditions. ESLs are developed for all chemicals, even if they have limited toxicity information. ESLs are used in the air permitting process to assess the protectiveness of substance-specific emission rate limits for facilities undergoing air permit reviews. Evaluations of modeled worst-case ground-level air concentrations are conducted to determine the potential for adverse effects to occur due to the operation of a proposed facility. ESLs are screening levels, not ambient air standards. If predicted airborne levels of a chemical exceed its ESL, adverse health or welfare effects would not necessarily be expected to result, but a more in-depth review would be triggered, as described in *Modeling and Effects Review Applicability: How to Determine the Scope of Modeling and Effects Review for Air Permits* (TCEQ 2009a) (www.tceq.state.tx.us/assets/public/permitting/air/Guidance/NewSourceReview/mera.pdf).

The exposure duration generally associated with short-term ESLs is 1 h, although exposure may occur on an intermittent basis. This duration is consistent with TCEQ air permit modeling, consistent with pound per hour emission rate limits in air permits. Short-term ESLs for exposure durations other than 1 h may be derived based on reproductive/developmental toxicity (Chapter 4). Long-term ESLs are associated with a lifetime exposure duration which is commonly assumed to be 70 years. For application in

air permitting, long-term ESLs are used to evaluate modeled worst-case annual average concentrations, consistent with ton per year emission rate limits in air permits.

Short-term ESLs are based on data concerning acute health effects, odor potential, and acute vegetation effects, while long-term ESLs are based on data concerning chronic health or vegetation effects. Therefore, before a short-term or long-term ESL can be selected, available information on each of these health and welfare effects is obtained as described in the following chapters.

## *1.5.2 Health-Based ESLs*

When available information about a chemical is inadequate to derive an acute ReV for calculation of a health-based ESL, a default ESL or generic ReV or ESL may be determined, as discussed in Chapter 3 and Chapter 4. If adequate data are not available to derive a chronic ReV for calculation of a chronic, health-based ESL, route-to-route extrapolation, or a surrogate chemical approach will be considered as discussed in Chapter 3 and Chapter 5 to calculate a generic ReV or ESL. If adequate data are not available to derive a URF, a URF will not be developed. Otherwise, health-based ESLs are calculated from ReV and URF values as described in the following sections using the risk management objectives stated in Section 1.4.

### 1.5.2.1 Calculation of ESLs for Threshold Effects

An HQ is defined as the ratio of the exposure level (E) to the ReV (Equation 1-1):

**Equation 1-1 HQ**

$$\mathrm{HQ} = \frac{\mathrm{E}}{\mathrm{ReV}}$$

The E and ReV are expressed in the same units ($\mu g/m^3$) and represent the same exposure period (i.e., acute or chronic). This equation can be rearranged (Equation 1-2) to solve for the exposure concentration that corresponds to a risk management-specified HQ for a specified exposure period:

**Equation 1-2 Exposure Concentration for Threshold Effects**

$$\mathrm{E} = \mathrm{HQ} \times \mathrm{ReV}$$

For threshold effects, ESLs that correspond to an HQ of 0.3 for an acute or chronic exposure period are calculated as follows (Equation 1-3 and Equation 1-4):

**Equation 1-3 Acute ESL**

$$^{\mathrm{acute}}\mathrm{ESL} = \mathrm{HQ} \times \text{acute ReV} = 0.3 \times \text{acute ReV}$$

**Equation 1-4 Chronic ESL Threshold Carcinogen or Noncarcinogen**

$$^{\mathrm{chronic}}\mathrm{ESL}_{\mathrm{threshold(c)}} \text{ or } ^{\mathrm{chronic}}\mathrm{ESL}_{\mathrm{threshold(nc)}} = \mathrm{HQ} \times \text{chronic ReV} = 0.3 \times \text{chronic ReV}$$

The $^{acute}ESL$, $^{chronic}ESL_{threshold(c)}$ or $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) used for threshold effects are not used to evaluate ambient air monitoring data. Acute and chronic ReVs are used as health-based AMCVs (Section 1.6).

#### 1.5.2.2 Calculation of ESLs for Nonthreshold Effects

The URF is expressed as risk per unit lifetime exposure, where exposure (E) is typically in units of 1 µg/m$^3$ (i.e., URF = risk/E, or risk per µg/m$^3$). This URF equation can be rearranged to solve for E (µg/m$^3$) for a chronic exposure period that corresponds to a specified no significant excess risk level (Equation 1-5 and Equation 1-6):

**Equation 1-5 URF**

$$\text{Risk Level} = \text{E} \times \text{URF}$$

**Equation 1-6 Exposure Concentration for Nonthreshold Effects**

$$\text{E} = \frac{\text{No Significant Risk Level}}{\text{URF}}$$

For nonthreshold effects, the continuous lifetime exposure concentration of a chemical that corresponds to TCEQ's no significant excess risk level of 1 x $10^{-5}$ ($^{chronic}ESL_{nonthreshold}$) is calculated as follows (Equation 1-7):

**Equation 1-7 Chronic ESL Nonthreshold Carcinogen or Noncarcinogen**

$$^{chronic}ESL_{nonthreshold(c)} \text{ or } ^{chronic}ESL_{nonthreshold(nc)} = \frac{1 \times 10^{-5}}{\text{URF}}$$

However, when the nonthreshold effect is cancer mediated through a mutagenic MOA, consideration of early-life exposure (Section 5.7.5) results in the following chronic ESL calculation (Equation 1-8):

**Equation 1-8 Chronic ESL Nonthreshold Carcinogen Mediated Through a Mutagenic MOA**

$$^{chronic}ESL_{nonthreshold(c)} = \frac{6 \times 10^{-6}}{\text{URF}}$$

The $^{chronic}ESL_{nonthreshold(c)}$ and $^{chronic}ESL_{nonthreshold(nc)}$ are used in air permitting and as chronic health-based AMCVs for evaluation of ambient air monitoring data.

### *1.5.3 Determination of Short-Term and Long-Term ESLs for Air Permitting*

The preceding sections introduce the derivation of health-based ReVs and URFs. Chapter 2 describes the development of odor- and vegetation-based ESLs. A short-term ESL is determined by choosing the lowest value of the following health- and welfare-based ESLs (as available):

$^{acute}ESL$ or $^{acute}ESL_{generic}$
$^{acute}ESL_{odor}$ or generic $^{acute}ESL_{odor}$
$^{acute}ESL_{veg}$

A long-term ESL is determined by choosing the lowest value of the following health- and welfare-based ESLs (as available):

$^{chronic}ESL_{nonthreshold(c)}$
$^{chronic}ESL_{nonthreshold(nc)}$
$^{chronic}ESL_{threshold(c)}$
$^{chronic}ESL_{threshold(nc)}$
$^{chronic}ESL_{generic}$
$^{chronic}ESL_{veg}$

If the Guidelines have not yet been used to develop a health-based ReV, original ESLs, termed interim ESLs, are used. The processes whereby health- and welfare-based ESLs are developed and then used to determine the short-term ESL (Figure 1-1) and long-term ESL (Figure 1-2a and Figure 1-2b) are shown on the following pages. Go to www.tceq.state.tx.us/implementation/tox/esl/list_main.html to download previous and current ESL lists for Air Permitting.

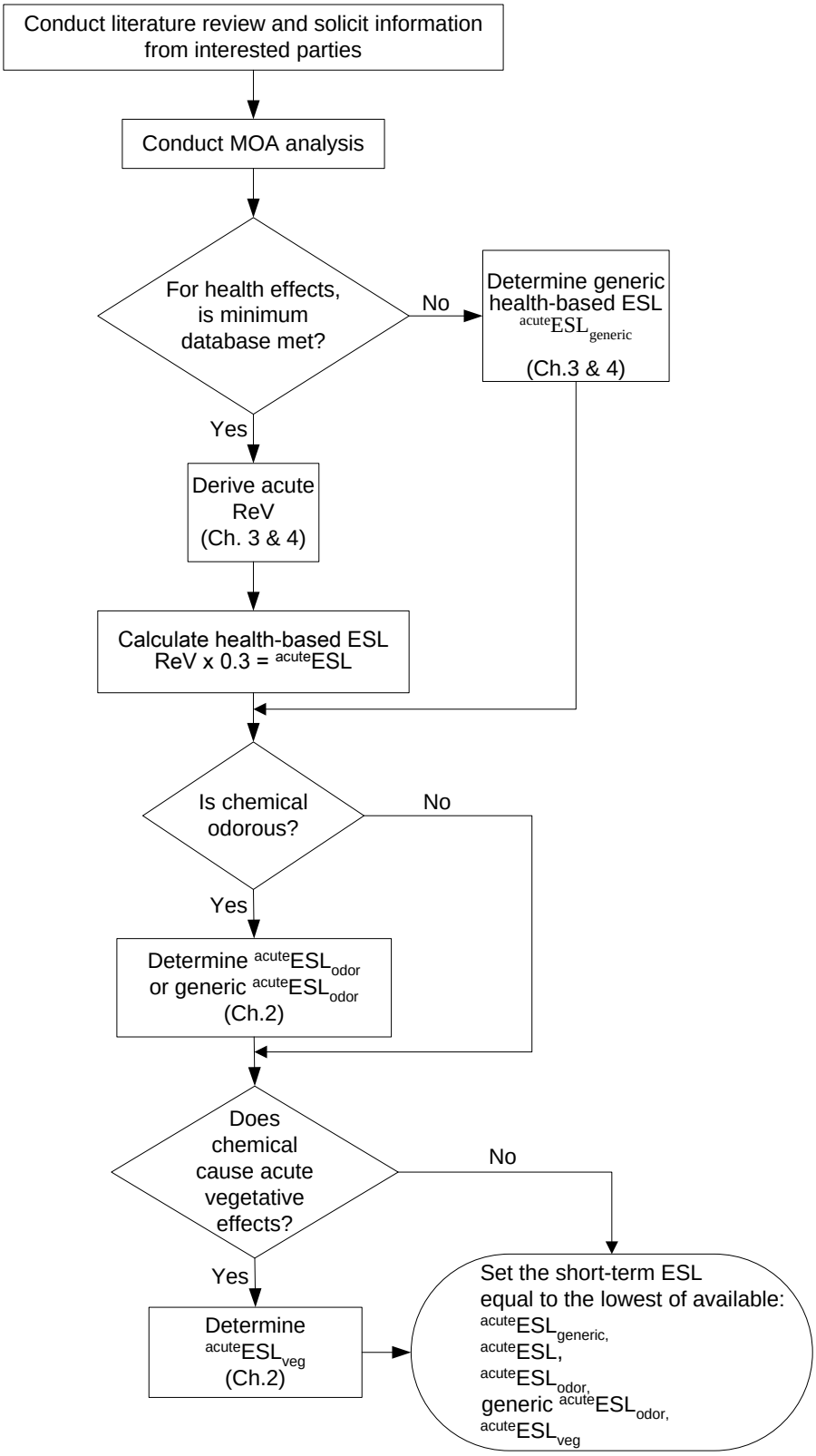


**Figure 1-1 Short-Term ESL development for air permitting**

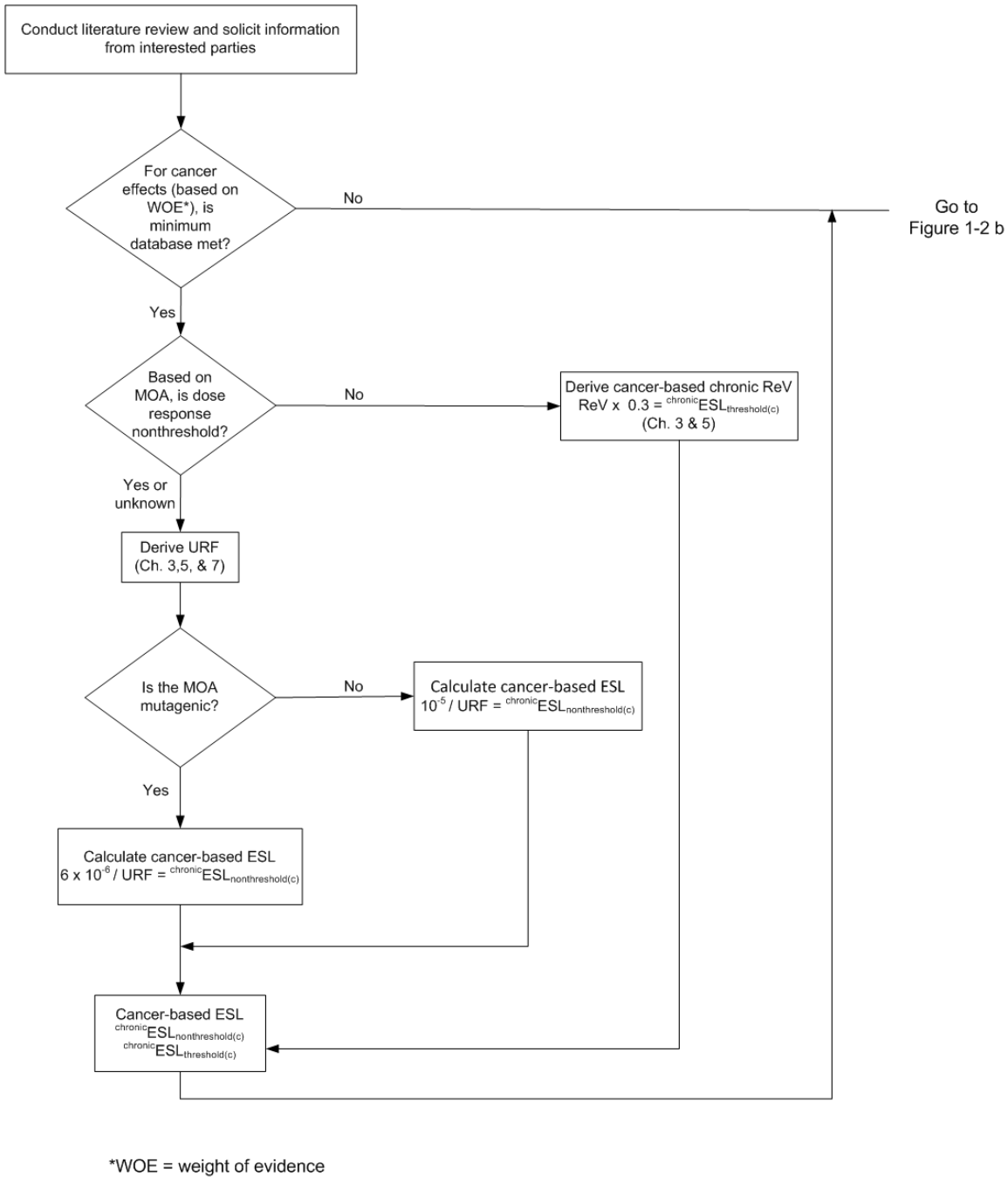


**Figure 1-2a Long-Term ESL development for air permitting**

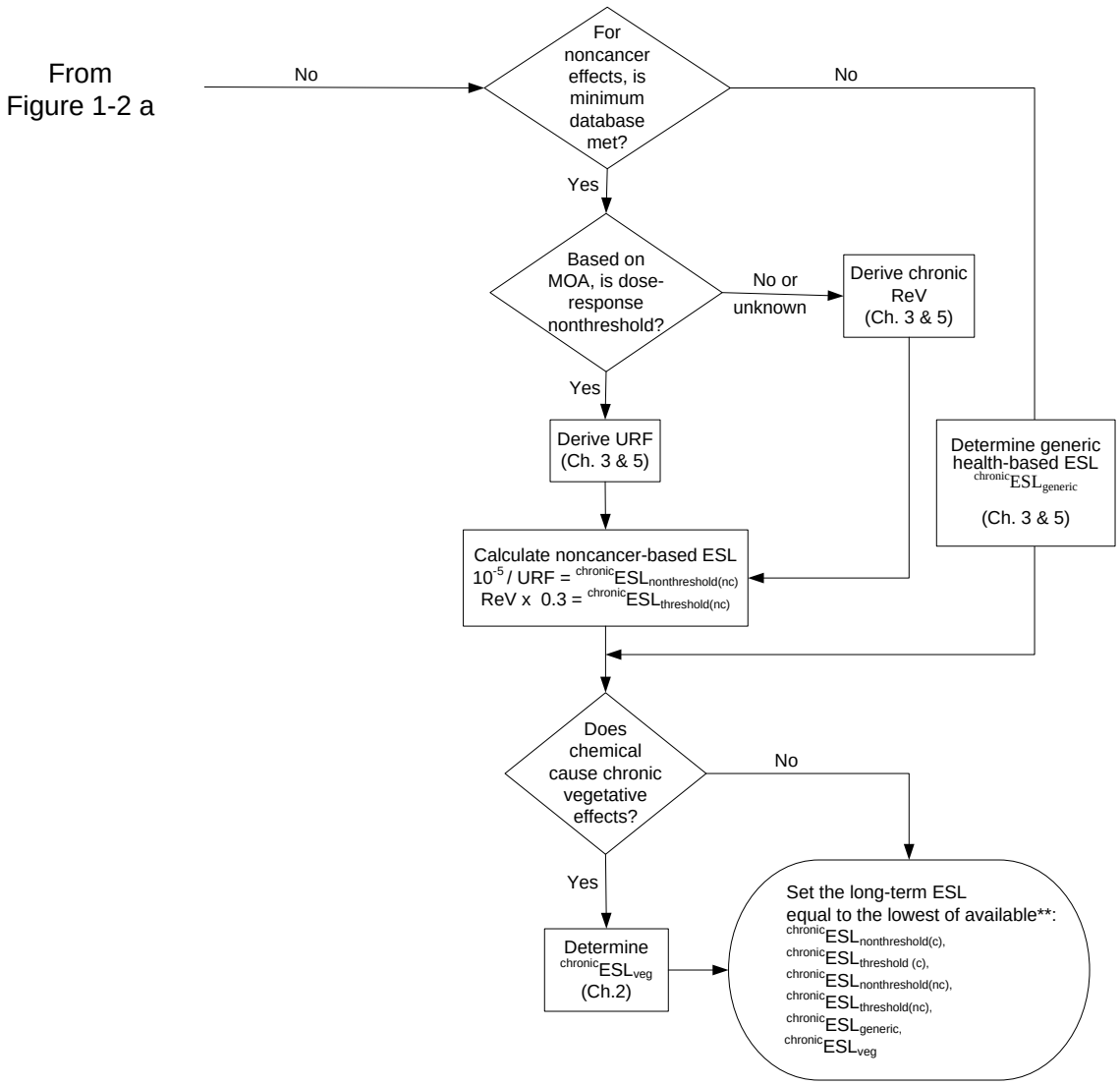


**Figure 1-2b Long-Term ESL development for air permitting**

### Exemption of Substances from ESL Development

ESLs are developed for all substances determined by the TCEQ to be airborne toxicants. Substances not considered to be airborne toxicants of significance are exempt from ESL development. A substance is accorded exemption status by the TCEQ if the scientific evidence or prior regulatory experience indicates that the substance should not be classified as an airborne toxicant. In addition, the TCEQ does not develop ESLs for constituents with specific National Ambient Air Quality Standards (NAAQS) or specific Texas state standards (Table 1-1).

**Table 1-1 List of Chemicals with NAAQS and/or Texas State Standards**

| NAAQS | State Standard |
|---|---|
| Sulfur dioxide | Sulfur dioxide |
| Inhalable particulate matter ($PM_{10}$) | Hydrogen sulfide |
| Fine particulate matter ($PM_{2.5}$) | Sulfuric acid |
| Nitrogen dioxide | |
| Carbon monoxide | |
| Lead (elemental) | |
| Ozone | |

Substances may be added or removed from the exempt list if scientific evidence or regulatory experience dictates a change in status. The TCEQ strongly encourages interested parties (e.g., industry trade associations, individual companies, environmental groups, academia, etc.) to submit technical information to aid in the categorization of substances as exempt or not. Examples of substances currently exempt from ESL development are shown in Table 1-2.

**Table 1-2 Examples of Substances Exempt from ESL Development**

| Substance | Comment |
|---|---|
| Argon | major component of ambient air; simple asphyxiant |
| Carbon dioxide | major component of ambient air |
| Ethane | simple asphyxiant |
| Helium | simple asphyxiant |
| Hydrogen | simple asphyxiant |
| Methane | simple asphyxiant |
| Neon | simple asphyxiant |

| Substance | Comment |
|---|---|
| Nitrogen | major component of ambient air; simple asphyxiant |
| Propane | simple asphyxiant |
| Propylene | simple asphyxiant |
| Fruit juices (apple, orange, etc.) | generally considered as safe |
| Sweeteners (sugar, molasses, corn syrup, etc.) | generally considered as safe |
| Cooking oils (corn oil, olive oil, etc.) | generally considered as safe |
| Food seasonings (soy sauce, salt, pepper, etc.) | generally considered as safe |
| Water (bottled, tap, etc.) | generally considered as safe |

Polymers tend to be of lesser ecological and toxicological concern than other classes of chemicals due to their generally high molecular weight and associated low reactivity and membrane permeability. As a result, regulators have established criteria to exempt polymers and some of their constituent units from standard registration procedures and data requirements. The following list shows the exemption criteria based on specifications in Part 723.250 of the US Code of Federal Regulations (CFR) (723.250 40 CFR Ch. 1 (7/1/04 Edition)). For polymers meeting any of these three criteria, a short-term ESL is not derived. Instead, these polymers are evaluated based on the $PM_{10}$ and $PM_{2.5}$ NAAQS:

- Average molecular weight (MW) ≥ 1000 and < 10,000 daltons (da) and contains < 10% oligomeric material < 500 d and < 25% oligomeric material < 1,000 da and contains only certain reactive functional groups, or
- Average MW > 10,000 da and contains < 2% oligomeric material < 500 da and < 5% oligomeric material < 1,000 da, or
- Is a polyester.

# 1.6 AMCVs for Air Monitoring

## *1.6.1 Problem Formulation*

AMCVs are used to evaluate air monitoring data. “AMCV” is a collective term used to describe chemical-specific air concentrations set to protect human health and welfare. Short-term AMCVs are based on data concerning acute health effects, odor potential, and acute vegetation effects, while long-term AMCVs are based on data concerning chronic health or vegetation effects. Exposure to an air concentration at or below the AMCV is not likely to cause an adverse health effect in the general public, including sensitive

subgroups such as children, the elderly, pregnant women, and people with preexisting health conditions.

Air monitoring data is a measured concentration of a chemical in ambient air. Short-term AMCVs are generally associated with an exposure duration of 1 h, and are typically used to evaluate instantaneous to 1-h reported air concentrations, which are snapshots in time. Long-term AMCVs, associated with a lifetime exposure duration commonly assumed to be 70 years, are used to evaluate annual average air concentrations.

### *1.6.2 How AMCVs Relate to ReVs and ESLs*

There are significant differences between the procedures used for performing health effect reviews for air permitting and the various forms of ambient air monitoring data, as shown in Table 1-3.

**Table 1-3 Differences between Air Permitting and Air Monitoring**

| Air Permitting | Air Monitoring |
|---|---|
| ESLs are developed for thousands of chemicals. | A limited number of chemicals can be monitored (approximately 120). |
| Site-wide modeled concentrations are evaluated on a case-by-case and chemical-by-chemical basis. The impacts from multiple chemicals or from different sites are not included in the review. | Air concentrations of chemicals collected in air monitoring samples reflect multiple chemicals or emissions from different facilities and sources (i.e., can be both cumulative across chemicals and aggregate across sources and time). |
| The maximum ground-level concentration ($GLC_{max}$) is predicted under the worst-case scenario by air dispersion models. | Chemical concentrations in air are analytically determined. They represent a snapshot in time that provides insight into ambient air concentrations of targeted compounds during the sampling event. |
| If predicted maximum $GLC_{max}$ is equal to or below the short-term or long-term ESL, the TCEQ does not evaluate the impacts. However, if the $GLC_{max}$ > ESLs, then the TCEQ will review according to the 3-Tiered Effects Evaluation Procedures. | The TCEQ routinely evaluates all TCEQ air monitoring data and performs a health effects evaluation. |
| The short-term ESL, based on acute exposure health and welfare data, is compared to the modeled 1-hour $GLC_{max}$, unless otherwise specified. | The short-term AMCV, based on acute exposure health and welfare data, is compared to monitored concentrations that can be instantaneous or up to 1-hour, which represent a point in time for a specific location. |
| The long-term ESL, based on chronic or | The long-term AMCV, based on chronic |

| Air Permitting | Air Monitoring |
|---|---|
| lifetime exposure health and vegetative data, is compared to the worst-case annual $GLC_{max}$. | health and vegetative data, is used to evaluate annual averaged monitored concentrations or annual concentrations averaged over multiple years (if available), which represent multiple points in time for a specific location. |
| Multiple sources of one chemical and exposure to multiple chemicals (i.e., to account for cumulative risks) need to be accounted for. If a ReV has been developed for a chemical, an extra buffer is used to calculate health-based ESLs that are 70% lower than the ReV. | For chemicals for which a ReV has been calculated, an extra buffer is not needed to account for cumulative risk for air monitoring samples. The ReV, a health-protective concentration, is appropriate. |
| The terms "short-term ESL" and "long-term ESL" have specific meanings and uses in the air permitting program and regulatory guidance. | TCEQ staff uses all comparison values (i.e., odor-, vegetative-, and health-based values). |
| ESLs are the terminology used for air permitting. | AMCVs are the terminology used for ambient air monitoring because of the significant differences from the air permitting program. |

Because of these differences, different risk management objectives are used for air monitoring, as discussed in Section 1.4.3. The TCEQ has begun using the term "AMCVs" in evaluations of air monitoring data. As stated above, the term "AMCVs" is a collective term and refers to all odor-, vegetative-, and health-based values used in reviewing air monitoring data. The use of different values and different terminology is appropriate because the air monitoring and air permitting programs perform different functions in the protection of human health and welfare. The main difference between values used in air monitoring and air permitting involve the use of the ReV. The ReV is used for air monitoring whereas the health-based ESL, which is 70% lower than the ReV, is used in air permitting. It should be noted that for air permitting, using the modeled maximum ground-level concentration ($GLC_{max}$) and the ESL to evaluate modeling data may be overly conservative. Table 1-4 show the relationship between different types of AMCVs and ESLs.

**Table 1-4 How AMCVs Relate to ESLs**

| AMCV | Definition |
|---|---|
| Odor AMCV | $^{acute}ESL_{odor}$ |
| Short-term vegetation AMCV | $^{acute}ESL_{veg}$ |
| Long-term vegetation AMCV | $^{chronic}ESL_{veg}$ |

| AMCV | Definition |
|---|---|
| Short-term health AMCV | Acute ReV, generic acute ReV, $^{acute}ESL_{generic,}$ or interim acute ESL[1] |
| Long-term health AMCV | lowest value of the chronic ReV [threshold(c)], chronic ReV [threshold(nc)], generic chronic ReV, $^{chronic}ESL_{nonthreshold(c)}$, $^{chronic}ESL_{nonthreshold(nc),}$ or interim chronic ESL [1] |

[1] If the Guidelines have not yet been used to develop a health-based ReV, original ESLs, termed interim ESLs, are used.

Go to www.tceq.state.tx.us/implementation/tox/AirToxics.html to download the list of the odor-, vegetative-, and health-based AMCVs.

## 1.7 Summary of Toxicity Factors in TCEQ Program Areas

The TCEQ develops ReV, URF, RfD, SFo, and ESL values and designates AMCV values to provide toxicological support to multiple program areas within the TCEQ. In the air permit review process, the TCEQ utilizes short- and long-term ESLs to evaluate proposed emissions for their potential to adversely affect human health and welfare (Table 1-5). For evaluation of ambient air monitoring results, AMCVs are used to assess the potential for exposure to the measured concentrations to adversely affect human health and welfare (Table 1-5).

**Table 1-5 Uses of ESLs and AMCVs in Air Permitting and Air Monitoring**

| | Air Permitting<br>ESLs | Air Monitoring [1]<br>AMCVs |
|---|---|---|
| **Short-term Exposure** | **Short-Term ESL** is defined as the lowest value of:<br>$^{acute}ESL_{generic}$,<br>$^{acute}ESL$,<br>$^{acute}ESL_{odor}$,<br>generic $^{acute}ESL_{odor}$, or<br>$^{acute}ESL_{veg}$<br>(Figure 1-1) | **Short-Term Health** [2] =<br>Acute ReV,<br>generic acute ReV,<br>$^{acute}ESL_{generic}$, or<br>interim ESL[3] |
| | | **Odor** = $^{acute}ESL_{odor}$ |
| | | **Short-Term Vegetation** = $^{acute}ESL_{veg}$ |
| **Long-term Exposure** | **Long-Term ESL** is defined as the lowest value of:<br>$^{chronic}ESL_{nonthreshold(c)}$,<br>$^{chronic}ESL_{nonthreshold(nc)}$,<br>$^{chronic}ESL_{threshold(c)}$,<br>$^{chronic}ESL_{threshold(nc)}$,<br>$^{chronic}ESL_{veg}$, or<br>$^{chronic}ESL_{generic}$<br>(Figure 1-2a and Figure 1-2b) | **Long-Term Health** is the lowest value of:<br>Chronic ReV [threshold(c)],<br>Chronic ReV [threshold(nc)],<br>generic chronic ReV,<br>$^{chronic}ESL_{nonthreshold(c)}$, or<br>$^{chronic}ESL_{nonthreshold(nc)}$ |
| | | **Long-Term Vegetation** = $^{chronic}ESL_{veg}$ |

[1] All values are used in the review of measured analytical concentrations for air monitoring data
[2] Short-Term health AMCVs are usually designated for 1 h exposure duration.
[3] If the Guidelines have not yet been used to develop a health-based ReV, original ESLs, termed interim ESLs, are used in both program areas

Lastly, in accordance with rule requirements and guidance, the TCEQ uses chronic ReV, URF, RfD, and SFo values as toxicity factors for both the current TRRP rule (30 TAC §350) and the dated 1993 Risk Reduction Rule (Subchapters A and S of 30 TAC §335) to derive health-protective environmental media (e.g., soil, groundwater) cleanup levels for the TCEQ's remediation program. Please refer to the current TRRP rule (30 TAC §350) and dated 1993 Risk Reduction Rule (Subchapters A and S of 30 TAC §335) for information regarding how toxicity factors are used to calculate media cleanup levels as this is beyond the scope of this document.

## 1.8 Toxicity Factor Development Support Document (DSD)

The purpose of the DSD is to provide a summary of information on the toxicity factor development process and the key toxicity studies/information used to derive inhalation and oral toxicity factors. First, several summary tables of key information are provided

followed by a brief summary of occurrence and use of the chemical. As discussed in Section 3.2, the following analytical approach is used to derive toxicity factors for chemicals: review essential data (i.e., especially dose-response) including physical/chemical properties and select key studies; conduct an MOA analysis; choose the appropriate dose metric; determine the POD for each key study; conduct appropriate dosimetric modeling; select critical effect; and extrapolate from the adjusted POD to lower exposures based on the MOA analysis. These key steps are discussed in the DSD for each chemical. Finally, a section entitled "Other Relevant Information" may be included, if additional information pertinent to an understanding of the toxicity of the compound is available. At the end of the DSD, there are two separate reference sections: a list of the references of key studies discussed in the DSD and a list of references of other studies that were reviewed and considered by the TCEQ staff but were not discussed in the DSD.

Often, toxicity factors for a chemical without existing toxicity factors are needed on an expedited basis (e.g., within weeks). Due to time limitations, DSDs are not developed for toxicity factors developed in these situations. However, documentation is created which verifies derivation of the values consistent with these guidelines. In the absence of such time constraints, a DSD is developed for toxicity factors.

## 1.9 Selection of Chemicals and Data Solicitation for Air Programs

On an approximately annual basis, the TCEQ selects about 10-15 chemicals for the development of inhalation toxicity factors. Selection of the specific chemicals is made in consultation with TCEQ upper management and considers the following:

- Mass of emissions reported
- Frequency with which the chemical is permitted
- Ambient monitoring data
- Public input

The TCEQ publishes the list of chemicals under consideration for ESL development on the TCEQ website approximately once per year and encourages submission of relevant data from interested parties (e.g., citizens, industry trade associations, individual companies, environmental groups, academia, etc.).

## 1.10 Selection of Chemicals and Data Solicitation for Remediation

Toxicity factors are developed on an as-needed basis for remediation programs. For example, some site contaminants may not have existing toxicity factors developed by other agencies (e.g., USEPA, ATSDR). Requests for toxicity factors for such chemicals typically come from the TCEQ project manager or an outside environmental consultant

assessing a remediation site. Additionally, the TCEQ may identify a chemical for toxicity factor development because the existing factors are outdated. Having up-to-date oral toxicity factors (i.e., RfD, SFo) is of particularly high importance because they are typically the drivers (i.e., the critical concentration-limiting factors) in calculations of media cleanup values for remediation sites.

## 1.11 Public Comment and Peer-Review of DSDs

A Development Team composed of TCEQ toxicologists conducts the data evaluation, data selection, and development for each chemical under review. The product of this effort is a Draft DSD which is then circulated to other TCEQ toxicologists for review and comment. Suggested changes/revisions are incorporated, resulting in a Proposed DSD.

The Proposed DSD is published on the TCEQ website for a 90-day public review and comment period. For data-rich or controversial substances, additional time may be allowed so interested parties will have adequate time to submit comments on the Proposed DSD. Following the review and comment period, the Development Team reviews the comments that were received, addresses and resolves relevant issues, and seeks internal consensus on the original or modified values and the accompanying scientific rationale. Following resolution of relevant issues raised through public review and comment, the ReV, ESL, URF, RfD and/or SFo values are classified as final. The public comments, TCEQ response to public comments, and the final DSD are posted on the TCEQ website. The chemical may be reviewed again if compelling new data become available.

Individual DSDs are not routinely submitted for external scientific peer review, although scientists are encouraged to comment on the DSDs during the public comment period. External scientific peer reviews are expensive and the TCEQ does not have the resources to conduct peer reviews for the approximately 10-15 chemicals for which it plans to develop toxicity values each year. However, this regulatory guidance document did undergo external scientific peer review and public comment (TERA 2011). The TCEQ may occasionally decide to conduct an external scientific peer review of an individual DSD if sufficient public interest is expressed and if resources are available (e.g., 1,3 butadiene (TCEQ 2008), nickel and nickel compounds (TCEQ 2011), and inorganic arsenic and arsenic compounds (TCEQ 2012)).

# Chapter 2 Welfare-Based ESLs

## 2.1 Background Information Regarding Air Quality and Protection of Welfare

For the purposes of welfare-based ESL development, welfare effects include odor nuisance and vegetation damage. In addition, protection of animals is indirectly addressed through the development of human health-based ESLs. Toxicity values developed for protection of animals are typically based on the lowest concentration at which an adverse effect is reported in animals. Most human health toxicity values, on the other hand, are based on NOAELs in animals that are divided by inter- and intra-species uncertainty factors to ensure protection for humans because it is assumed that humans are more sensitive than animal species. Therefore, it is assumed that human health-based ESLs also protect animals. However, if sufficient toxicity data indicate a need for specific animals, ESLs will be developed (e.g., an ESL for cattle fluorosis caused by hydrogen fluoride). Other federal and/or state programs address additional welfare concerns such as corrosion and visibility (haze). Acute and chronic welfare-based ESLs are used in air permitting and welfare-based AMCVs are used for evaluation of ambient air monitoring data. While health-based ESLs and AMCVs may differ due to the different applications of these values, the welfare-based AMCV is the same value as the welfare-based ESL.

## 2.2 Odor-Based ESLs

Odor is one of the leading causes (70-80%) of complaints received by environmental regulatory agencies in North America and Europe (Leonardos 1996, Nicell 2009, Shusterman 1992). Noxious, unpleasant odors may impair intended property use, interfere with business operations, cause discomfort or induce adverse health effects in humans and animals on the property (Nicell 2009). Frequent exposure to high concentrations of odorous chemicals (i.e., with unpleasant odors), typically three to five times greater than the odor detection threshold (defined below), may cause a variety of indirect health effects, including headache, nausea, anorexia, vomiting, dizziness, shortness of breath, and certain types of mental stress (Cone and Shusterman 1991, Nicell 2009, Schiffman and Williams 2005, Shusterman 1999, Shusterman 2001, Willhite and Dydek 1989, Willhite and Dydek 1991). In addition, a number of studies suggest that odorants may be irritating to the respiratory tract and, after relatively longer exposure durations, can worsen asthma for some people (Cain and Murphy 1980, Sakula 1984, Shim and Williams 1986, Stein and Ottenberg 1958). The potential impact of unpleasant odors on welfare and quality of life for exposed individuals mandates effective regulation of chemical emissions to prevent nuisance odorous conditions.

Texas is the only state in the United States that regulates odor nuisance using odor-based values. The TCEQ is required by the Texas Clean Air Act (Chapter 382 of the THSC) to conduct air permit reviews and ensure that the construction of a facility or modification of an existing facility will use at least the best available control technology and be protective of human health and physical property.

The intent of an odor-based value is regulation of odor with the intention to prevent odor nuisance conditions, rather than prevention of odor detection. Odor nuisance generally occurs when short-term emissions from a source are of character, duration, intensity, and frequency to constitute a nuisance condition as described in TCEQ guidance (*Odor Complaint Investigation Procedures*, TCEQ 2007b). Briefly, when the TCEQ investigates an odor complaint, evidence is gathered to evaluate four primary characteristics of odor (FIDO procedure, TCEQ 2007b):

- frequency (how often an odor is experienced);
- intensity (how strong is the odor);
- duration (the duration that the odor is experienced); and
- offensiveness (how unpleasant the odor is to most people).

Given that these characteristics are the primary basis upon which the TCEQ will evaluate odor complaints, it is important for odor-based values to be derived with the intention of preventing odor nuisance conditions.

For more detailed information on how the TCEQ will develop odor values, please see the TCEQ odor position paper, *Approaches to Derive Odor-Based Values* (TCEQ 2015 [currently proposed and in public comment]).

## 2.3 Vegetation-Based ESLs

Vegetation-based ESLs ($^{acute}ESL_{veg}$ and $^{chronic}ESL_{veg}$) are set at the lowest-observed-effects level (LOEL) or critical level. The World Health Organization (WHO 2000a) defines the vegetation critical level as the concentration of pollutants in the atmosphere above which direct adverse effects on plants may occur according to present knowledge. Relatively few data exist to describe chemical toxicity in plants. While vegetation effects of a few chemicals—such as ethylene, sulfur dioxide, hydrogen fluoride, perchloroethylene, nitrogeneous pollutants (e.g., $NO_x$, $NH_3$ and $NH_4^+$), and ozone—have been studied, vegetation effect levels and no-effect levels of most chemicals are not available. Any available vegetation toxicity data is identified during the data gathering phase for each chemical's ESL development. Identification of particular adverse effects (hazard identification) and measurements of magnitude of effects at various exposure concentrations and durations (dose-response assessment) are of particular interest. However, threshold values or critical levels for effects on vegetation are not clearly defined in the literature, even for USEPA criteria pollutants such as ozone (probably the best studied). These thresholds may depend on species and on environmental conditions of relative humidity, temperature, and water availability.

Hazard identification focuses on: (1) plant species that are native to Texas or known to be grown in the state; and (2) relatively moderate adverse effects such as defoliation, abscission of flower buds, epinasty, failure of seed filling and disproportionate leaf growth, rather than milder effects such as slight dry sepal injury (observed after the sepals are dried). However, mild effects will be considered if data exist or become available to suggest that mild effects progress to moderate effects under conditions of chronic exposure.

Relevant toxicity information is obtained from published scientific literature and plant experts as necessary. Several publications provide general information about air pollution and plant damage and are available in the TCEQ State Library Collection (Flagler 1998, Jacobson and Hill 1970, Dugger 1974, Bell 2002, Heck and Brandt 1977, Granett and Taylor 1977, U.S. Department of Agriculture 1974).

# Chapter 3 Common Procedures Used to Derive Acute and Chronic Toxicity Factors

## 3.1 Federal and State Guidance Documents

The procedures used to develop acute and chronic toxicity factors employ the four-step risk assessment process formalized by the National Research Council (NRC) in *Risk Assessment in the Federal Government* (NRC 1983) and *Science and Judgment in Risk Assessment* (NRC 1994) as well as procedures recommended in numerous USEPA risk assessment guidance documents and the scientific literature. The TCEQ also considered guidance in *Science and Decisions Advancing Risk Assessment* (NRC 2009). There are similarities as well as unique differences in the procedures used to derive acute versus chronic values. This chapter discusses common procedures used to derive acute and chronic toxicity factors. Chapter 4 addresses the procedures that are unique to the derivation of acute ReVs and ESLs and Chapter 5 addresses the procedures that are unique to the derivation of chronic ReV, RfD, URF and SFo values. Acute and chronic ReV values as well as chronic RfD, URF and SFo values are hereafter referred to as toxicity factors.

The procedures for developing chronic toxicity values are fairly well established. The Integrated Risk Information System (IRIS) and federal and state agencies have published numerous chronic toxicity values for chemicals using these established guidelines. However, the procedures for developing acute toxicity values other than those used for emergency response and planning (NRC 2001) are still being formalized. The TCEQ reviewed numerous federal and state guidance documents and scientific articles. The following guidance documents are used by USEPA to perform IRIS assessments:

### *3.1.1 USEPA Cancer Guidelines*

- USEPA 2007. Framework for Determining a Mutagenic Mode of Action for Carcinogenicity. Review Draft. EPA 120/R-07/002-A, Sep 2007. www.epa.gov/osa/mmoaframework/pdfs/MMOA-ERD-FINAL-83007.pdf
- USEPA 2005a. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F, Mar 2005. www.epa.gov/cancerguidelines/
- USEPA 2005b. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F, Mar 2005. www.epa.gov/cancerguidelines/guidelines-carcinogen-supplement.htm

### *3.1.2 USEPA Risk Guidelines (Other than Cancer)*

- USEPA 2014. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation.

EPA/100/R-14/002F www2.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf

- USEPA 2011a. Recommended Use of BW ¾ as the Default Method in Derivation of the Oral Reference Dose. EPA/100/R11/001. Office of the Science Advisor. Washington, D.C. www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf
- USEPA 2002a. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F, Dec 2002. www.epa.gov/raf/publications/review-reference-dose.htm
- USEPA 2000c. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/002, Aug 2000. cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533
- USEPA 1998a. Guidelines for Neurotoxicity Risk Assessment. EPA/630/R-95/001F, Apr 1998. www.epa.gov/raf/publications/guidelines-neurotoxicity-risk-assessment.htm
- USEPA 1996e. Guidelines for Reproductive Toxicity Risk Assessment. EPA/630/R-96/009, Oct 1996. www.epa.gov/raf/publications/guidelines-reproductive-tox-risk-assessment.htm
- USEPA 1994a. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F, Oct 1994. cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993
- USEPA 1991. Guidelines for Developmental Toxicity Risk Assessment. EPA/600/FR-91/001, Dec 1991. www.epa.gov/raf/publications/guidelines-dev-toxicity-risk-assessment.htm
- USEPA 1986a. Guidelines for Mutagenicity Risk Assessment. EPA/630/R-98/003, Sep 1986. www.epa.gov/raf/publications/guidelines-mutagenicityl-risk-assessment.htm
- USEPA 1986b. Guidelines for the Health Risk Assessment of Chemical Mixtures (PDF). EPA/630/R-98/002, Sep 1986. cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22567

### *3.1.3 USEPA Science Policy Council Guidelines*

- USEPA 2006. Science Policy Council Handbook: Peer Review. Third edition. Office of Science Policy, Office of Research and Development, Washington, DC. EPA/100/B-06/002. www.epa.gov/spc/2peerrev.htm
- USEPA 2000d. Science Policy Council Handbook: Risk Characterization. Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-00-002. www.epa.gov/spc/2riskchr.htm
- USEPA 2000e. Science Policy Council Handbook: Peer Review (PDF) Second edition. Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-00-001. www.epa.gov/iris/pdfs/Policy_IRIS_Peer_Reviews.pdf

### 3.1.4 NCEA Guidelines for Peer Review

- NCEA 2009. Policy and Procedures for Conducting IRIS Peer Reviews (PDF). www.epa.gov/iris/pdfs/Policy_IRIS_Peer_Reviews.pdf

### 3.1.5 Other Guidance Documents and Technical Panel Reports

- USEPA 2000a. Benchmark Dose Technical Guidance Document (PDF) External Review Draft. EPA/630/R-00/001, Oct 2000. www.epa.gov/nceawww1/pdfs/bmds/BMD-External_10_13_2000.pdf
- USEPA 1994b. Interim policy for particle size and limit concentration issues in inhalation toxicity studies: Notice of availability. Federal Register Notice 59(206): 53799. cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=186068
- USEPA 1988. Recommendations for and Documentation of Biological Values for use in Risk Assessment. EPA 600/6-87/008, Feb 1988. cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

### 3.1.6 References Cited in Older Assessment Documents but Superseded by More Recent Guidance

- USEPA 1999c. Guidelines for Carcinogen Risk Assessment Review draft. NCEA-F-0644, Jul 1999. www.epa.gov/cancerguidelines/draft-guidelines-carcinogen-ra-1999.htm
- USEPA 1996a. Proposed Guidelines for Carcinogen Risk Assessment (PDF). EPA/600/P-92/003C, Apr 1996. www.epa.gov/raf/publications/pdfs/propcra_1996.pdf
- USEPA 1993b. Reference Dose (RfD): Description and Use in Health Risk Assessments Mar 1993. www.epa.gov/iris/rfd.htm
- USEPA 1992b. EPA's Approach for Assessing the Risks Associated with Chronic Exposures to Carcinogens Jan 1992. www.epa.gov/iris/carcino.htm
- USEPA 1986. Guidelines for Carcinogen Risk Assessment. EPA/630/R-00/004, Sep 1986. www.epa.gov/cancerguidelines/guidelines-carcinogen-risk-assessment-1986.htm

### 3.1.7 References from other State and Federal Agencies

- OEHHA 2008. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. www.oehha.ca.gov/air/hot_spots/2008/NoncancerTSD_final.pdf
- ATSDR 2007. Guidance for the Preparation of a Twenty First Set Toxicological Profile. www.atsdr.cdc.gov/toxprofiles/guidance/set_21_guidance.pdf
- NRC 2001. Standing Operating Procedures (SOP) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (PDF). www.epa.gov/opptintr/aegl/pubs/sop.pdf
- NRC 2007. Scientific Review of the Proposed Risk Assessment Bulletin from the Office of Management and Budget. www.nap.edu/catalog/11811.html

- FDA 2002 Guidance for Industry Immunotoxicology Evaluation of Investigational New Drugs, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079239.pdf

### 3.1.8 Major International Guidance Documents of Interest

- REACH, Health Canada
- WHO 2006. Environmental Health Criteria 237: Principles for Evaluation Health Risks in Children Associated with Exposure to Chemicals. whqlibdoc.who.int/publications/2006/924157237X_eng.pdf

The TCEQ closely follows procedures provided in the above mentioned guidance documents so a detailed discussion of procedures that are well established is not included here. Instead, a brief summary describing these procedures is included with a reference to the appropriate guidance document. However, if the procedures were not clearly defined in the guidance documents, if there were differences between the procedures recommended in these guidance documents, or if the TCEQ employed different procedures than those recommended in the guidance documents, then a discussion is included to clarify the approaches that the TCEQ uses in deriving toxicity factors.

### 3.1.9 Other References


- Dourson, M.L., L. Knauf and J. Swartout. 1992. On reference dose (RfD) and its underlying toxicity database. Tox. Ind. Health 8(3): 171-189.
- United States Environmental Protection Agency (USEPA 2005d). Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. Risk Assessment Forum. EPA/630/P-03/003F, November. Available at www.epa.gov/raf/publications/pdfs/AGEGROUPS.PDF


## 3.2 Overview for Development of Toxicity Values

Animal toxicity studies generally fall into one of the following exposure duration categories:

- Acute - exposure to a chemical for less than or equal to 24 h
- Subacute - repeated or continuous exposure to a chemical > 1 day to 1 month or less
- Subchronic - repeated or continuous exposure for 1-3 months, usually a 90-day study in typically used animal species (e.g., rodents).
- Chronic - repeated or continuous exposure for longer than 3 months, most commonly a 2-year bioassay in typically used animal species (e.g., rodents).

Since the focus of a 1-h acute ReV is generally a 1-h exposure duration, acute exposure studies are preferentially used to derive these acute ReVs. Acute as well as subacute

studies may be used to derive the 1-h ReV (i.e., if the only toxicity information for a chemical is from a well-conducted subacute study lasting from 1 day to 4 weeks, it is used to derive an acute 1-h ReV corresponding to the desired exposure duration). It is acceptable risk assessment practice to incorporate longer-term data from toxicity studies to develop acute toxicity values corresponding to shorter duration exposures when it is justified by the MOA analysis (Section 4.2.3). Chronic experimental exposure data is preferentially used to derive chronic toxicity dose-response estimates, although subchronic data may be used with the potential for additional application of an uncertainty factor to account for the effect of exposure duration, as discussed in Section 5.5.4. Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans or more than approximately 90 days to 2 years in common laboratory animal species (e.g., rodents) is generally considered a chronic exposure duration (USEPA IRIS Glossary: www.epa.gov/iris/help_gloss.htm). Some studies (e.g., developmental, immune, or reproductive parameter studies) have exposure durations that are neither acute nor chronic. These studies may still be appropriate for use as key studies in the development of acute or chronic toxicity factors. For example, developmental toxicity studies can be used to develop both acute and chronic toxicity factors.

Toxicity factors are derived from dose-response assessments of adverse health effects that have been scientifically demonstrated to result from exposure to specific chemicals, or for which a significant body of scientific evidence suggests that such a causal and biologically plausible relationship exists. The following analytical approach is used to derive toxicity factors for chemicals as well as to evaluate toxicity factors derived by others:

1) Review essential data (i.e., especially dose-response) including physical/chemical properties and select key studies
2) Conduct an MOA analysis
3) Choose the appropriate dose metric considering toxicokinetics and MOA
4) Determine the POD for each key study
5) Conduct appropriate dosimetric modeling
6) Select critical effect, based on human equivalent exposure after considering each key study
7) Extrapolate from the adjusted POD to lower exposures based on MOA analysis.

## 3.3 Review Essential Data and Select Key Studies

### *3.3.1 Consideration of Physical and Chemical Properties*

The following sections provide information on the importance of physical and chemical properties for oral and inhalation exposure and provide definitions and meanings of physical/chemical parameters provided by USEPA (2005c) as well as used by the TCEQ to describe key physical/chemical parameters in the DSDs. If not readily available, the

TCEQ will estimate necessary physical/chemical parameters using available methods (e.g., Lyman et al. 1990).

#### 3.3.1.1 Inhalation Exposure

The physical and chemical characteristics of a chemical influence the nature of its toxic effect since they influence deposition and retention within the respiratory tract, translocation within the respiratory system, and distribution to other tissues (USEPA 1994a). For a particle or aerosol, the mean diameter and size distribution determine respiratory tract deposition and toxic potential. For gases and vapors, water solubility and reactivity are major determinants of uptake and toxic effect. Reactivity is defined to include both the propensity for dissociation as well as the ability to serve as a substrate for metabolism in the respiratory tract. Gases that are water soluble and reactive are likely to exhibit portal-of-entry effects. Gases that are not water soluble or reactive are relatively inert to the airways and penetrate into the pulmonary region. Section 3.1.2 of the Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (USEPA 1994a), hereafter, referred to as the RfC Methodology, provides a detailed discussion of the importance of physical/chemical characteristics of an inhaled chemical and their contribution to the toxic effect. While physical and chemical characteristics of a chemical can influence the nature of its toxic effect, the dose-response data of a chemical largely drive its toxicity assessment.

#### 3.3.1.2 Oral Exposure

Physical/chemical parameters will affect the toxicokinetics and, therefore, the MOA of the chemical when exposure is through the oral route. The physical and chemical characteristics are also important for determining the environmental fate and transport of contaminants being assessed under TCEQ remediation programs (e.g., TRRP). Although the Toxicology Division (TD) develops toxicity factors (e.g., RfD, SFo) for use in TCEQ remediation programs, another section at TCEQ is responsible for developing the physical/chemical parameters for specific chemicals. Therefore, the TD does not gather physical/chemical parameters when developing toxicity factors (e.g., RfD, SFo) exclusively for use in TCEQ remediation programs.

#### 3.3.1.3 Water Solubility Values (USEPA 2005c)

Water solubility is the degree to which a chemical will dissolve in a liter of water. Water solubility classifications (mg/L or ppm) have been defined by USEPA (2005) as follows:

- Very soluble > 10,000 mg/L
- Soluble > 1,000 -10,000 mg/L
- Moderately soluble > 100 -1,000 mg/L
- Slightly soluble > 0.1 -100 mg/L
- Insoluble < 0.1 mg/L

#### 3.3.1.4 Log $K_{ow}$ Rules of Thumb (USEPA 2005c)

$K_{ow}$ is a partition coefficient at the equilibrium ratio of the concentration of a substance dissolved in an organic solvent (octanol) to the concentration of the same substance

dissolved in water. $K_{ow}$ (also referred to as $P_{ow}$) is often reported as a log due to the extremely wide range of measured $K_{ow}$ values. A log $K_{ow}$ of zero indicates an equal affinity for lipids and for water. There is a unique relationship between log $K_{ow}$ and the ability to bioconcentrate in organisms: as log $K_{ow}$ increases, the solubility in lipids increases. This means an increase in the potential to bioconcentrate in organisms is associated with an increase in log $K_{ow}$ (i.e., $K_{ow} \geq 4$). This relationship begins to change around log $K_{ow}$ of 6. For chemicals with log $K_{ow}$ exceeding 6 the potential to bioconcentrate begins to drop and approaches zero at a log $K_{ow}$ of 12. A log $K_{ow}$ indicates to the assessor:

- Log $K_{ow}$ <1 Highly soluble in water (hydrophilic)
- Log $K_{ow}$ >4 Not very soluble in water (hydrophobic)
- Log $K_{ow}$ >8 Not readily bioavailable
- Log $K_{ow}$ >10 Difficult to measure experimentally (essentially insoluble in water, not bioavailable).

$K_{ow}$ affects absorption through biological membranes:

- Liquids with a log $K_{ow}$ of 2-4 tend to absorb well through the skin
- Chemicals with a log $K_{ow}$ > 4 tend to not absorb well
- Chemicals with a log $K_{ow}$ of 5-6 tend to bioconcentrate
- Chemicals with a log $K_{ow}$ of >6 tend to not bioconcentrate

#### 3.3.1.5 Melting Point (USEPA 2005c)

Melting point (MP) is the temperature at which a chemical changes from solid to liquid. MP indicates the state (solid-liquid-gas) of the chemical in the ambient environment and provides clues to other chemical properties.

- MP <100 °C – increased volatility and higher potential exposures
- MP > 25 °C – solid
- MP < 25 °C – liquid
- High MP indicates low water solubility
- Low MP indicates increased absorption is possible through the skin, GI tract, or lungs
- The range of measured MPs indicates it purity: narrow = more pure, wide = less pure

#### 3.3.1.6 Vapor Pressure

Vapor pressure (VP), the pressure at which a liquid and its vapor are in equilibrium at a given temperature, gives clues to other chemical properties. VP determines the maximum air concentration a particular chemical is able to obtain. For air permit reviews, the TCEQ considers chemicals with VP < 0.01 mm Hg (at 25 °C room temperature) as PM and chemicals with VP > 0.01 mm Hg as vapors.

#### 3.3.1.7 Boiling Point (USEPA 2005c)

Boiling Point (BP), the temperature at which the VP of a chemical in a liquid state equals atmospheric pressure, gives clues to other chemical properties. A high BP indicates low VP (e.g., structurally large substances with molecular weight > 200, like polymers. A BP < 25 °C indicates the chemical is a gas. For air permit reviews, the TCEQ considers chemicals with BP > 204 °C (> 400 °F) particulate matter (PM).

### *3.3.2 Review Essential Data*

The TCEQ uses scientifically defensible studies, identified through reviewing the scientific literature available from reputable sources, to assess the underlying data used to develop toxicity factors (e.g., to demonstrate adverse effects due to exposure and dose-response data). Sources of information include, but are not limited to, the following: electronic databases, peer-reviewed journals, government databases, published books and documents from the public and private sectors, and other information such as nonpeer-reviewed reports of studies by private companies that may provide information not available elsewhere.

#### 3.3.2.1 Examples of databases

TOXNET (toxnet.nlm.nih.gov) is supported by the National Library of Medicine and includes several searchable databases including:

- ChemIDplus - Dictionary of over 370,000 chemicals
- Hazardous Substances Data Bank
- Toxicology Literature Online (TOXLINE)
- Chemical Carcinogenesis Research Information System
- Developmental and Reproductive Toxicology Database
- Genetic Toxicology Data Bank
- Integrated Risk Information System (IRIS) (www.epa.gov/iris)

Other searchable databases include:

- National Cancer Institute www.cancer.gov/
- Public Medicine (PUBMED) (www.ncbi.nlm.nih.gov/PubMed)
- Registry of Toxic Effects of Chemical Substances (RTECS) (www.cdc.gov/niosh/rtecs/)
- National Technical Information Service (NTIS) (www.ntis.gov)
- Federal Research in Progress (www.ntis.gov/products/fedrip.aspx)
- Defense Technical Information Center (www.dtic.mil)
- Chemfinder (chemfinder.cambridgesoft.com/)
- Toxicity and Exposure Assessment for Children's Health (TEACH) (www.epa.gov/teach/)

#### 3.3.2.2 Examples of European databases

- European Chemical Substances Information System (ESIS)

- (ecb.jrc.ec.europa.eu/esis/)
- Screening Information Datasets (SIDS) for High Volume Chemicals (www.chem.unep.ch/irptc/sids/oecdsids/indexcasnumb.htm and www.chem.unep.ch/irptc/sids/OECDSIDS/INDEXCHEMIC.htm)
- eChemPortal (webnet3.oecd.org/echemportal/)
- International Programme on Chemical Safety (IPCS) Inchem: Chemical Safety Information from Intergovernmental Organizations (www.inchem.org/)

#### 3.3.2.3 Examples of published books and documents from the public and private sectors

- General References for Toxicology and Chemical Information
- Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles (www.atsdr.cdc.gov/)
- Current Contents, Life Sciences edition
- Health Effects Assessment Summary Tables (HEAST) (USEPA 1997)
- Kirk-Othmer Encyclopedia of Chemical Technology
- International Agency for Research on Cancer (IARC) (www.iarc.fr)
- Merck Index
- National Toxicology Program (NTP) (ntp-server.niehs.nih.gov)
- Patty's Industrial Hygiene and Toxicology
- General References for Regulatory Information and Standards
- American Industrial Hygiene Association (AIHA) (www.aiha.org)
- American Conference of Government and Industrial Hygienists (ACGIH) (www.acgih.org/home.htm)
- National Ambient Air Quality Standards (NAAQS) (www.epa.gov/ttn/naaqs)
- National Institute for Occupational Safety and Health (NIOSH) (www.cdc.gov/niosh/homepage.html)
- Occupational Safety and Health Administration (OSHA) (www.osha.gov)
- Federal Republic of Germany Maximum Concentration Values in the Workplace (MAK)
- EPA Health Effects Documents
- California Environmental Protection Agency (Cal EPA) (www.calepa.ca.gov)

### *3.3.3 Select Key Studies*

#### 3.3.3.1 Overview

Evaluation and selection of key studies follows the guidelines detailed by USEPA (1994a, 2005a) and NRC (2001). Studies that contribute most significantly to the WOE and identify critical effects relevant to humans are selected as key studies. For example, inhalation exposure studies typically take precedence over oral exposure studies for determining inhalation toxicity factors and oral exposure studies typically take precedence over inhalation studies for determining oral toxicity factors. Key studies are used to estimate a threshold for adverse effects that have thresholds and to identify the critical adverse effect. These studies may involve a human population evaluated in an epidemiological, clinical or experimental exposure setting, or they may involve experimentation with laboratory animals. Several factors are considered in this process.

The most important factors are a dose-response relationship, as well as a temporal association between exposure to the compound and the adverse health effect. When reviewing potential key study results in the context of other relevant scientific studies, other important considerations include the reproducibility of findings, evidence supporting a biologically-plausible mechanism or MOA for the effects reported and consistency with other studies. The strength, consistency, and specificity of the association between chemical exposure and adverse effect are also assessed, particularly when considering epidemiological studies. Section 2.2.1.7 of the 2005 Cancer Guidelines (USEPA 2005a) provides an in depth discussion of these issues and the evidence for causality first developed by Sir Bradford Hill in 1965. As mentioned previously, some studies (e.g., developmental, immune, or reproductive parameter studies) have exposure durations that are neither acute nor chronic, but still may be appropriate for use as key studies in the development of acute or chronic toxicity factors.

### 3.3.3.2 Sensitive Subpopulations

In some cases, studies are available for sensitive subpopulations. These may include children, older adults, pregnant women, or individuals with preexisting health conditions (e.g., studies in asthmatics after inhalation exposure to irritants). Critical life stages or windows of susceptibility should be identified, if possible, for chemicals. Studies based on sensitive members of the population are often used as key studies, especially if the critical effect in sensitive subpopulations is observed at lower concentrations/doses than in the general population. If a toxicity assessment is conducted where the critical effect was measured in a sensitive population or the potential increased sensitivity of children or other sensitive subpopulations was accounted for through use of appropriate uncertainty factors, then these subpopulations are protected (Section 3.3.3.2.1).

#### 3.3.3.2.1 Child/Adult Risk Differences

Regulatory initiatives including the 1996 Food Quality Protection Act, USEPA's Cancer Guidelines (USEPA 2005a), and USEPA's Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (USEPA 2005b), have focused attention on specific differences between adults and children. These Guidelines include information to inform TCEQ staff about possible differences between children and adults that are important to consider when developing acute and chronic toxicity factors. In the context of a toxicity assessment, chemically-induced adverse effects that occur during any developmental life stage (e.g., from conception to maturation), which potentially result in adverse effects in children, may be of concern. Children are developing and growing and differ from adults in a number of ways, including rapid growth of tissues and organs, a different rate of metabolism, and physiological and biochemical processes (NRC 1993).

Regulatory and scientific study definitions of susceptible, vulnerable, and sensitive subpopulations vary. The TCEQ defines susceptible as a capacity characterized by biological or intrinsic factors (e.g., metabolic factors, genetic polymorphisms, toxicodynamics, pre-existing disease, lifestage, gender) that may modify the effect of a specific exposure, leading to a higher health risk at a given exposure level (Hines et al.

2010, Snodgrass 1992, USEPA 2011b). Thus, individuals in a susceptible subpopulation may experience adverse health effects at lower levels of exposure than the general population or more severe effects at the same exposure level. Conversely, vulnerable is defined as a capacity for increased risk of adverse effects due to non-biological or extrinsic factors (e.g., lifestyle choices) (USEPA 2011b). As dose-response assessments typically seek to incorporate data on the intrinsic biological factors relevant to identifying susceptible subpopulations, or otherwise account for the lack of these data (e.g., through application of an UFH), for purposes of this document the TCEQ generally uses the term sensitive as synonymous with susceptible (i.e., a capacity for higher risk due to biological or intrinsic factors).

A number of factors, including their rapidly developing tissues and biological systems, detoxification processes, and exposure may be different from those of adults, and therefore, children may be more or less sensitive to environmental toxicants (Bruckner 2000, Ginsberg et al. 2002, Ginsberg et al. 2004, Hines et al. 2010). In addition, toxicodynamics and diet and behavior patterns influence the increased or decreased susceptibility of children (Snodgrass 1992). For example, children breathe more than adults on a per kg body weight basis and eat and drink more than adults on a per kg body weight basis. Thus, tissue doses of some chemicals can be higher in children although the significance of the higher tissue doses varies depending on the mechanism of toxicity (OEHHA 2008). There is also a large amount of variability in developing children, even within a narrow age range. A number of recent references and guidance documents should be consulted for further information on differences between adults and children and their effects on risk assessment, including Daston et al. (2004), Bruckner (2000), WHO (2006), OEHHA (2008), USEPA (2006), Olin and Sonawane (2003), Anderson (2002), Dorne (2010), Clewell et al. (2004), Sarangapani et al. (2003), and Hines et al. (2010).

Children and adults may differ in their susceptibility to chemicals and those differences should be evaluated on a case-by-case basis (Guzelian and Henry 1992). Although it is often assumed that children are more sensitive to the potential adverse health effects from environmental toxicants, data show that the susceptibility depends on the chemical and the exposure scenario (Guzelian and Henry 1992). There may be no differences in susceptibility between children and adults, although in some cases, children may be more or less sensitive (Guzelian and Henry 1992, Bruckner 2000).

In some instances, specific data may raise uncertainties about a high concern for children. In those cases, the TCEQ will analyze the degree of concern and evaluate the weight of evidence (WOE) for that chemical. This process will involve examining the level of concern for sensitivity/susceptibility and assessing whether traditional uncertainty factors already incorporated into the risk assessment are adequate to protect the safety of infants and children.

The USEPA (2006) defines life stages as “temporal stages of life that have distinct anatomical, physiological, and behavioral or functional characteristics that contribute to potential differences in vulnerability to environmental exposures.” The TCEQ considers anatomical and physiological characteristics at various developmental life stages and ages (Table 3-1) to assess toxicity data and data gaps in order to inform the toxicity

assessment and selection of uncertainty factors. Different organ systems develop at different rates, but it has been shown that for each developmental stage, there are both broad windows of susceptibility and more specific periods of susceptibility (Faustman et al. 2000 in WHO 2006). Certain systems and agents (e.g., central nervous system development and radiation exposure) have been well studied; however, in some cases the exact time when organ systems are susceptible to the actions of toxicants is unknown.

#### 3.3.3.2.1.1 Toxicokinetic Differences

Toxicokinetics was defined by Renwick (1993) as all processes contributing to the concentration and duration of exposure of the active chemical toxicant at the target tissue. Toxicokinetic factors that may be important for assessing differences between adults and children include information regarding the main pathways of absorption, distribution, chemical biotransformation, and clearance that can be used to determine the child-specific toxicokinetics that may alter chemical fate (Daston et al. 2004). Neonates (infants less than one month old) and young children may be better or less able than adults to deal with toxicants because of differences in metabolic capacity (Spielberg 1992, NRC 1993, Dorne et al. 2005). Where the parent chemical is the toxic form as opposed to a metabolite, the increased sensitivity of neonates may be related to their very low metabolizing capacity. Hepatic clearance is also immature in neonates due to the presence of fewer enzymes available for xenobiotic metabolism, which can lead to potentially slower clearance and higher systemic dose due to less first pass metabolism (Ginsberg et al. 2004, USEPA 2006b). Differences in susceptibility between adults and children should be evaluated on a case-by-case basis. For example, the fetal/infant kidney is vulnerable to renal toxicity of certain compounds because of its morphological and functional characteristics. However, sometimes the fetal/infant kidney is more tolerant to certain compounds compared to the adult kidney because of its reduced glomerular filtration rate (GFR), concentrating capability, and active transportation (Suzuki 2009, Hines et al. 2010). Information on the developmental profiles of enzymes or organ systems can help identify particularly susceptible age groups (USEPA 2006b).

**Table 3-1 Anatomical and Physiological Characteristics of Developmental Life Stages Through Adolescence***

| Life Stages | Approximate Age Groups | Anatomy/Physiology Characteristics |
|---|---|---|
| Prenatal | Conception to birth | Fusion of gametes to form a new organism. Larger population of stem cells with a greater degree of genetic/epigenetic instability. Metabolic enzyme systems start to develop. Rapid growth and weight gain. |
| Infant | Birth to <3 months | Rapid growth and weight gain. Proportion of body fat increases. Deficiencies in hepatic enzyme activity. Immature immune system functions. High oxygen requirements (leading to higher inhalation rates). Stomach more alkaline. Increases in extracellular fluid. Renal function less than predicted by surface area. |
| | 3 to <6 months | Rapid growth and weight gain. Proportion of body fat increases. Deficiencies in hepatic enzyme activity. Immature immune system functions. Increases in extracellular fluid. Renal function less than predicted by surface area. |
| | 6 to <12 months | Rapid growth and weight gain. Body fat increase begins to level off. Deficiencies in hepatic enzyme activity. Immature immune system functions. Rapid decrease in extracellular fluid. Can begin predicting renal function by surface area. |
| | 1 to <3 years | Some hepatic enzyme activities peaks, then falls back to adult range. Most immune system functions have matured. Extracellular fluid becomes more consistently related to body size. |
| Child | 3 to <10 years | Period of relatively stable weight gain and skeletal growth (as opposed to a period marked by growth spurts). |
| Adolescent | 10 to <16/18 years[a] | Rapid skeletal growth. Epiphyseal closure may take until age 20. Rapid reproductive and endocrine system changes, inclusive of puberty. |

* Adapted from USEPA (2005d, 2006b)

[a] The upper age limit of adolescence differs in various guidance documents, but generally ranges from 18 (WHO 2006) to 21 years (EPA 2002a). Age adjustments for carcinogens acting through a mutagenic MOA vary from those in Table 3-1 (EPA 2005b).

Within the first few years of life, some metabolic pathways responsible for xenobiotic biotransformation rapidly develop. For example, cytochrome P450 (CYP)-dependent

metabolism is low at birth; however, by 2-3 years enzymatic activity exceeds adult values, and by puberty, CYP-dependent metabolism is at adult levels (Anderson 2002). Young children have an increased ability to metabolize drugs or chemicals eliminated by CYP-dependent metabolism (Anderson 2002). Children are more resistant to the hepatotoxicity of acetaminophen when compared to adults because children metabolize the parent compound differently (children via sulfation and adults primarily through glucuronidation). Many metabolic enzymes have distinct developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Leeder and Kearns 1997, Komori et al. 1990, Vieira et al. 1996, NRC 1993). Whether differences in metabolism will make the child more or less susceptible depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification.

The comparison of clearance (volume of blood from which chemical is eliminated per unit time) and half-life (time taken to reduce the initial blood concentration by 50%) between adults and children can be used to evaluate toxicokinetic differences (WHO 2006). Ginsberg et al. (2002) compiled toxicokinetic parameters, including elimination half-lives and volumes of distribution, for children and adults for 45 therapeutic drugs via oral exposure. Results showed that for those chemicals with clearance data (27 substrates), premature to 2-6 months of age infants showed significantly lower clearance ($P<0.01$) than adults whereas 6 month to 12-yr-old children had significantly higher clearance ($P<0.0001$) than adults. Hattis et al. (2003) later analyzed the toxicokinetic parameters to define mean differences between adults and children. They found that the half-lives of orally administered drugs in children 2 months to 18 years were within a factor of 3.2 of the adult half-lives (i.e., the toxicokinetic intraspecies uncertainty factor ($UF_{H-K}$) of 3.16 would be expected to protect children – refer to Section 3.11.1). However, 27% of the 0- to 1-week age group and 19% of the 1-week to 2-month age group had half-lives that exceeded the adult mean half-lives by more than the 3-fold $UF_{H-K}$. The authors pointed out that drugs are not always ideally representative of environmental toxicants and they note that most of the drugs evaluated have short half-lives (e.g., less than one day). In conclusion, differences between adults and children affecting the toxicokinetic portion of the $UF_H$ discussed in more detail in Section 3.11.1 should be evaluated on a chemical-by-chemical basis.

#### 3.3.3.2.1.2 Toxicodynamic Differences

Toxicodynamics can be defined as the mode or mechanism of action of the active toxicant at the target tissue site (Renwick 1993) and quantitative data regarding toxicodynamic differences between adults and children are limited. Systems, including the immune system, the respiratory system, the nervous system, the reproductive system, the digestive system, and the blood-brain barrier, undergo qualitative and quantitative changes with age (OEHHA 2008). While the specific mechanisms resulting in the toxicodynamic responses are often not completely understood, data generally indicate developing systems are more vulnerable than mature systems (OEHHA 2008).

Examples of toxicodynamic differences between adults and children involve specific organ systems such as the respiratory, immune, and nervous systems. According to

Daston et al. (2004), 80% of the alveoli present in the adult lung are formed after birth and numerous metabolic and biochemical functions of the lungs undergo development and maturation after birth. Lung development continues for up to eight years after birth and lung function growth continues through adolescence (OEHHA 2008). Particle deposition may be greater in children due to smaller diameters of the airways compared to adults (OEHHA 2008). The immune system also undergoes numerous changes through development. Lead is an example of an immunotoxicant that can affect the immune systems of adult and juvenile rodents differently, depending on the timing of exposure (Daston et al. 2004). Adverse effects of the nervous system can result from alterations of neurogenesis, changes in the timing of neuronal cell migration, and synaptic development (Daston et al. 2004). Myelin deposition in humans is greatest in the first two years of life, which is comparable to the first 35-40 days of life in the rodent (Daston et al. 2004). These examples illustrate the types of toxicodynamic information important to understanding chemical-specific differences, which when available, should be evaluated and included in the DSD.

The genetics of an organism influence the outcome of developmental exposure (WHO 2006). Genomics has provided valuable information on gene–environment interactions. Studies are becoming available that show the existence of genetic polymorphisms for developmentally important genes that may enhance the susceptibility of children (WHO 2006). An example of a gene-environment interaction affecting children is that of heavy maternal cigarette smoking and cleft lip and/or palate in the offspring. If an allelic variant for transforming growth factor-alpha (TGF-α) is present, the association between smoking and cleft lip and/or palate is highly significant. Without the allelic variant, the association is only marginally significant (Hwang et al. 1995 in WHO 2006). In conclusion, differences between adults and children affecting the toxicodynamic portion of the $UF_H$ discussed in more detail in Section 3.11.1 should be evaluated on a chemical-by-chemical basis.

#### 3.3.3.2.1.3 Differences in the Oral Route of Exposure

Differences between children and adults are also present in the oral route of exposure. It is important to consider this when gathering and evaluating chemical data. For instance, gastrointestinal tract absorption can be different between children and adults, which has implications for metals absorption. An example of this would be lead, which is more toxic to children than adults. Children absorb up to 50 percent of ingested lead, about five times more than adults. First pass effects should also be considered when evaluating oral child/adult differences. In addition, gastric pH is higher in newborns (pH 6-8) than in adults (pH1-3) and differences in ionization and absorption of certain chemicals can result (Radde 1985 in WHO 2006). Adult levels of gastric acid production are not achieved until about two years of age. The higher gastric pH in newborns and infants may lead to enhanced bioavailability of weakly basic compounds but reduced bioavailability of weakly acidic compounds (Alcorn & McNamara 2003 in WHO 2006).

#### 3.3.3.2.1.4 Summary

It is important to develop acute and chronic toxicity factors that protect sensitive subpopulations such as children (Section 1.2), although the range of variability in sensitivity in the human population to different chemicals is often uncertain. The TCEQ

uses a WOE approach to evaluate the level of concern for children's toxicity on a case-by-case basis and to determine appropriate intrahuman and database uncertainty factors. This WOE approach is also used by USEPA (2002) and Health Canada (2008) in evaluating child/adult differences regarding pesticides. The level of concern for the toxicity of a chemical for children will be primarily determined by reviewing information relevant to the sensitivity of children and the seriousness of the endpoint(s) observed in the chemical's database. An evaluation of the chemical's database as a whole is important as no single consideration should determine the overall level of concern. Table 3-2 highlights some of the specific pieces of information for a chemical from human and/or animal data that may be used to evaluate the degree of concern (e.g., high or low). Specific sections of Chapter 3, Chapter 4, and Chapter 5 will provide information on how the TCEQ conducts toxicity assessments specifically to protect not only children, but other sensitive members of the population. If a toxicity assessment is conducted where the critical effect was measured in a sensitive population or the potential increased sensitivity of children or other sensitive subpopulations was accounted for through use of appropriate uncertainty factors, then the toxicity values are expected to be protective of children.

**Table 3-2 Evaluating Degree of Concern for Children's Toxicity - A WOE Approach (Health Canada 2008)**

| Considerations | Degree of Concern | |
|---|---|---|
| | **High** | **Low** |
| Sensitivity or susceptibility of the young | Qualitative or quantitative sensitivity. | Absence of sensitivity. |
| Seriousness of the endpoint(s) | Serious (irreversible effects such as causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death). | Less serious (reversible effects or adaptive responses, mild irritation). |
| Dose response | Steep dose response (small increment in exposure can have significant impact). Shallow dose response (less certainty about precision of NOAEL). | Good data on dose response (allows for confident identification of NOAEL or benchmark dose). |
| Toxicokinetics and/or metabolism | Metabolic profile indicates higher internal dose of active moiety in young compared to adult or in humans compared to animals.<br>Animal or human evidence | Metabolic profile indicates lower internal dose of active moiety in young compared to adults or in humans compared to animals. |

| Considerations | Degree of Concern | |
|---|---|---|
| | **High** | **Low** |
| | of significant placental or lactational transfer. | Evidence of no significant placental or lactational transfer in animals or humans. |
| Mode of action | Mode of action supports relevance to humans. Evidence that humans are more sensitive than the animal model. Mode of action may lead to several developmental effects. | Evidence that mode of action is species-specific and thus not relevant to humans.<br>Evidence indicates that humans are less sensitive than the animal model. |
| Confidence in study and/or endpoint | Low quality database.<br>Study limitations.<br>Poorly defined NOAEL. | High quality database.<br>Well-conducted study.<br>Well-defined NOAEL. |
| Human information | Effects found in humans related to exposure. | No adverse human effects associated with exposure. |

#### 3.3.3.3 Human Studies

In general, human data are preferred when developing toxicity factors. This data may include both epidemiologic studies as well as reports of individual cases or clusters of events. Carefully designed studies with precise measures of exposure can best evaluate exposure-effect relationships. Epidemiologic studies that presume exposure based on occupation or residence (i.e., ecological epidemiology) may contribute to qualitative assessments, but are limited in their utility for quantitative risk assessments due to the broad categorical groupings which result in a lack of accurate exposure data. Reports of individual cases or clusters of events may generate exposure-outcome associations and support associations suggested by other human or animal data, but must be evaluated in the context of other studies in risk assessments.

##### 3.3.3.3.1 Epidemiology Studies

Epidemiology is the study of the determinants, occurrence, and distribution of health and disease in a defined population (Brachman 1996). Epidemiology studies provide data regarding associations between exposure and health effects that are useful in hazard identification, and if accompanied by sufficiently accurate and reliable exposure data, may be useful in the dose-response assessment for a toxicant. Epidemiological studies may be descriptive, analytical, or experimental in design. Descriptive studies can involve populations (ecological studies) or individuals (case reports and cross-sectional studies). Analytical designs include observational studies (cross-sectional, case-control, and cohort

studies), and experimental designs include intervention and randomized clinical trials. Use of epidemiological studies is often limited by such issues as confounding factors (e.g., predisposing lifestyles and preexisting health conditions)not being adequately controlled for, reliability of the exposure data, and lack of biological plausibility between exposure and the purported effect. Data from epidemiological studies relating exposure to an effect known to be caused by a chemical have been used by various organizations to establish inhalation toxicity factors. Additionally, a recent study by Adami et al. (2011) suggests incorporating epidemiology studies with biological plausibility when determining causal relationships between an agent and an effect. The TD evaluates epidemiological studies in combination with experimental evidence from animal models and plausible biological mechanisms to derive toxicity factors. Chapter 7 provides more detailed guidelines for using epidemiology studies to derive toxicity factors.

#### 3.3.3.3.1.1 Experimental Epidemiology: Controlled Exposure and Clinical Studies

Human controlled exposure or clinical studies involve well-controlled environments in which short-term effects of exposure to a toxicant are documented. Moreover, they can provide data about the distribution of the toxicant within the body and may identify biomarkers of exposure or early effects. Their short duration is useful in the derivation of acute toxicity factors, but limits their use in chronic toxicity factor development, as do their small sample size and the noninvasive nature of the post-exposure evaluations. IPCS (2005) provides the following guidance concerning small sample size of human subjects:

> *The number of subjects within the population, or within the major subgroup if there are two or more groups, should be sufficient to provide an accurate measure of the central tendency. As a guide, the standard error (standard deviation [SD] of the sample divided by the square root of the sample size) should be less than approximately 20% of the mean. Based on available data, this would normally involve a minimum number of approximately five subjects or samples from five individuals, unless the variability is very low (i.e., small coefficient of variability).*

#### 3.3.3.3.1.2 Descriptive and Analytical Epidemiology: Population Exposure Studies

Population exposure studies involve monitoring of exposure and disease incidence across groups of individuals. Cross-sectional studies examine concurrent exposure and disease incidence. Case-control studies select subjects based on disease status (cases matched with disease-free controls) and then compare exposures, while cohort studies select disease-free individuals and then compare disease rates by exposure status (exposed versus non-exposed). These studies are especially useful as they are designed to examine multiple health effects of an exposure over time, and allow for collection of a wider variety of data and thus limit confounding. Ecological epidemiology studies describe population-wide trends (e.g., toxicant levels between two cities correlated with disease incidence in those populations). However, these types of studies are not suitable for deriving toxicity factors as they cannot establish a cause-and-effect relationship between exposure and disease occurrence. This is due to the presence of confounding variables (e.g., other factors causing the outcome)that are not adequately controlled for, as well as the limitation that associations observed between variables on a population-wide level do not necessarily represent an association when individuals are considered (i.e., “ecological

fallacy"). Well-designed and well-executed population exposure studies can provide correlative information about exposures to a toxicant and the human health effects that may be linked to those exposures, but not causative information.

#### 3.3.3.3.2 Case Reports, Occupational Studies, and Field Studies

Case reports can provide confirmation that effects seen in laboratory animal studies also occur in exposed human populations, and are useful in hazard identification. Since case reports frequently involve accidental exposure to high concentrations, they may be useful in the derivation of acute toxicity factors if the exposure concentrations are available and reasonably reliable. However, their small sample size, short exposure duration, and high exposure concentrations may limit their use in the derivation of chronic toxicity factors.

Occupational studies involve the application of epidemiologic methods to populations of workers and may involve exposures to chemical, biological, or physical agents to determine if the exposures result in adverse health effects. Alternatively, epidemiologic studies may involve the evaluation of workers with a common adverse health effect to determine if an agent may explain their disease (Merril and Timmreck 2006). These studies are some of the most helpful sources of information with regard to the development of toxicity factors. Data from occupational exposures may aid risk assessors in determining the concentration or dose of a constituent at which exposures may occur without expectation of significant adverse health effects, the lowest concentrations at which exposures may induce adverse health effects, or the potency of a carcinogen. Exposure conditions from occupational studies, mostly involving exposures of eight-hours per day for five days per week, can be extrapolated to chronic, twenty-four hour per day scenarios for application to the general public. Occupational acute exposure data used to set short-term occupational exposure limits can be useful as part of an acute toxicity assessment.

Field epidemiology involves the application of epidemiologic methods to unexpected health problems when a rapid on-site investigation is necessary for timely intervention (e.g., disease outbreaks) (Merrill and Timmreck 2006). Well-designed and well-executed field studies can provide correlative information regarding exposures to a toxicant and the human health effects that may be associated with those exposures.

### 3.3.3.4 Laboratory Animal Data

When relevant and sufficient human studies are not available, laboratory animal data are used to develop toxicity factors. Several factors are considered when selecting key animal studies. For example, the adverse effect observed in laboratory animals must be relevant in humans as discussed as part of an IPCS framework illustrated in Figure 3-1 (Boobis et al. 2006). In general, non-human primates are considered most similar to humans in their response to chemical exposures. Comparison of human and animal pharmacokinetics and metabolism are considered when selecting relevant animal model and studies. Choosing the most sensitive adverse health effect observed in animals and an assumption of

relevance to humans is a precautionary procedure in the absence of definitive data regarding relevance to human health.

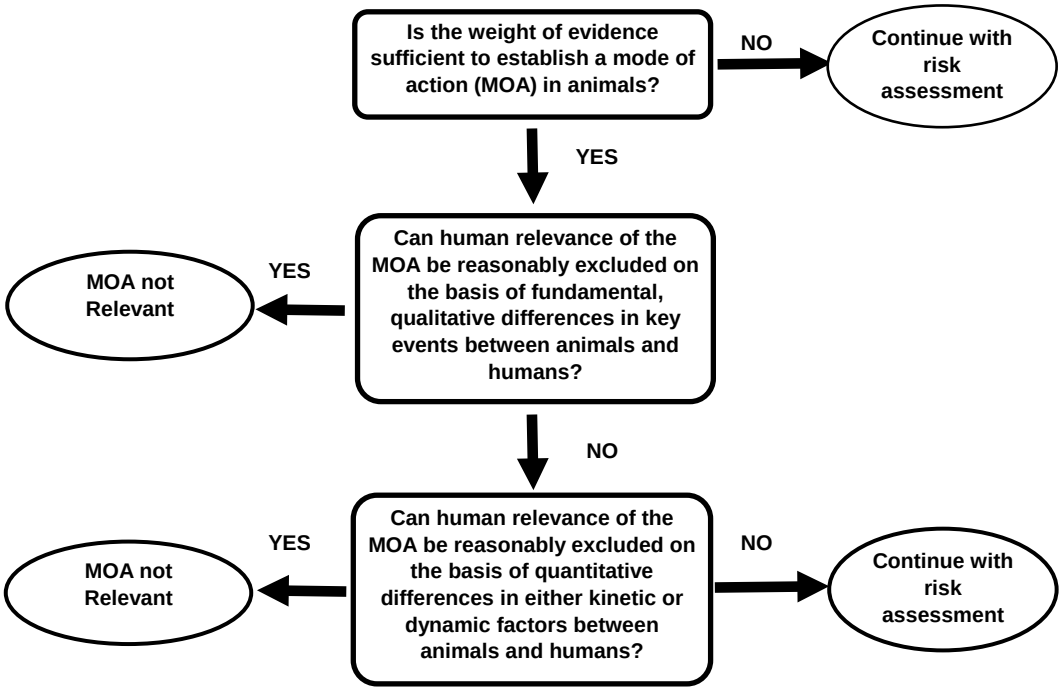


**Figure 3-1 Main steps in evaluating the human relevance of an animal MOA to humans**

The questions in the above figure have been designed to enable an unequivocal answer yes or no, but recognizing the need for judgment regarding sufficiency of WOE. Answers leading to the left side of the diagram indicate that the WOE is such that the MOA is not considered relevant to humans. Answers leading to the right side of the diagram indicate either that the WOE is such that the MOA is likely to be relevant to humans or that it is not possible to reach a conclusion regarding likely relevance to humans, due to uncertainties in the available information. In these cases, the assessment would proceed to risk characterization. It should be noted that only at this stage would human exposure be included in the evaluation. (from Boobis et al. 2006, reproduced with permission from Informa Healthcare).

## 3.4 Conduct an MOA Analysis

MOA is the series of events leading to induction of the critical toxic endpoint (IPCS 2001, Andersen et al. 2005). The key and obligatory steps that describe the alterations in cellular or organ function leading to toxicity should be described (Figure 3-2). This is in contrast to mechanism of action, which is a detailed understanding at the molecular level of all the steps leading to an adverse effect (USEPA 2005a). It is important to conduct an MOA analysis that describes in detail, to the extent possible, the potential for toxicity and the nature of the dose-response curve. This analysis involves consideration of a chemical's toxicity based on physical and chemical characteristics (e.g., does the chemical have properties that indicate it is likely to be reactive in the portal of entry (POE)) as well as empirical data obtained from experimental studies, as discussed above.

Section 5.7.2 dicusses evaluation of the carcinogenic MOA in detail. MOA information can be used to make decisions about the relevance of animal data to humans, assist in identifying potentially sensitive subpopulations, and model health effects including tumor incidence and key precursor event data. Based on the chemical's MOA analysis:

- The most appropriate dose metric can be chosen to conduct a dose-response assessment;
- A decision can be made on whether the chemical has a threshold or nonthreshold dose-response;
- An evaluation of whether the adverse effect is relevant to humans can be conducted; and
- An assessment can be done on whether children (or another group) may be more sensitive than adults to the relevant adverse effect.

**Figure 3-2 Different steps or key events from exposure to a chemical to the development of adverse effects**

Adapted from Julien et al. (2009).

## 3.5 Choose the Appropriate Dose Metric

Exposure dose or concentration of parent chemical, the most common dose metric available, is an external or applied dose whereas the remainder of the dose metrics shown above are internal. It is important to clearly distinguish between exposure concentration and dose to the critical target tissues since they are not always proportional to each other. The nature and the putative MOA of the toxic response are used to choose an appropriate measure of "dose." Potential dose metrics are discussed by Jarabek (1995a) and include (from most commonly available to less commonly available):

- Exposure dose or concentration of parent chemical
- Blood concentration of parent chemical
- Area under blood concentration curve of parent chemical
- Tissue concentration of parent chemical
- Area under tissue concentration curve
- Tissue concentration of metabolite
- Area under tissue concentration of stable metabolite
- Area under tissue concentration of reactive metabolite

Available dose metrics, including those which may be more closely related to the toxic effect (e.g., toxic metabolite level at the target tissue), the MOA, and information on toxicokinetics (i.e., absorption, distribution, metabolism, elimination) should be discussed and used to choose the most appropriate dose metric. Toxicokinetic information is especially important to assess whether children may be more sensitive than adults to the adverse effects produced after chemical exposure (see Section 3.3.3.2).

Important considerations in choosing appropriate dose metrics to evaluate toxic responses are illustrated by the differences between acute and chronic exposure to benzene. When considering acute high-concentration benzene exposure, an appropriate dose metric to describe central nervous system (CNS) depression would be the parent compound blood concentration, whereas for chronic relatively lower-level exposure that produces erythroid precursor perturbations, an appropriate dose metric would be the area under the tissue concentration curve for toxic metabolites (Jarabek 1995a).

## 3.6 Determine the POD

The POD is the point on the dose-response curve that marks the beginning of a low-dose extrapolation for an adverse effect. When choosing the critical adverse effect, it is important to note that all effects reported for a substance are not necessarily considered adverse. For example, exposure to a chemical may result in increases of protective enzymes in a tissue which would not be considered an adverse effect. However, at higher concentrations, the chemical may cause tissue necrosis, an adverse effect.

### 3.6.1 Determination of Adverse Effects

An adverse effect may be considered to be a change (biochemical, functional, or structural) that may impair performance and generally has a detrimental effect on growth, development or life span when observed in a non-clinical toxicology model (Dorato and Engelhardt 2005). The USEPA defines an adverse effect as "any effect resulting in functional impairment and/or pathological lesions that may affect the performance of the whole organism, or that reduce an organism's ability to respond to an additional challenge" (USEPA 1994a).

Adversity typically implies some induction of functional impairment or generation of pathological lesion(s) that affects the performance of the whole organism or reduces an organism's ability to withstand or respond to additional environmental challenges. Consistent with the goal of public health to control exposures before the occurrence of functional impairment of the whole organism (NRC 2007a), the TCEQ calculates conservative health-based toxicity factors to protect against adverse effects. The National Research Council (NRC) recommended identifying measurable adverse effects or biologic changes that occur at a point in which they are minor, reversible, or subclinical and that do not affect sensitive individuals within the population. The California EPA follows NRC (2007a) in recommending a cautious and health-protective approach to the determination of whether a given biological endpoint is appropriate to consider frankly "adverse," or is a biologically significant precursor lesion, in which case it would be a suitable endpoint for consideration in a toxicity assessment. However, a precursor may be selected as the critical effect only if it is the immediate precursor of the toxic effect. Alternatively, an effect may be a non-adverse adaptive or incidental change, which occurs either as a result of treatment or merely by chance and unrelated to study treatment or exposure (OEHHA 2008). Emphasis on substituting high throughput *in vitro* assay data *in lieu* of traditional animal toxicity testing data for risk assessment is increasing (e.g., NRC 2007b). Advanced predictive methods (e.g., computational systems biology toxicity pathway models) must be developed, validated, and accepted by the scientific community for clearly and reliably distinguishing non-adverse responses (or levels of responses) for *in vitro* endpoints (e.g., adaptive) from those that should be deemed adverse at the cellular level (e.g., produce progressive toxicity pathway perturbations sufficient to cause adverse effects *in vivo*). Guidelines need to be established before appropriate PODs for use in risk assessment can be determined through *in vitro*-to-*in vivo* dosimetric extrapolation (e.g., Boekelheide and Andersen 2010).

Lewis et al. (2002) proposed a definition for biologically significant effect to assist in differentiating between adverse and non-adverse effects consistently:

> *Biologically significant effect: A response (to a stimulus) in an organism or other biological system that is considered to have substantial or noteworthy effect (positive or negative) on the well-being of the biological system. The concept is to be distinguished from statistically significant effects or changes, which may or may not be meaningful to the general state of health of the system.*

In general, there are two types of significant biological responses. First, there are the normal biological responses, which will manifest in response to stress, such as sweating in exercise or losing weight when caloric intake is restricted. These changes often represent normal homeostatic reactions to stimuli. Second, there are the abnormal biological responses, which may be caused by chemicals or other stresses. Either of these biological responses could be significantly different from the normal baseline when analyzed by statistics or may show no statistical differences from control. Therefore, one must be cautious in relating a statistical finding to a true adverse biological effect (Lewis et al. 2002).

#### 3.6.1.1 Recognition of Adverse and Non-Adverse Effect

It is important to identify the highest exposure level in toxicity studies that does not cause treatment-related adverse effects that could be considered relevant to human health. Lewis et al. (2002) stated "that toxicity studies are of necessity limited to a small number of quantitative observation points (dose or concentration levels), although the biological response may represent a continuum of change with changing dose."

The judgment on the adverse nature of an observation in a toxicology study is often subject to debate and reinterpretation. Decisions about the amount of change necessary to consider an effect adverse must always be made using professional scientific judgment and must be viewed in light of all the data available on the endpoint of concern. Relevant toxicological data and other information (e.g., physiological, reference intervals) relevant to the endpoint under consideration must be reviewed before deciding whether an effect is biologically significant and adverse, and how the results fit with what is known about the underlying MOA. Biological significance is the determination that the observed effect (a biochemical change, functional impairment, or pathological lesion) is likely to impair the performance or reduce the ability of an individual organism to function or to respond to additional challenge from the agent even though there may be no statistically significant differences from control. Biological significance is also attributed to effects that are consistent with the sequence of events that occur in a known MOA.

While biological significance concerns whether an effect is adverse, statistical significance concerns whether an effect actually occurred. That is, statistical significance quantifies the likelihood that the observed effect is not due to chance alone and therefore could truly be an effect induced in response to the chemical exposure of interest. Thus, statistical significance is required to determine if an effect has actually occurred, and if so, then whether the observed effect is biologically significant and adverse can be evaluated. Precedence is given to biological significance because a statistically significant change that lacks biological significance is not considered an adverse response (USEPA 2002a).

#### 3.6.1.2 Evaluation Process

The European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC 2002) and Lewis et al. (2002) have presented a structured approach to determine if a response in a toxicology study is adverse or non-adverse. This approach includes an evaluation of the adaptive, transient/persistent, and progressive nature of the response, its association with

other effects, the occurrence of functional impairment, and the primary or secondary nature of the response.

Briefly, the evaluation process involves two main steps. In the first, the toxicologist must decide whether differences from control values are treatment-related or if they are chance deviations. In the second step, only those differences judged to be effects based on statistical or biological significance are further evaluated in order to discriminate between those that are adverse and those that are not. For each step, criteria are described that can be used to make consistent judgments. In differentiating an effect from a chance finding, consideration is given among other things to dose-response, spurious measurements in individual parameters, the precision of the measurement under evaluation, ranges of natural variation and the overall biological plausibility of the observation. In discriminating between adverse and non-adverse effects consideration is given to whether:

- the effect is an adaptive response;
- it is transient, the magnitude of the effect, its association with effects in other related endpoints;
- it is a precursor (not immediately causing an effect) to a more significant effect;
- it has an effect on the overall function of the organism;
- it is a specific effect on an organ or organ system or secondary to general toxicity; or
- the effect is a predictable consequence of the experimental model.

Finally, in interpreting complex studies, it is recognized that a WOE approach, combining the criteria outlined here to reach an overall judgment, is the optimal way of applying the evaluation process.

#### 3.6.1.3 Nature and Severity of Adverse Effects

The toxic effects of chemicals are of varying types and degrees of severity. Following an acute exposure to a toxicant, such as highly reactive and water soluble chemicals, effects on the upper and lower respiratory tract may be observed as POE effects. Toxic effects from airborne substances may also be due to exposure via the skin and eyes (e.g., irritation). Systemic effects may result from absorption and distribution of toxicant (e.g., moderately water-soluble or relatively water-insoluble chemicals) to a site distant from its entry point. Certain chemicals, after a single exposure, have the potential to produce delayed adverse effects.

Not all effects reported for a substance are necessarily considered adverse (e.g., adaptive biochemical responses such as enzyme induction) (Sherwin 1983, ATS 2000). Adverse effects may occur with a range of severity from mild (sensory or subjective effects, which are reversible) to severe (clinically significant pathological changes, disabling or strongly objectionable sensory effects, persistent or irreversible histological or functional damage), or even to life-threatening (OEHHA 2008). The OEHHA criteria for determining the severity of an inhalation effect is presented in Appendix B (OEHHA 2008). Similar criteria for different biological endpoints from available toxicity studies as NOAELs and less serious and serious lowest-observed-adverse-effect-levels (LOAELs)

have been provided by ATSDR (2007). Tables 3-1 to 3-17of ATSDR (2007) list seventeen organ or system categories and classifies the degrees of severity within the system categories.

It is noted that toxicity factors are set to protect the general public health and the biological endpoint of choice for determination will generally be a mild effect. However, a more severe effect may be used if it is in fact the most sensitive endpoint that occurs at the lowest exposure level (for example irreversible developmental effects), or if no data on mild effects are available. Under such circumstances, additional UFs may be used in order to provide adequate public health protection. This practice is consistent with those used by other agencies (USEPA 2002a, ATSDR 2007, and OEHHA 2008).

### 3.6.1.4 Listing of Adverse Effects

ATSDR (2007) lists a classification of endpoints as non-adverse, less serious, and serious effects to provide guidance for the derivation of its minimal risk levels (MRLs) (Sections 3.6.1.4.1 to 3.6.1.4.4). To provide more specific guidance and encourage more consistent MRL derivation, the ATSDR further presents seventeen system categories in greater detail. Refer to Tables 3-1 to 3-17of the *Guidance for the Preparation of a Twenty First Set Toxicological Profile* (ATSDR 2007) (www.atsdr.cdc.gov/toxprofiles/guidance/set_21_guidance.pdf) for the rationale for specific system categories, and the limitations for use of these categories per ATSDR. The TCEQ modifies the ATSDR list in the following subsections. However, this is not an exhaustive list, but is included to provide a general overview; as always best scientific judgment should be exercised.

#### 3.6.1.4.1 Non-Adverse Effects

- Weight loss or decrease in body weight gain of less than 10% in adult animals
- Weight loss or decrease in body weight gain of less than 5% in fetuses
- Changes in organ weight of non-target organ tissues that are not associated with abnormal morphologic or biochemical changes
- Increased mortality over controls that is not significant ($p>0.05$)
- Some adaptive responses

#### 3.6.1.4.2 Less Serious Effects

- Reversible cellular alterations at the ultrastructural level (e.g., dilated endoplasmic reticulum, loss of microvilli, myelin figures) and at the light-microscopy level (e.g., cloudy swelling, hydropic degeneration, fatty change)
- Mild necrosis (dependent upon location, distribution, and magnitude), metaplasia, or atrophy with no apparent decrement of organ function
- Mild to moderate serum chemistry changes (e.g., increased 1-3 and 3-20 times the normal ranges of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) are considered mild and moderate, respectively (Thapa and Walia 2007))
- Organ weight change in known target organ tissue that is not associated with morphologic or biochemical alterations

- Mild behavioral effects as measured by behavioral function tests
- Weight loss or decrease in body weight gain of 10-19% (assuming normal food consumption and when weight loss is due to a systemic effect of toxicant)
- Some adaptive responses (e.g., hepatic CYP p-450 induction)

#### 3.6.1.4.3 Transitional Effects (Between Less Serious and Serious)

Some mild to moderate effects (such as necrosis, atrophy, metaplasia, and serum chemistry alterations) could be classified as less serious or serious based on their reversibility, the organ affected, or the degree of associated dysfunction. The TCEQ will consider the degree of the response when distinguishing between less serious and serious effects.

#### 3.6.1.4.4 Serious Effects

- Death
- Clinical effects of significant organ impairment (e.g., convulsions, icterus, cyanosis)
- Moderate to severe morphologic changes (such as necrosis, metaplasia, or atrophy) in organ tissues that could result in severe dysfunction (e.g., marked necrosis of hepatocytes or renal tubules)
- Moderate to major behavioral effects as measured by behavioral function tests
- Weight loss or decrease in body weight gain of 20% or greater (assuming normal food consumption)
- Major serum chemistry changes (e.g., increased > 20 times the normal ranges of SGOT and SGPT (Thapa and Walia 2007))
- Major metabolic effects (e.g., ketosis, acidosis, alkalosis)
- Cancer effects

### *3.6.2 Definitions of PODs*

A review of regulatory and other scientific literature and of current practices conducted by Lewis et al. (2002) revealed a lack of consistency in definition and application of frequently used terms such as adverse effect, no-observed-effect level (NOEL), NOAEL, LOAEL, biologically significant effect or toxicologically significant effect. Table 3-3, adapted from USEPA (2002), defines these terms, which the TCEQ will generally use to promote consistency.

**Table 3-3 Definitions of POD Terms**

| Term | Definition |
|---|---|
| Point of Departure (POD) | The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMDL or BMCL), or a NOAEL or LOAEL for an observed incidence or change in level of response. |
| Benchmark Dose (BMD) or Concentration (BMC) | A dose or concentration that produces a predetermined change (called the benchmark response or BMR) in a specified response rate of an adverse effect compared to background. |
| BMDL OR BMCL | A statistical lower confidence limit on the dose or concentration at the BMD or BMC, respectively. The TCEQ uses a 95 % lower confidence level. |
| Benchmark Response (BMR) | A predetermined response rate change for an adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. For quantal responses (as opposed to continuous response) the change in response rate over background corresponding to the BMR is usually in the range of 5-10%, which is the limit of responses typically observed in well-conducted animal experiments. |
| No-Observed-Adverse-Effect Level (NOAEL) | The highest exposure level at which there are no biologically or statistically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects. |
| Lowest-Observed-Adverse-Effect Level (LOAEL) | The lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group. The highest exposure concentration which results in biological effects that are not considered adverse may be termed the LOEL which is identical to the NOAEL. |
| No-Observed-Effect Level (NOEL) | The highest exposure level at which there are no effects (adverse or non-adverse) observed in the exposed population, when compared with its appropriate control. |
| Free Standing NOAEL | A NOAEL not associated with any biological or statistical effect identified from a study with several dose levels or with only one dose level |

The POD can be a NOAEL or LOAEL for an observed incidence or change in level of response for a chemical (Figure 3-3). The NOAEL is the highest exposure level at which there are no biologically or statistically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Some effects may be produced at the NOAEL, but they are not considered adverse, as discussed in previous sections. Generally, the TCEQ considers the LOAEL as the lowest exposure level at which there are biologically and statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group. The NOAEL approach has been criticized because it does not use the full dataset of the dose-response curve and is dependent on choice of dose for study (i.e., spacing between doses). For studies with greater variation in endpoint measurement or smaller sample size, the NOAEL approach tends to result in a higher NOAEL being determined based on statistical comparison to the controls. In addition, some experimental studies only identify a LOAEL.

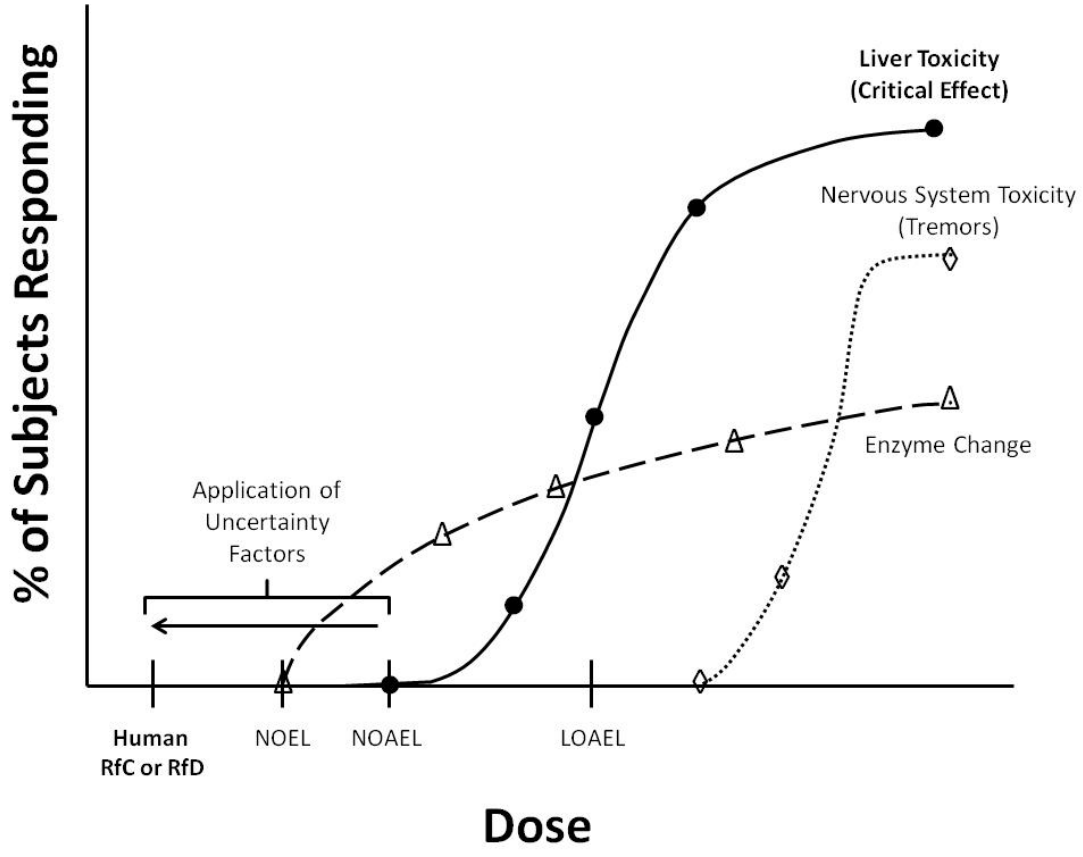


**Figure 3-3 Dose-response assessment for a chemical with a threshold MOA**

A dose may exist below the minimum health effect level for which no adverse effects occur. The USEPA typically assumes that at low doses the body's natural protective mechanisms prevent or repair any damage caused by the pollutant, so there is no ill effect at low doses. Even long-term (chronic) exposures below the threshold are not expected to have adverse effects. The dose-response relationship (the response occurring with increasing dose) varies with pollutant, individual sensitivity, and type of health effect (adapted from Exhibit 12-3B of USEPA 2004a).

If there exist multiple, non-identical NOAELs and LOAELs for the same compound and critical effect, the study of the best quality reporting the highest value for a NOAEL (preferred) or the lowest value for the LOAEL is used for the development of toxicity values. Scientific data as well as professional scientific judgment should be used to decide the most appropriate POD.

A NOAEL not associated with any biological or statistical effect identified from a study with several dose levels or with only one dose level (i.e., free-standing NOAEL) is typically unsuitable for derivation of a toxicity value (USEPA 1994a). However, the TCEQ must develop toxicity values for many chemicals with limited toxicity data. In many cases, the chemical is not very toxic, and even high doses or concentrations do not produce an adverse effect. A free-standing NOAEL without an associated LOAEL identified in the same study may be used in deriving a toxicity value, but only if there are no other suitable studies, and so long as the overall health hazard data (including any case reports or studies with shorter durations) for that substance are consistent with the free-standing NOAEL study. For example, another study may have identified a free-standing LOAEL just above the dose range tested in the study that identified a free-standing NOAEL and both evaluated similar endpoints.

### *3.6.3 Benchmark Dose Modeling*

As an alternative to the NOAEL/LOAEL approach for identifying a POD, a mathematical model can be used to fit the entire dose-response data for a chemical with a threshold MOA so that the concentration corresponding to an estimated incidence or change in level of response (i.e., BMD) as well as the BMDL (i.e., a statistical lower confidence limit on the dose at the BMD) from a dose-response model can be determined (Figure 3-4). The advantages of BMD modeling are it uses the full dataset of the dose-response curve, accounts for the greater uncertainty due to smaller sample size or greater variation, and can estimate a POD comparable to a NOAEL when a NOAEL cannot be established. However, BMD modeling also has some disadvantages. Travis et al. (2005) discusses the advantages and disadvantages of both the BMD and NOAEL approach. When possible, the TCEQ performs BMD modeling following established guidelines because of the advantages of this approach over the NOAEL/LOAEL approach (USEPA 2012b, 2000a, 1995). However, the TCEQ considers guidance from the NRC (2001):

> *Because of uncertainties that may be associated with extrapolations beyond the experimental data, the estimated values are compared with the empirical data. Estimated values that conflict with empirical data will generally not be used.*

The terms BMD and BMDL are used when performing benchmark modeling for oral exposure studies, while the terms BMC and BMCL are use for benchmark modeling for inhalation exposures. Similar mathematical modeling procedures are followed for choosing a POD for chemicals with a nonthreshold MOA including carcinogenic chemicals. Traditionally, the terminology differs for carcinogenic chemicals. The term effective dose (ED) is the central estimate and is analogous to the term “BMD” whereas the term lower bound of ED (LED) is the lower 95% confidence limit and is analogous to the term “BMDL. Refer to Section 5.7.3 for a discussion of choosing a POD for carcinogenic chemicals.

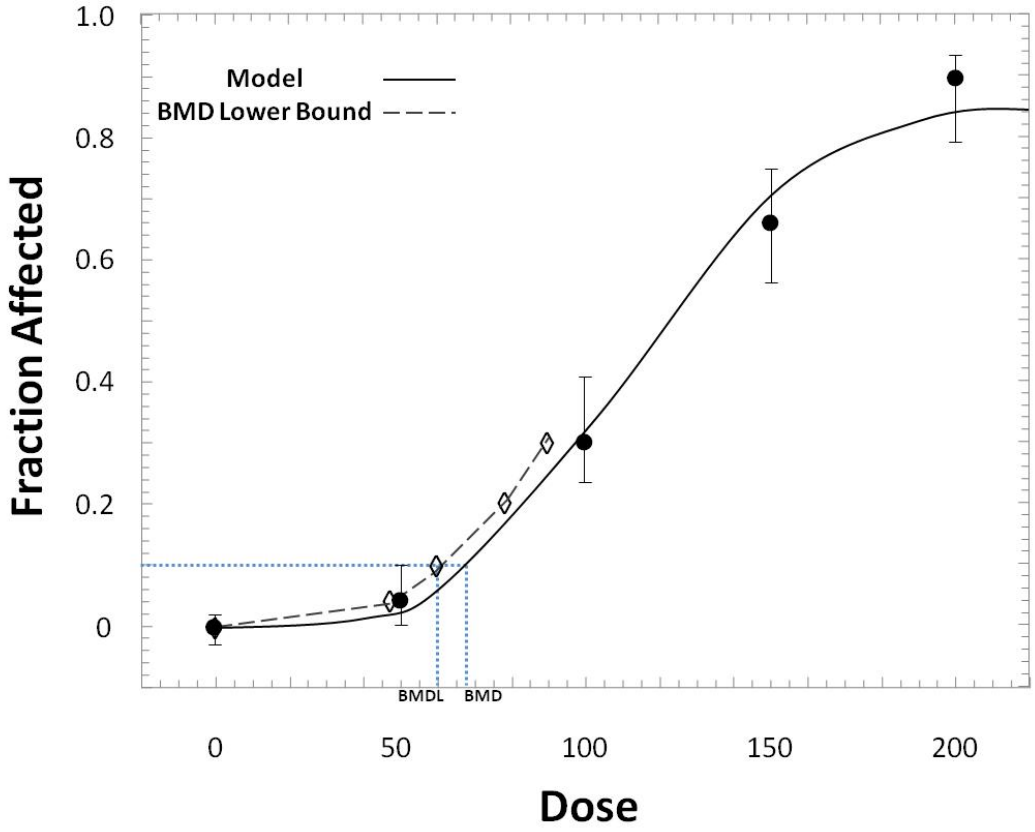


**Figure 3-4 Sample of a model fit to dichotomous data, with BMD and BMDL indicated**

The fraction of animals affected in each dose group is indicated by filled circles. The error bars indicate 95% confidence intervals for the fraction affected. The BMR for this example is an extra risk of 10%. The dashed curve indicates the BMDL for a range of BMRs. The dose labeled BMDL corresponds to the lower end of a one-sided 95% confidence interval for the BMD. (adapted from Figure 1 from USEPA 2000a)

Certain toxicity data are not amenable to BMD modeling. The quality of the experimental study as well as the nature of the data collected during the study determines whether the dose-response data can be modeled using BMD modeling (USEPA 2012b, 2000a, 1995) or whether a NOAEL/LOAEL approach is used. For example, when there is a maximum response at all doses, there are inadequate response data lower on the dose-response curve, then the data are not amenable to BMD modeling. When BMD modeling cannot be performed, acceptable exposure doses or concentrations are determined using the NOAEL or LOAEL as the POD.

### 3.6.3.1 Dichotomous Data

Dichotomous data are modeled using dichotomous models in the USEPA's BMDS software (Version 2.1.2 or a later version) and guidance in USEPA (2012b, 2000a). Model updates are available from www.epa.gov/ncea/bmds/index.html.

If there is an accepted level of change in the endpoint that is considered to be biologically significant, then that amount of change is chosen for determination of the POD (USEPA 2012b, 2000d). For dichotomous data, this level is referred to as the BMR. The level of the BMR chosen for BMD modeling is the lowest dose level that can be supported by the data. Typically, this lowest dose level is either the $BMR_{05}$ or $BMR_{10}$, which are observable levels of effect in the standard animal bioassay, as discussed by Barnes et al. (1995). For some epidemiological studies of sufficient quality, a $BMR_{01}$ or $BMR_{001}$ (Grant et al. 2009) may be adequately modeled.

Several investigators have compared the BMDL (1, 5, or 10%) to the NOAEL or LOAEL (Kimmel 1990, Farland and Dourson 1992, Gaylor 1992, Faustman 1996, Fowles et al. 1999, Filipsson et al. 2003). It has been suggested that an additional UF be applied to a BMDL if there is reason to believe it is comparable to a LOAEL (i.e., based on severity of the adverse effect or a flat dose-response curve). Since the BMR (1, 5, or 10%) should represent a response level of no significant concern, the corresponding BMDL should be comparable to the NOAEL rather than the LOAEL. Therefore, the TCEQ does not routinely apply an additional UF. However, severity of response is considered when determining the level of the BMR. If the endpoint of concern is more severe or detrimental, then a lower level BMR (e.g., 1% or 5%) is modeled in order to be health-protective. The steepness of the dose-response curve may also be considered in the choice of BMR. However, unless information about the MOA through which the toxic agent causes the particular effect is available, a level of the BMR should not be extrapolated to doses outside the tested dose range (Filipsson et al. 2003). Large extrapolations (e.g., to a 1% response level from a standard assay showing observable effect at the 10% level) are not appropriate. Additional information concerning consideration of severity of response when selecting the BMR level is provided by the CalEPA Department of Pesticide Regulation (DPR 2004a, 2004b). No matter what BMR level is chosen to model the data, the $BMD_{10}$ and $BMDL_{10}$ should be calculated and presented for comparison purposes as suggested by USEPA (2012b, 2000a).

#### 3.6.3.2 Continuous Data

Continuous data are modeled using continuous models in USEPA's BMDS software (Version 2.1.2 or a later version) and guidance in USEPA (2012b, 2000a, 1995). Model updates are available from www.epa.gov/ncea/bmds/index.html. The TCEQ does not usually attempt to change continuous data into dichotomous data and model the resulting dose-response curve with dichotomous models as it potentially results in loss of information about the magnitude of response and should generally be avoided (USEPA 2012b, 2000a). However, the TCEQ evaluates the most appropriate BMD modeling procedures on a case-by-case basis considering applicable guidance (e.g., USEPA 2012b) and the utility of the available approaches for continuous data contained therein (e.g., continuous models, hybrid approach).

In order to distinguish continuous data from dichotomous data, Dekkers et al. (2001) recommended the term "critical effect size" (CES) be used instead of the term "BMR," since for continuous data, the effect measure is expressed on a continuous scale. A CES defines the demarcation between non-adverse and adverse changes in toxicological effect parameters for continuous data (Dekkers et al. 2001). For example, a CES of 10% or

$CES_{10}$ for continuous data (i.e., a 10% change in the mean of a treated group compared to the control mean) is not the same as a BMR of 10% or $BMR_{10}$ (i.e., 10% of total animals responding for dichotomous data).

If there is an accepted level of change in a continuous endpoint that is considered to be biologically significant and sub-adverse (e.g., 10% decrease in body weight), then that amount of change is chosen for determination of the POD. Otherwise, the CES result for one SD ($CES_{1\ SD}$) is considered to be nonadverse. A $CES_{1\ SD}$ from control mean corresponds to an approximately 10% excess risk for individuals below the $1.4^{th}$ percentile or above the $98.6^{th}$ percentile of the control distribution for normally distributed effects (USEPA 2012b). No matter what CES response level is chosen to model the data, the $CES_{1\ SD}$ should be calculated and presented for comparison purposes as suggested by USEPA (2012b, 2000a).

## 3.7 Conduct Appropriate Dosimetric Modeling

When the POD for each key study is determined, adjustments are made to account for differences between experimental and desired exposure durations and/or differences in anatomy and physiology in experimental animals and humans, (i.e., the respiratory systems for inhalation exposure or gastrointestinal systems for oral exposures) including sensitive subpopulations such as children. For example, different respiratory mathematical dosimetry models have been used to account for chemical disposition, toxicant-target interactions, and tissue responses (USEPA 1994a, Jarabek 1995b, Hanna et al. 2001). A comprehensive biologically-based dose-response model links mechanistic determinants of chemical disposition, toxicant-target interactions, and tissue responses into an overall model of pathogenesis (Figure 3-5; most quantitative method). The proposed stages between exposure and response include processes relating exposure to consequent tissue dose (i.e., toxicokinetics) and processes that determine response to the tissue dose (i.e., toxicodynamics). If empirical data are not available to construct a comprehensive biologically-based dose-response model for a chemical (the vast majority of cases at present), then response can be related to exposure by incorporating and integrating as much mechanistic data as possible to allow a more accurate characterization of the pathogenic process. At the rudimentary level, response is related to exposure without consideration of internal dose (Figure 3-5, qualitative method).

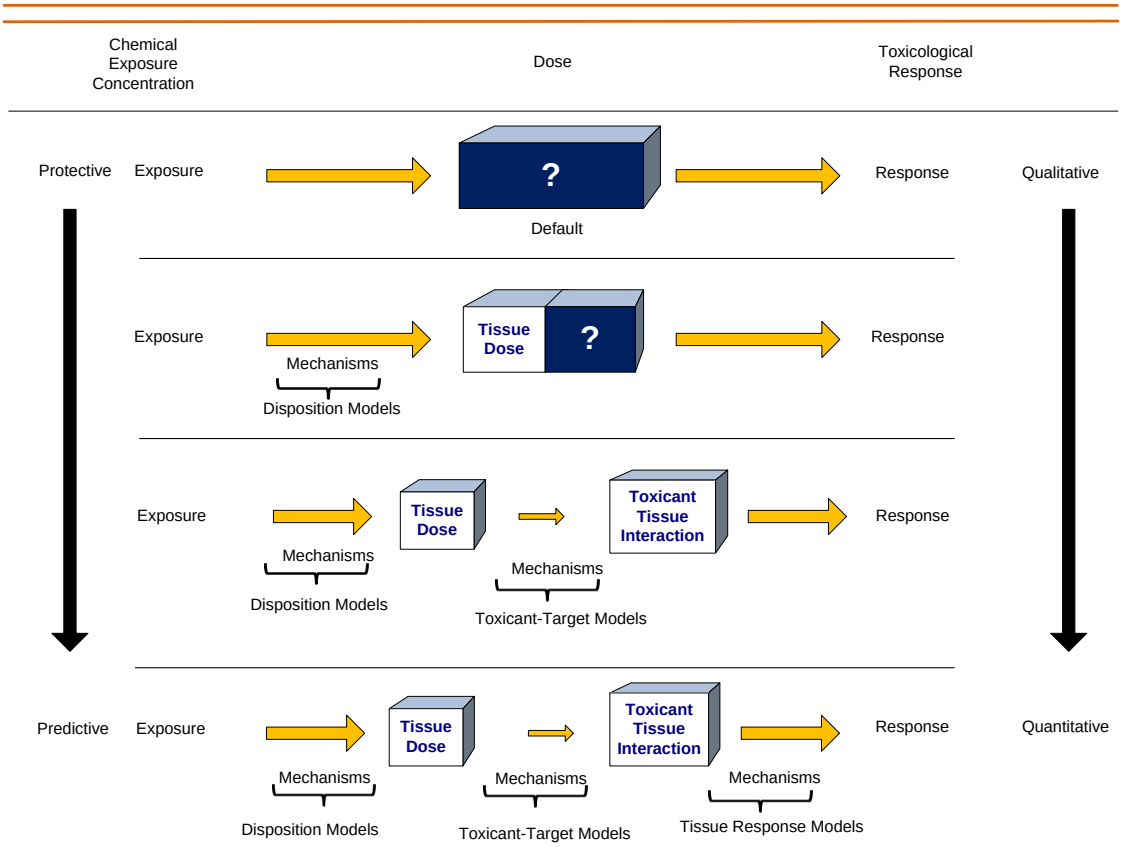


**Figure 3-5 Schematic characterization of the comprehensive exposure dose-response continuum**

This figure illustrates the evolution of protective to predictive dose-response estimates (adapted from Figure 1-2 from USEPA 1994a).

## *3.7.1 Physiologically-Based Pharmacokinetic Model*

Physiologically-based pharmacokinetic (PBPK) compartmental models are used to characterize pharmacokinetic (a.k.a. toxicokinetic) behavior of a chemical. Available chemical or agent partitioning data on blood flow rates and metabolic and other processes which the chemical undergoes within each compartment are used to construct a mass-balance framework. The TCEQ will use verified PBPK models to perform dosimetric adjustments for both oral and inhalation exposure following guidance provided by USEPA (2006a). USEPA (2006b) provides guidance on assessing the impact of human age and interindividual difference in physiology and biochemistry.

As with inhalation exposure, PBPK modeling is the preferred approach for dosimetric adjustments when assessing oral exposure (USEPA 2011a). For inhalation exposure, PBPK models have principally been used to describe a chemical's systemic distribution (i.e., gas absorption, as opposed to particles, in the respiratory tract) and have focused on the limiting case of gases with high lipid solubility where uptake is determined by perfusion (e.g., volatile organic compounds). The respiratory tract is regarded as a conduit to pulmonary absorption and systemic delivery of dose in particular for effects occurring systemically. Therefore, blood flow, not the diffusional mass transport across

the blood-gas barrier, is considered to be of prime importance in achieving equilibrium concentrations in the body. In addition to PBPK, there are several types of inhalation dosimetry models.

## *3.7.2 Inhalation Models*

In order to understand inhalation dosimetry models, a distinction must be made between the equilibrium assumption in which transport is dependent on regional blood flow and dynamic models in which transport occurs across a concentration gradient near the transport barrier. The following sections which are based on information presented by Hanna et al. (2001) briefly discuss the differences between basic inhalation dosimetry models and provide general considerations for choosing model structures.

### 3.7.2.1 Flow-Limited or Perfusion-Limited Model

Flow-limited or perfusion-limited models are relevant to lipid-soluble gases that are absorbed in the alveolar region of the lung. The permeability of the transport barrier (or membrane) is significantly greater than the flow or perfusion to the transport barrier so the transport of chemicals to the systemic circulation is dependent on the flow volume or perfusion rate. The alveolar ventilation rate determines the alveolar gas-phase concentration, and the equilibrium partition coefficient of the gas is used to establish the equilibrium between blood concentration and the alveolar gas concentration. Blood flow, blood distribution, and the equilibrium condition determine transport to systemic compartments.

### 3.7.2.2 Membrane-Limited Transport Model

In a membrane-limited transport model, the membrane or transport barrier itself limits the rate at which the chemical permeates the barrier to enter the systemic circulation or to act on the tissue itself. Perfusion rate does not limit intracellular or tissue concentrations. Equilibrium is not established since it is assumed that a concentration gradient exists between the tissue and blood. Diffusion within the blood is typically ignored because it is of minor significance compared to the gradient in the tissue. Diffusion in the gas stream itself may result in the establishment of a significant concentration gradient that also affects the rate of uptake. Therefore, this case requires a model capable of describing the dynamic transport process both in the gas phase and within the tissue.

### 3.7.2.3 Distributed Parameter Model

Distributed parameter models have been used to describe the uptake of gases that are water-soluble and/or reactive within the airway tissue. Since these gases distribute regionally within the airways, models must differentiate between the various respiratory tract regions rather than focus on the blood-gas exchange region alone. However, it is possible for a metabolite to be sufficiently stable to distribute to the systemic circulation. The transport of these gases is determined by the transport of the gas along the concentration gradient from within the gas stream extending laterally to the liquid/tissue compartment. The equilibrium assumption used in flow-limited or perfusion-limited models is inappropriate. In distributed parameter models it is assumed that a quasi-steady-state concentration gradient exists.

### 3.7.2.4 Gas-Phase Limited Transport Model

The gas-phase limited transport model has been used for chemicals where the tissue is almost an infinite sink so the gas-phase concentration gradient completely controls the rate of uptake (i.e., highly water-soluble gases that are readily absorbed by the airway lining and gases that react nearly completely within the airway lining). The rate at which the gas can cross the gas-phase concentration gradient, or gas-phase transport barrier, to the tissue limits the rate of absorption. As a consequence, equilibrium cannot be assumed between the gas-phase concentration and the transport barrier of the airway surface because the gas-phase concentration gradient represents a barrier to transport and requires the mass to diffuse across this barrier.

### 3.7.2.5 Considerations of Hierarchy of Model Structures

Any method used to extrapolate dose across species must be sufficiently robust to describe the exposure-dose relationship in animal species and must also predict human dose to allow dosimetric adjustment(s) to be made. A dosimetric model must be able to describe the anatomy, physiology, and metabolism of the species of interest; however, introducing unnecessary parameters may contribute to additional uncertainty especially when experimental data are used to "fit" the model. In addition, model verification is essential to the modeling framework as discussed in Section 3.2.3 of the RfC Methodology. Every effort should be made to obtain a solution appropriate to the physical/chemical properties of the specific gas.

The following are considerations of hierarchy of model structures for exposure-dose response and interspecies extrapolation (USEPA 1994a):

**Optimal Model Structures**

- Structure describes all significant mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
- Uses chemical-specific and species-specific parameters
- Dose metric(s) described at level of detail commensurate with toxicity data

**Default Model structure**

- Limited or default description of mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
- Uses categorical or default values for chemical and species parameters
- Dose metric(s) at generic level of detail

Optimal models are preferred to default models. The development of calibrated inhalation optimal/preferred dosimetry models with predictive capability for hazard assessment is an active, ongoing area of research (USEPA 2006). The TCEQ uses available results from calibrated, predictive PBPK model or other inhalation dosimetry models, as discussed by Hanna et al. (2001) and Jarabek (1995b), to perform dosimetric adjustments from laboratory animal data to a human equivalent concentration (HEC) or to perform exposure duration adjustments for both acute and chronic ReVs. Preference will be given to inhalation dosimetry models published in the scientific literature. Default procedures discussed in Chapter 3, Chapter 4, and Chapter 5 are followed only if information to

perform PBPK or other optimal/preferred inhalation dosimetry models is not available or if time and resource constraints do not allow for the development of a PBPK model. Examples of inhalation dosimetry models developed after the RfC Methodology was published (USEPA 1994a) that are used by the TCEQ based on MOA, chemical-specific, and species-specific information are:

- The International Commission on Radiological Protection 66 Human Respiratory Tract Model for Radiological Protection (ICRP 66 1994). Snipes et al. (1997) used the ICRP66 human respiratory tract dosimetry model to investigate lung burdens from exposures to environmental aerosols.
- The Multiple-Path Particle Dosimetry (MPPD) Model, version 2, for performing dosimetric adjustments from rat to human (CIIT 2004). Jarebek et al. (2005) used the 2004 MPPD model to investigate different aspects of dosimetric adjustments of inhaled poorly soluble particles. When using the MPPD Model, there are some different-than-default settings the TCEQ uses.
  1. The default minute volume ($V_E$) used by the Model for humans (7,500 mL/min) does not correspond to the default value (13,800 mL/min) given by USEPA (1994a), which is used in the RDDR calculation. Neither USEPA (1994a) nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values which correspond to the default USEPA $V_E$. These values are needed for input into the MPPD so that both the MPPD Model and RDDR calculation use the same human $V_E$. Therefore, the TCEQ used human tidal volume and breathing frequency values from de Winter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculated the tidal volume (842.74 mL/breath) and breathing frequency (16.375 breaths/min) values corresponding to the default USEPA $V_E$ for input into the MPPD Model. See the Nickel and Inorganic Nickel Compounds DSD Appendix F for calculations (TCEQ 2011).
  2. The default for the MPPD program is to not have the inhalability adjustment factor checked. Due to interspecies differences in the inhalability of certain particulate sizes (Menache et al. 1995), which may affect interspecies dosimetric adjustment, in general, the TCEQ will opt to check this box.
- A hybrid computational fluid dynamics and PBPK model as discussed by USEPA (2009b).

## 3.8 Default Exposure Duration Adjustments

### *3.8.1 Acute and Chronic Inhalation Exposures*

If an experimental study is available for the specific exposure period being evaluated, no adjustment for exposure duration is required. However, experimental studies may involve exposure durations in humans or experimental animals that are different than the desired exposure duration (i.e., the POD from the original study should be adjusted to the desired exposure duration ($POD_{ADJ}$)). For acute exposures, it may be necessary to adjust data

from experiments conducted at different short-term exposure durations to a 1-h or 24-h exposure duration. Chapter 4 discusses exposure duration adjustments that are unique for specific types of chemicals and health effects from acute exposures. Woodall et al. (2000) provides several examples of how to perform acute duration adjustments using different methods and discusses the uncertainty associated with acute duration adjustments. For chronic exposure, it may be necessary to adjust discontinuous human or animal exposure regimens to continuous exposure. Chapter 5 discusses exposure duration adjustments that are unique for chronic exposures. Common procedures and principles for acute or chronic exposure durations adjustments are discussed in the following subsections.

In the absence of a calibrated, predictive PBPK or other inhalation dosimetry model, duration adjustments are based on the relationship of the product of concentration and time. However, certain health effects such as irritation, narcosis, or asphyxia may be more dependent on concentration than duration so exposure concentrations are not adjusted for these health effects. For a chemical where concentration and duration both play a role in producing an adverse effect, the magnitude of response to a chemical exposure can be correlated with both the duration of the exposure and concentration since the internal dose of a chemical at the target tissue, and therefore the response, is dependent on the combination of these components. Haber's rule (Equation 3-1) states the product of the exposure concentration (C) and exposure duration (T) required to produce an adverse effect is equal to a constant level or severity of response (K) (Rinehart and Hatch 1964):

**Equation 3-1 Haber's Rule**

$$C \times T = K$$

The most commonly used "K" level of response used to relate C x T is an $LC_{50}$ value, but other constant biological endpoints could be the used. Exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant K. This cumulative exposure constant produces a specific quantitative and qualitative response. However, an assessment by ten Berge et al. (1986) of $LC_{50}$ data for certain chemicals revealed that there was an exponential relationship between exposure concentration and exposure duration for specific chemicals. Therefore, it is more appropriate to express the relationship as $C^n \times T = K$, where "n" represents a chemical- and endpoint-specific exponent (Figure 3-6). When the health endpoint evaluated was lethality, ten Berge et al. (1986) showed that only one of 20 chemicals had a value of "n" less than 1, whereas the other chemicals had values that ranged from 1 to 3.5. Haber's rule is the special case where n = 1 and both concentration and duration play an equal role in the induction of a specific adverse health effect(s).

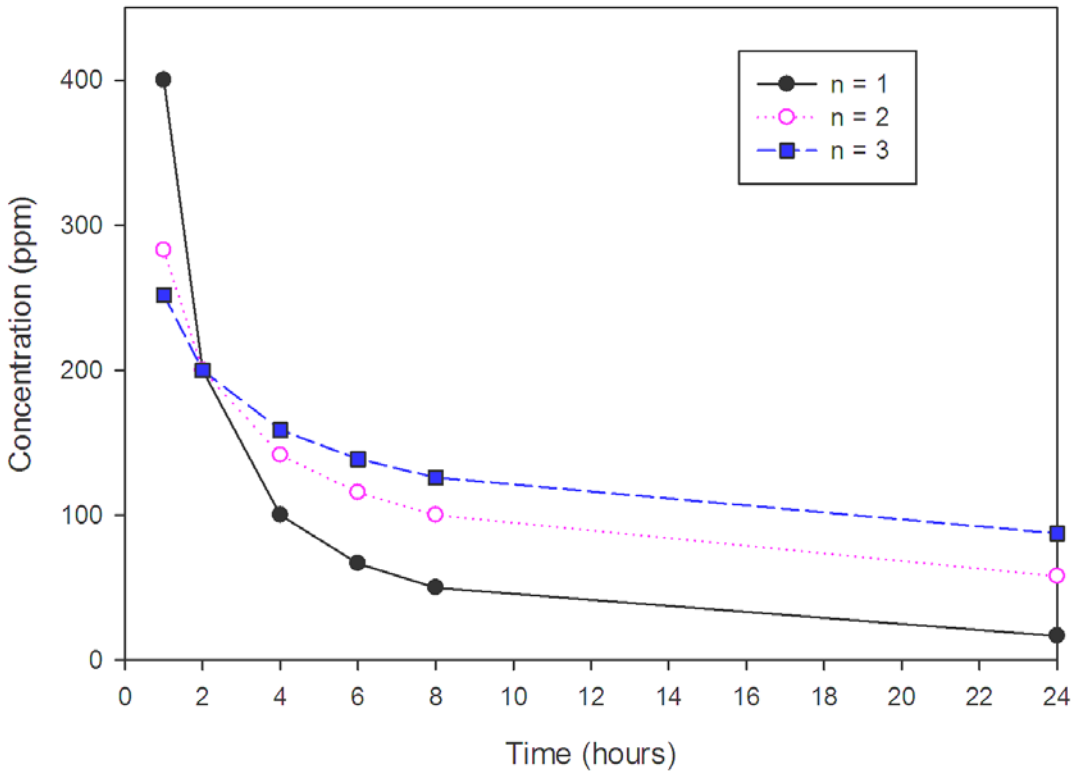


**Figure 3-6 $C^n$ x T = K for different values of "n"**

This figure illustrates the relationship of $C^n$ x T = K for a 1-, 4-, 6-, 8-, and 24-h exposure duration, for different values of "n" for a hypothetical case where experimental data are available for a 2-h exposure duration to an air concentration of 200 ppm. When extrapolating from a 2-h exposure to a 1-h exposure: if n = 1, the adjusted concentration is approximately 400 ppm; if n = 2, the adjusted concentration is approximately 300 ppm, whereas if n = 3, the adjusted concentration is approximately 250 ppm.

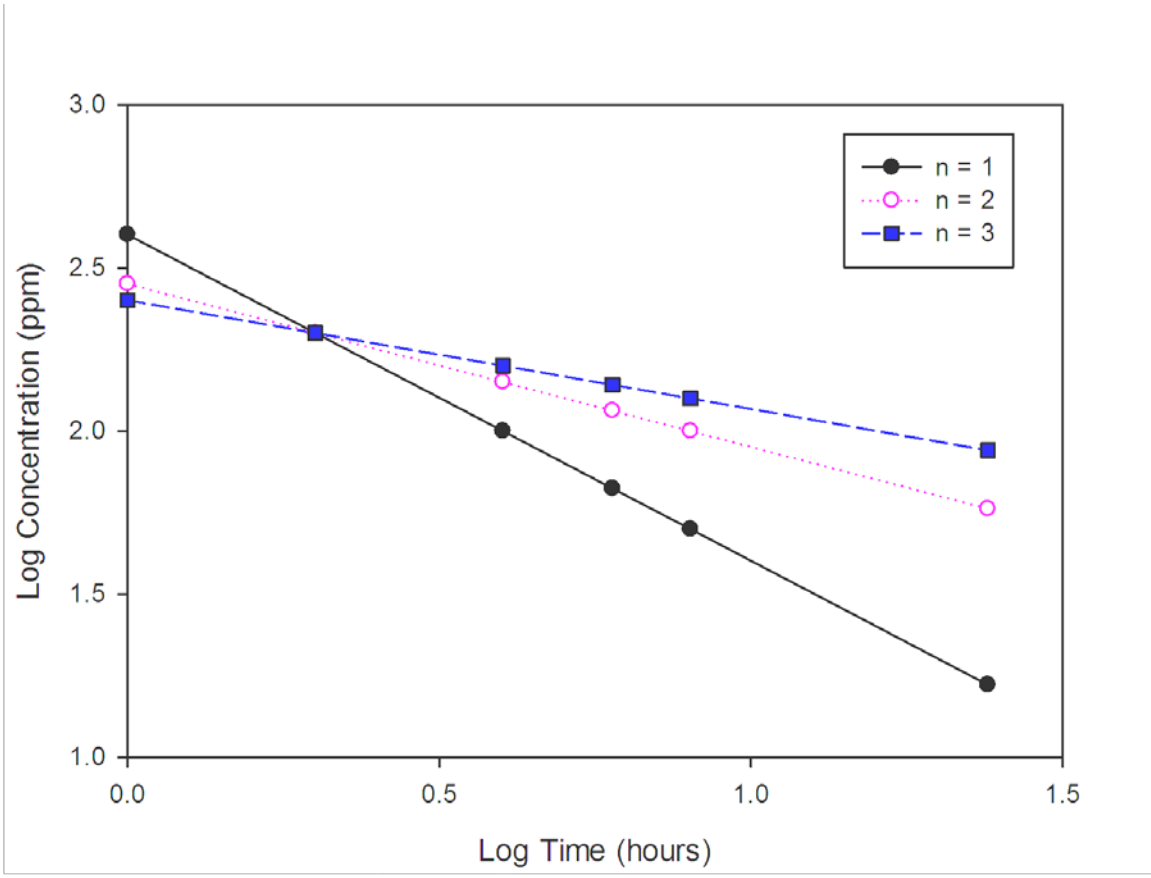


**Figure 3-7 n Log C + Log T = K for different values of "n"**

Figure 3-7 illustrates the linear relationship between log concentration versus log time for the data from Figure 3-6.

Since the relationship between C and T is linear on a log-log scale (Figure 3-7) and could easily be solved by simple calculations, toxicologists in the past have readily used this relationship to perform duration adjustments.

If an acceptable "n" value is not available from the scientific literature, the TCEQ derives a chemical- and endpoint-specific "n" value if adequate experimental data at different exposure durations are available. C and T data are modeled using the ten Berge model in USEPA's BMDS software (Version 2.1.2 or a later version) and procedures for curve fitting and statistical testing of the generated curve recommended by the NRC (2001). The experimental data are deemed to be adequate if the different exposure durations of the studies are similar to the desired exposure duration; the studies evaluate the appropriate health effect endpoint; and the quality and quantity of the data are adequate (NRC 2001). Categorical regression can also be used to perform duration adjustments, as discussed by Woodall et al. (2000).

Exposure duration adjustments using this procedure are only conducted over a limited time extrapolation. For example, a subacute exposure study would not be extrapolated to a chronic exposure nor would a 3-day continuous exposure duration study be extrapolated to a 1-h exposure duration. A subacute study could be used to develop 1-h ReV (Section

4.2.3). If a chemical- and endpoint- specific value of "n" cannot be determined, then conservative default procedures specific to short-term duration adjustments as discussed in Chapter 4 or long-term duration adjustments as discussed in Chapter 5 are used to perform duration adjustments.

### *3.8.2 Chronic Oral Exposures*

Duration adjustments for chronic oral exposures are discussed in Section 5.2.

### *3.8.3 Adjustments for a Free-Standing NOAEL*

In some cases, only a free standing NOAEL is available for a chemical, so information on the slope of the dose-response relationship for the chemical is unknown. When using a free-standing NOAEL, duration adjustments from a shorter exposure duration to a longer exposure duration will be conducted using "n" = 1, since it results in a more conservative value. However, longer-term data should also be examined to decide if the extrapolation is too conservative and the numbers adjusted accordingly. Duration adjustments will not be conducted from a longer duration study to a shorter duration study unless there are data for shorter exposure durations showing that an adjustment is scientifically defensible.

## 3.9 Default Dosimetry Inhalation Adjustments from Animal-to-Human Exposure

Dosimetric adjustments from animal-to-human exposure differ for inhalation and oral exposure (USEPA 2002a). Therefore, these adjustments are discussed separately. The following sections discuss default dosimetry adjustments from animal-to-human exposure for both acute and chronic ReVs and chronic URFs for inhalation exposure. The default dosimetry adjustments from animal-to-human exposure used to develop chronic RfD and SFo values for oral exposure are discussed in Section 5.3.

Anatomy and physiology differ between the respiratory systems of experimental animals and humans. Therefore, dose-response data obtained from animal studies should be adjusted to be relevant for humans. Ideally, detailed MOA, chemical-specific, and species-specific data would be available so that PBPK models or optimal/preferred inhalation dosimetry models (Section 3.7) could be used to describe the disposition of the chemical in humans based on the experimental animal species (Hanna et al. 2001). However, when such data are not available, simplified mathematical models based on the generalized mass transport model can be used as discussed in the RfC Methodology. These models in reduced form are used in conjunction with a category scheme for gases based on an evaluation of a chemical's physical/chemical and toxicologic properties to calculate default animal-to-human dosimetric adjustment factors (DAFs). A framework for choosing model structure as well as calculating different default DAFs is based on the fundamental knowledge that absorption rate is determined by water solubility and reactivity. Chapter 3 and Appendices G-J of the RfC Methodology discuss issues relating to particles, the categorization scheme of gases, and the simplified assumptions in the inhalation dosimetry models that were adopted in order to calculate DAFs for the

respiratory region. It is essential to refer to the RfC Methodology (USEPA 1994a) for a thorough understanding of these default dosimetric adjustments.

Depending on whether the chemical is a gas or particle, PODs derived from animal studies are adjusted using DAFs for respiratory tract regions to account for these differences as follows (Equation 3-2):

**Equation 3-2 $POD_{HEC}$ Derived from Animal Studies**

$$POD_{HEC} = POD_{ADJ} \times DAF_r$$

Where:

$POD_{HEC}$ = human equivalent concentration POD
$POD_{ADJ}$ = POD from animal studies, adjusted for exposure duration
$DAF_r$ = dosimetric adjustment factor for respiratory tract region

Depending on the physical/chemical characteristics of gases, the $DAF_r$ is either the regional gas dose ratio ($RGDR_r$) or the ratio of the blood:gas partition coefficient in the experimental species to the blood:gas partition coefficient in humans ($(H_{b/g})_A/(H_{b/g})_H$). For particles, the $DAF_r$ is the regional deposited dose ratio ($RDDR_r$). The $DAF_r$ accounts for the animal-to-human differences in regional deposition and absorption within the respiratory tract (i.e., extrathoracic (ET), trachiobronchial (TB), pulmonary (PU), thoracic (TH), or Total). The following sections briefly discuss the $DAF_r$ for gases and particles. Although the selected dose metric may differ between acute and chronic evaluations (e.g., peak concentration may be more appropriate than area-under-the-curve, or deposited dose may be more appropriate than retained dose (Jarabek 1995a, Jarabek et al. 2005), application of these dosimetric adjustments is the same for acute and chronic exposure.

### *3.9.1 Default Dosimetry Adjustments for Gases*

The physical/chemical properties of a chemical, such as reactivity and lipid and water solubility, influence whether gaseous toxicants affect the respiratory system (POE effects) or more distal organ systems. These properties also determine the effective dose achieved in each respiratory region (i.e., ET, TB, or PU). Table 3-4 lists the gas category scheme including physical/chemical characteristics, toxicokinetic properties, and default model assumptions.

**Table 3-4 Gas Category Scheme Specifies Dosimetric Adjustments***

| Category | Description |
|---|---|
| Category 1: | |
| Physical/chemical characteristics: | Highly "reactive" and water soluble |
| Toxicokinetic properties: | Interact with the respiratory tract as the portal of entry |
| Default model: | Three respiratory-tract compartments<br>Uptake defined by regional overall mass-transfer coefficient |
| Category 2: | |
| Physical/chemical characteristics: | Water soluble, but some blood accumulation can occur |
| Toxicokinetic properties: | Both respiratory and remote effects |
| Default model: | Structure includes both respiratory-tract compartments and remote distribution<br>Uptake defined by overall mass-transfer coefficient and flow-limited perfusion distribution |
| Category 3: | |
| Physical/chemical characteristics: | Poorly water soluble |
| Toxicokinetic properties: | Remote effects |
| Default model: | Respiratory tract depicted as one compartment<br>Uptake defined by partition coefficient and flow-limited perfusion |

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Category 1 includes gases that are highly water soluble and undergo rapid, irreversible reactions in the respiratory tract (e.g., hydrogen fluoride, chlorine, formaldehyde, and volatile organic acids and esters). Category 1 gases often exert POE effects. Category 2 includes moderately water-soluble gases that may remain within the respiratory system and/or migrate within the blood to distal organ systems (e.g., sulfur dioxide, xylene, propanol, and isoamyl alcohol). Category 3 includes gases that are relatively insoluble in water (e.g., 1,3-butadiene and dichloromethane). Inhaled Category 3 gases may be toxic to organ systems distal to the respiratory system.

For Category 1 gases, the $DAF_r$ for inhaled gases is the $RGDR_r$. When the critical effect is in the extrathoracic (ET) respiratory tract region, which includes the nasal and oral

passages, pharynx, and larynx, a default DAF of 1 will be applied. Internal dose equivalency in the ET region for rats (and other laboratory animals) and humans is achieved through similar external air exposure concentrations, not external air exposure concentrations adjusted by the ratio of ventilation (VE) to surface area (SA) (see Equation 3-3). The DAF of 1 is based on information on animal-to-human inhalation gas dosimetric adjustments from recommendations in USEPA (2009b, 2011c, 2012a). These three USEPA documents summarize new scientific developments and advancements in animal-to-human inhalation dosimetry for gases and vapors from those previously provided in the RfC Methodology (USEPA 1994a).

For the tracheobronchial (TB) and pulmonary (PU) regions, the DAFr for inhaled gases is the $RGDR_r$, which is defined as the ratio of regional gas dose in the experimental animal species to that of humans for the respiratory region of interest $(RGD)_A/(RGD)_H$ (USEPA 1994a). Based on USEPA (2009b, 2011c, 2012a), no change to dosimetric adjustments for the TB and PU regions were made. The USEPA (2009b, 2011c, 2012a) review supported principles and default procedures outlined in the RfC Methodology (USEPA 1994a) for these regions.

The relevant dosimetric adjustment is provided by this gas dose ratio in the respiratory region of interest (i.e., where the POE effects are observed). After the appropriate $RGDR_r$ is determined, the $POD_{HEC}$ is calculated as follows (Equation 3-3):

**Equation 3-3 Dosimetric Adjustment for Category 1 Gases**

$$\mathrm{POD_{HEC}} = \mathrm{POD_{ADJ}} \times \mathrm{RGDR_r}$$

Where:

$\mathrm{RGDR_r} = \frac{(\mathrm{RGD})_\mathrm{A}}{(\mathrm{RGD})_\mathrm{H}}$ = the ratio of regional gas dose in the experimental animal species to that of humans for the region of interest.

For Category 3 gases, on the other hand, the adverse effect of interest is systemic, rather than POE. In this situation, the regional gas doses are not the relevant basis for dosimetric adjustment. Rather, movement of gas from the respiratory tract into the blood in the alveolar region is important. For Category 3 gases the $DAF_r$ is the ratio of the blood:gas partition coefficient in the experimental species to the blood:gas partition coefficient in humans $(H_{b/g})_A/(H_{b/g})_H$ (Equation 3-4):

**Equation 3-4 Dosimetric Adjustment for Category 3 Gases**

$$\mathrm{POD_{HEC}} = \mathrm{POD_{ADJ}} \times \frac{(\mathrm{H_{b/g}})_\mathrm{A}}{(\mathrm{H_{b/g}})_\mathrm{H}}$$

Where:

$H_{b/g}$ = ratio of the blood:gas partition coefficient
A = animal
H = human

There is no change to dosimetric adjustments for systemic health effects based on findings in USEPA (2009b, 2011c, 2012a). Modeling and partition coefficient

information suggests that the default DAF of 1 is appropriate, although it may be conservative (USEPA 1994a, USEPA 2012a).

More specific equations and information needed to calculate the $DAFs_r$ and determining when a default value is appropriate can be found in the RfC Methodology and related guidance document (USEPA 1994a, USEPA 2002a, USEPA 2009b, USEPA 2011c, USEPA 2012a). Dosimetry for Category 2 gases is under review by USEPA. Until new findings suggest otherwise, the TCEQ conducts dosimetric adjustments for Category 2 gases using either Category 1 or 3 dosimetry equations, whichever is most relevant. The decision of which one to use is based on whether the adverse effect occurs in the respiratory system or target organs distal to the respiratory system.

### *3.9.2 Default Dosimetry Adjustments for Particulate Matter*

Version 2.1, 2009 Multiple-Path Particle Dosimetry Model (Anjilvel and Asgharian 1995, RIVM 2002, CIIT 2004, ARA 2009) or the latest updated model is used for dosimetry adjustments for PM if the experimental animal is the rat and the necessary MOA and chemical-specific information is available. This model is appropriate for the derivation of both short- and long-term exposures if the proper dose metric is used. For example, normalized retained particle mass is more applicable than normalized deposited particle mass for chronic exposure (Jarabek et al. 2005).

For other animal species or when the necessary MOA and chemical-specific information are not available, the TCEQ uses the RDDR software for PM and procedures recommended in the RfC Methodology (USEPA 1994a). According to the RfC Methodology, the RDDR adjusts for the effective dose in a particular region of the respiratory tract as follows (USEPA 1994a) (Equation 3-5):

**Equation 3-5 RDDR**

$$RDDR_r = \frac{(V_E)_A}{(V_E)_H} \times \frac{DF_A}{DF_H} \times \frac{NF_H}{NF_A}$$

Where:

$RDDR_r$ = Regional Deposited Dose Ratio
$V_E$ = minute volume (mL/minute)
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor
A = animals
H = humans

This calculation accounts for breathing parameters and deposition of particles. For the respiratory tract, deposition fraction (DF) is the ratio of the number or mass of particles deposited in the respiratory tract to the number or mass of particles inhaled. Regional deposition fractions are specific to particles deposited in the region of interest (see Table G-1 of USEPA 1994a), which is affected by deposition in regions through which the particles have already passed (USEPA 1994a). Surface area (SA is usually expressed in $cm^2$) is the recommended default normalizing factor (NF) for adverse effects in any or all regions of the respiratory tract, while body weight is used as the default for NF to

evaluate extrarespiratory effects (USEPA 1994a). The $RDDR_r$ may be extrathoracic ($RDDR_{ET}$), thoracic ($RDDR_{TH}$), tracheobronchial ($RDDR_{TB}$), pulmonary ($RDDR_{PU}$), the total respiratory tract or extrarespiratory. The $RDDR_{ET}$ includes the region from the external nares to the beginning of the trachea, and the $RDDR_{TH}$ includes the tracheobronchial ($RDDR_{TB}$) and pulmonary ($RDDR_{PU}$) regions. When justified by available data, use of the $RDDR_{TB}$ and $RDDR_{PU}$ in lieu of the $RDDR_{TH}$ can distinguish deposition and effects within the thoracic region.

## *3.9.3 Experimental and Ambient PM Exposures Differences*

There are a number of airborne chemical compounds that are present as PM ranging in size from 0.005-100 μm. Particles of concern for human health include coarse (2.5-10 μm) and fine (≤ 2.5 μm) particles. National Ambient Air Quality Standards (NAAQS) have been established by the USEPA to protect human health from exposure to both coarse and fine PM (USEPA 2004b). The TCEQ seeks to further protect human health by ensuring that chemicals comprising PM do not exceed levels that might cause adverse effects.

DSDs developed for particulate chemicals will report the PM size(s) from the experimental studies utilized to derive the inhalation toxicity factors in the main summary tables. In the event that an exceedance of an AMCV or ESL occurs for monitored or modeled PM levels, respectively, and significant differences in PM size, PM size distribution, and/or chemical form exist, further evaluation is necessary to better assess public health risk. The RfC Methodology (USEPA 1994a) discusses procedures that may be followed to evaluate differences between experimental and ambient exposures (Section 4.3.5.3 Additional Issues for Particle Dosimetry, page 4-41 of USEPA 1994a).

## *3.9.4 Child/Adult Risk Differences in Inhalation Dosimetry*

### 3.9.4.1 Comparison of Child/Adult Differences

#### 3.9.4.1.1 USEPA (2011c)

In 2011, USEPA evaluated developments and advancements in gas dosimetry since their 1994 RfC methodology was finalized. The RfC methodology concluded the $UF_H$ was sufficient to incorporate the range of response variability in human populations, including children. USEPA (2011c) found that methods are generally consistent in finding that there are higher inhaled doses in children, which may be in the range of up to 2-fold more than adult. However, in general, this range is within that built into the toxicokinetic portion ($UF_{H\text{-}k}$) of the $UF_H$. USEPA (2011c) concluded that insufficient quantitative evidence exists to revise the RfC methodology specifically for children. However, there are some chemicals for which children can exhibit a greater degree of sensitivity than adults. In those cases, they recommend consideration of alternative approaches or adjustments (e.g., PBPK models, flow models).

#### 3.9.4.1.2 Ginsberg et al. (2008)

Ginsberg et al. (2008) published a paper discussing different modeling approaches for estimating the dosimetry of inhaled toxicants in children. Some general findings from different modeling approaches indicate:

- For particle dosimetry, the difference in dose/surface area between children and adults is less than 2 for the ET region whereas for the TB region, children have a smaller dose/surface ratio. For the PU region, children had greater than three times higher dose/surface area for particles <1 micron. For retained particle dose (more important for chronic exposure than acute exposure), 14-year olds had consistently less retained dose than those of adults. Estimates for retained dose for 3-month olds are consistently higher than for adults (by <2x), and 3-year olds are in the middle.
- The impact of differences in amount of oronasal breathing is an important uncertainty.
- Dosimetry modeling for reactive gases did not show marked child/adult differences although this was dependent on the ventilation rates used in the modeling exercise. Garcia et al. (2009) using CFD nasal dosimetry modeling found that for formaldehyde (representative of other reactive, water-soluble gases), there was only a 1.6-fold difference between five adults and two children (age 7-8 years old).
- Internal dosimetry for Category 3 gases may be greater in children than adults with the difference dependent on the chemical's blood:air partition coefficient, rate of hepatic metabolism, and whether the parent compound or metabolite is of most concern.

#### 3.9.4.1.3 Haber et al. (2009)

Haber et al. (2009) (Appendix C *White Paper on Child-Adult Differences in Inhalation Dosimetry of Gases: Application to Selected Systemically-Acting Volatile Organic Chemicals*) presented a draft framework for evaluating age-related differences in inhalation dosimetry for systemically-active volatile organic compounds and the resulting impact on internal dose (Figure 3-8). The framework provides an approach to thinking about relative dose to child and adult. The broader framework and equations can be enhanced with additional chemical-specific information when appropriate when there may be a window of increased susceptibility. The White Paper was the result of three peer consultations and several Meeting Reports (TERA 2005a, 2005b, 2005c, 2007, 2008). Case studies were conducted to demonstrate the potential quantitative differences between children and adults for chemicals for which the parent, reactive metabolite, or stable metabolite was the toxic moiety of concern (Figure 3-8). Generally, the primary concern for toxicokinetic differences between children and adults is for the first year of life, when metabolism and renal clearance are undeveloped. Other conclusions are:

- While differences can produce greater or lesser risks for children relative to adults, from an applied perspective, the difference is most important when children are deemed to be at greater risk. If the window of susceptibility falls during childhood, the internal dose during that period of time is a key determinant of response, and it is important to consider the relative internal dose to children and adults for a given air concentration, regardless of the total exposure duration.

- For most chemicals, the ratio of mean child:mean adult was 2 or less, but the ratio can get large if the active form is a stable metabolite that is cleared efficiently in adults, but not in children.
- Steady state equations provided in the White Paper provide estimates of relative dose for common industrial chemicals similar to those obtained using sophisticated models. These equations can provide rough estimates of relative dose for other chemicals with key data (partition coefficient, active form, metabolic pathway).

Please refer to Appendix C (Haber et al. 2009) for additional discussion.

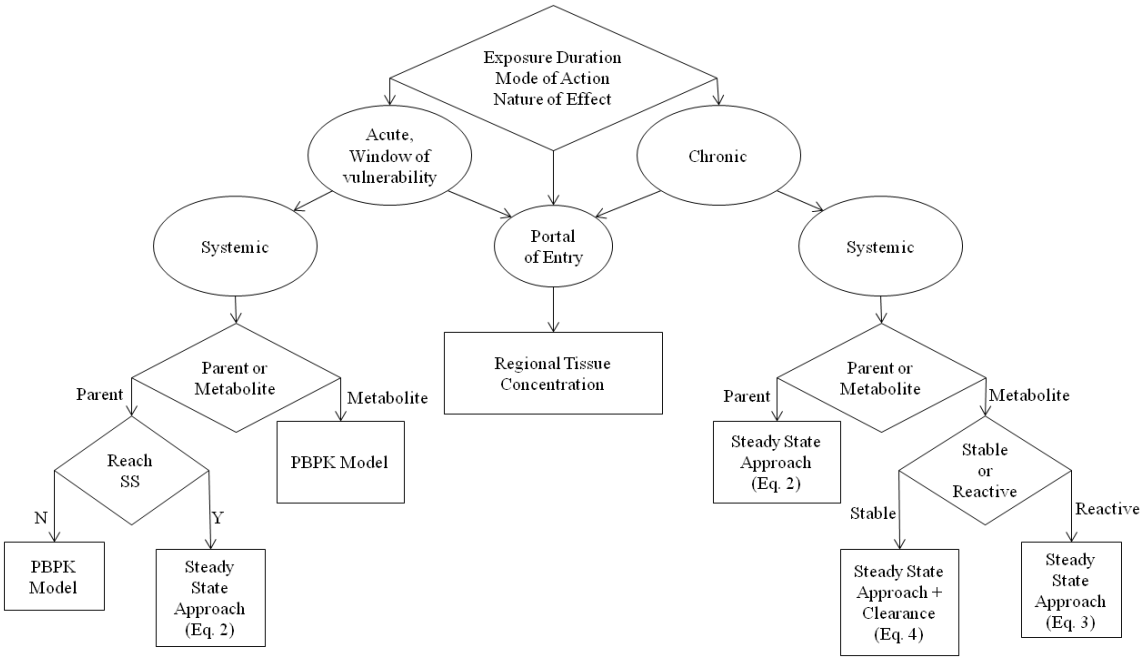


**Figure 3-8 Revised framework for evaluating the relative tissue dosimetry in adults and children for inhaled gases**

This figure is recreated from Haber et al. (2009), the original, along with the referenced equations, can be found in in Appendix C.

## 3.10 Select Critical Effect and Extrapolate from the POD to Lower Exposures

Dose-response assessments for each potential critical health effect are performed using the following steps: (1) derivation of a POD based on observed data, (2) dosimetric adjustment of the POD to a human equivalent concentration ($POD_{[HEC]}$ for inhalation concentration) or dose ($POD_{[HED]}$ for oral dose), (3) selection of the critical effect as the lowest human equivalent concentration or dose based on a toxicological or epidemiological study of acceptable quality for which the adverse effect has been scientifically demonstrated to be caused by the chemical exposure, and (4) extrapolation to lower exposures based on the MOA analysis.

MOA information may support a nonthreshold or threshold approach for dose-response extrapolations, as discussed previously in Chapter 1 and illustrated in Figure 3-9 (below). For carcinogenic effects, when the MOA information supports a nonthreshold MOA (i.e., the case for a carcinogen operating via a mutagenic MOA or when MOA is not understood), a linear default approach is typically used (Figure 3-9) and a URF or SFo is derived or a margin of exposure approach may be employed. A discussion of the procedures to perform carcinogenic assessments and extrapolations from the POD to lower exposures is discussed in more detail in Section 5.7.

If sufficient evidence is available to support a threshold MOA for the general population and any subpopulations of concern for either carcinogenic or noncarcinogenic effects, the default approach changes to a determination of a POD as discussed in Section 3.6 and application of UFs as discussed in Section 3.11 and a ReV or RfD is derived.

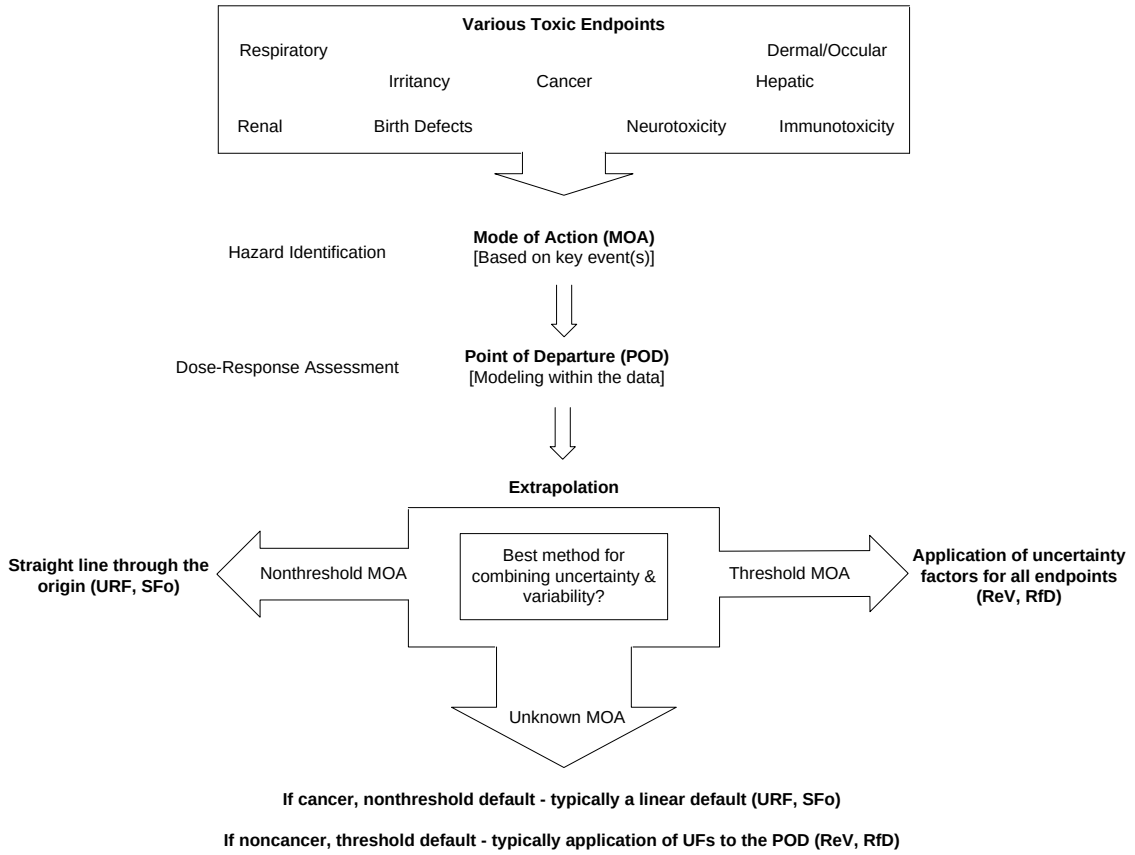


**Figure 3-9 A harmonized approach to extrapolate from the POD to lower exposures**

After all supporting data have been reviewed and evaluated and necessary dosimetric adjustments have been completed for the POD from each key study, the TCEQ identifies the relevant, adverse health effect observed at the lowest $POD_{[HEC]}$ or $POD_{[HED]}$ in the most appropriate, sensitive species. This is the critical adverse effect based on available dose-response data and represents the lowest dose at which a corresponding effect may be expected to occur in some humans. Then, extrapolation from the POD to lower exposures is performed. If more than one key study is available, a data array evaluation

may be useful to select the principal study that reflects optimal data on the critical effect (Figure 3-10).

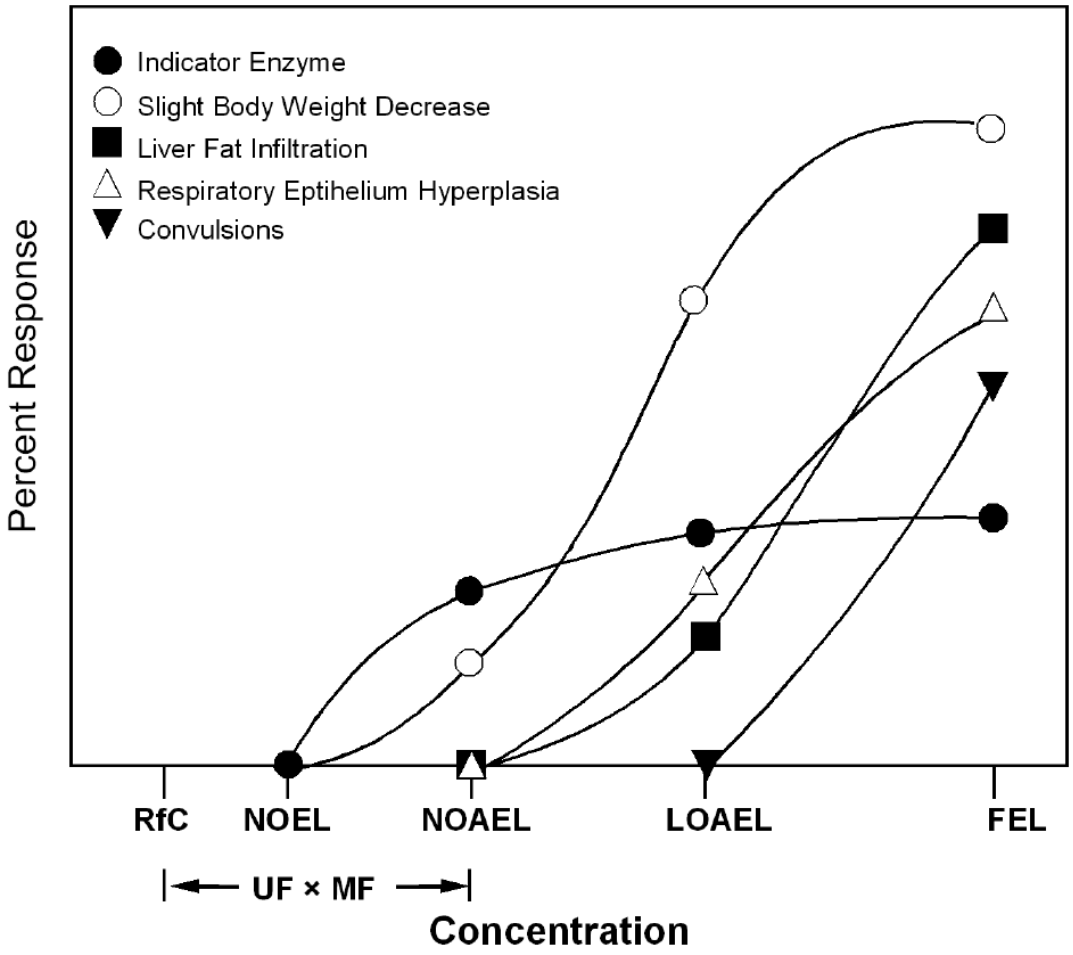


**Figure 3-10 Example of a dose-response array based on a threshold dose response**

The TCEQ does not use an MF to derive a ReV. FEL = frank effect level (Figure 4-11 from USEPA (1994a)).

If the critical adverse effect is prevented in potentially sensitive subpopulations, all other effects should also be prevented. Dose-response data points for all reported effects are examined as a component of this review, although a preference is given to choosing a mild adverse critical effect as opposed to a severe effect. If the only toxicity information available for a chemical is based on a severe effect and only a LOAEL is available, then the TCEQ considers using a greater LOAEL to NOAEL uncertainty factor to account for the uncertainty involved in using a severe effect as the critical effect or if the data are amenable to BMC modeling, a lower BMR or CES may be chosen (see Table 3-5). Steps and examples of decisions involved in selecting the critical effect are discussed in USEPA guidance (Section 4.3.8 and Table 4-7 of USEPA 1994a, USEPA 2002a). Issues of particular significance are as follows (USEPA 1994a):

- Delineation of all toxic effects and associated exposure levels;

- Determination, to the extent possible, of effect-specific experimental threshold regions (e.g., the $BMDL_{[HEC]}$ - $BMR_{[HEC]}$ or $NOAEL_{[HED]}$ – $LOAEL_{[HED]}$ interface or bracket);
- Determination of the critical effect defined as the one associated with the lowest $BMDL_{[HEC]}$ - $BMR_{[HEC]}$ or $NOAEL_{[HEC]}$ – $LOAEL_{[HEC]}$ interface or bracket (likewise for oral exposures);
- Consideration of species, POE effects, and/or route-specific differences in pharmacokinetic parameters and the slope of the dose-response curve.

## 3.11 Apply Appropriate Uncertainty Factors for Chemicals with a Threshold Dose Response

Most dose-response assessments have inherent uncertainty because the process requires some scientific judgment, use of default assumptions, and data extrapolations. Therefore, the acute or chronic ReV (Equation 3-6 and Equation 3-7), or chronic RfD (Equation 3-6), is derived from the $POD_{[HEC/HED]}$ for the critical effect with the application of UFs to account for uncertainty (a lack of knowledge) and variability (true heterogeneity or diversity) (USEPA 1994a, 2002a).

**Equation 3-6 Chronic ReV or RfD**

$$\text{Chronic ReV or RfD} = \frac{\text{POD}_{(\text{HEC or HED})}}{\text{UF}_\text{H} \times \text{UF}_\text{A} \times \text{UF}_\text{Sub} \times \text{UF}_\text{L} \times \text{UF}_\text{D}}$$

**Equation 3-7 Acute ReV**

$$\text{Acute ReV} = \frac{\text{POD}_{(\text{HEC or HED})}}{\text{UF}_\text{H} \times \text{UF}_\text{A} \times \text{UF}_\text{L} \times \text{UF}_\text{D}}$$

Where:

$UF_H$ = variation in susceptibility among the members of the human population (i.e., interindividual or intraspecies variability)
$UF_A$ = uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty)
$UF_{Sub}$ = uncertainty in extrapolating from data obtained in a subchronic study (e.g., less-than-lifetime exposure) to chronic exposure)
$UF_L$ = uncertainty in extrapolating from a LOAEL rather than from a NOAEL
$UF_D$ = uncertainty associated with an incomplete database.

Default factors of up to 10 have been commonly applied to account for each of these sources of uncertainty and variability. However, defaults are not always used and decisions will be made based on chemical-specific data. The exact value of UFs selected may depend on the quality of the studies available, the extent of the database, and scientific judgment (USEPA 1994a, 2002a). It is the goal of the TCEQ to allow default UFs to be replaced with actual data, if they are available. Bogdanffy and Jarabek (1995) as well as USEPA (USEPA 1994a, 2002a) discuss selection of UFs and cases where

default UFs can be replaced with chemical-specific data if the mode or mechanism of action of toxicants are known. The following sections provide a discussion of data considered by the TCEQ staff when selecting UFs and the rationale for making final chemical-specific determinations. Four of the five UFs ($UF_H$, $UF_A$, $UF_L$, and $UF_D$) are used to derive both acute and chronic ReVs, and chronic RfDs, and are discussed in the following sections. The $UF_D$ for acute ReVs and chronic ReVs/RfDs is discussed in more detail in Sections 4.4.2 and 5.5.2, respectively, because acute and chronic minimum database requirements differ. Since $UF_{Sub}$ only applies to the derivation of chronic toxicity factors, it is discussed in Chapter 5.

The general approach the TCEQ uses in applying UFs during the ReV and RfD derivation process is very similar to the approach discussed by USEPA (1994a, 2002a). Table 3-5 discusses the information and factors the TCEQ uses in considering whether a value other than a default value is appropriate as a chemical-specific UF. Specifically, Table 3-5 lists the process that is encompassed by each UF. Table 3-5 is taken from the RfC Methodology (Table 4-9 from USEPA 1994a) but is also applicable to UFs used to derive ReVs and RfDs.

**Table 3-5 The Use of Uncertainty Factors in Deriving an RfC or RfD**

| Standard Uncertainty Factors (UFs) | Processes Considered in UF Preview |
|---|---|
| **H = Human to sensitive human**<br>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<br>Sensitivity<br>Differences in mass (children, obese)<br>Concomitant exposures<br>Activity pattern<br>Does not account for idiosyncrasies |
| **A = Animal to human**<br>Extrapolation from valid results of long-term studies on laboratory animals when results of studies of human exposure aren't available or are inadequate. Intended to account for the uncertainty in extrapolating laboratory animal data to the case of average healthy humans. | Pharmacokinetics/Pharmacodynamics<br>Relevance of laboratory animal model<br>Species sensitivity |
| **Sub = Subchronic to chronic**<br>Extrapolation from less than chronic exposure results on laboratory animals or humans when there are no useful long-term human data.<br>Intended to account for the uncertainty in extrapolating from less than chronic NOAELS to chronic NOAELS. | Accumulation/Cumulative damage<br>Pharmacokinetics/Pharmacodynamics<br>Severity of effect<br>Recovery<br>Duration of study<br>Consistency of effect with duration |
| **L = LOAEL to NOAEL**<br>Derivation from a LOAEL instead of a NOAEL.<br>Intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. | Severity<br>Pharmacokinetics/Pharmacodynamics<br>Slope of dose-response curve<br>Trend, consistency of effect<br>Relationship of endpoints<br>Functional vs. histopathological evidence<br>Exposure uncertainties |
| **D = Incomplete to complete data**<br>Extrapolation from valid results in laboratory animals when the data are "incomplete."<br>Intended to account for the inability of any single laboratory animal study to adequately address all possible adverse outcomes in humans. | Quality of critical study<br>Data gaps<br>Power of critical study/supporting studies<br>Exposure uncertainties |

Although the USEPA approach (1994a, 2002a) addresses development of chronic toxicity factors, many aspects of the approach are also applicable to the development of acute toxicity factors. Typically, chronic toxicity values are not developed by USEPA for chemicals if all five areas of uncertainty are present, or if there is an absence of data on potential respiratory tract toxicity (relevant to TCEQ's derivation of a chronic ReV) or oral toxicity (relevant to derivation of an RfD).

However, due to State of Texas statutory requirements as discussed in Chapter 1, the TCEQ develops acute and chronic inhalation or chronic oral toxicity values even when there is a greater level of uncertainty (Section 3.15). Potential methods include using route-to-route extrapolation if specific criteria are met (Section 3.15.1) or a relative toxicity/relative potency surrogate approach (Section 3.15.2). Alternate approaches for chemicals with limited acute inhalation toxicity information to develop generic acute ReVs and ESLs may be used (Section 4.5) or alternate approaches for chemicals with limited chronic oral toxicity information may be used to develop chronic RfDs (Section 5.6).

### *3.11.1 Intraspecies ($UF_H$) and Interspecies ($UF_A$) Uncertainty Factors*

Toxicological responses may vary across species (interspecies variation) and among individuals within the human population (intraspecies variation) (USEPA 1994a). Therefore, the POD derived from experimental data is adjusted by interspecies and intraspecies UFs to account for known and unknown response variability. If toxicokinetic and toxicodynamic data are available, they may be used to support the selection of UFs other than default values of 10 (Bogdanffy and Jarabek 1995; IPCS 1999, 2005; ECETOC 2003). The primary approach to derive interspecies and intraspecies UFs is to develop non-default UFs based on scientific data (i.e., data-based UFs) (Renwick 1993, Renwick and Lazarus 1998, Dourson 1996, Dourson et al. 1996). Another approach involves the use of chemical-specific adjustment factors (CSAFs) (IPCS 2001, 2005) using available toxicokinetic and toxicodynamic data. Each of these approaches for dealing with $UF_H$ or $UF_A$ is discussed below.

#### 3.11.1.1 $UF_H$ or $UF_A$ Based on Scientific Data

Factors of 10 have been commonly applied by default to account for interspecies and intraspecies sources of variability. The factor of 10 is considered to protect the majority of the human population including children and the elderly. Renwick (1993) proposed that each of these UFs can be described in terms of differences in toxicokinetics and toxicodynamics. He defines toxicokinetics as all processes contributing to the concentration and duration of exposure of the active chemical toxicant at the target tissue, and toxicodynamics as the mode or mechanism of action of the active toxicant at the target tissue site. In regard to the $UF_H$, there are differences between children and adults in toxicokinetics (especially infants in their first months) and toxicodynamics (especially at different stages of development), which may render children more or less susceptible to the toxic effects of a substance. In situations where there are appropriate chemical-specific toxicokinetic and/or toxicodynamic data relevant to the $UF_H$ or $UF_A$, Renwick

(1993) suggested that the relevant default UF be replaced by a factor based on scientific data.

The $UF_A$ and the $UF_H$ of 10 can be divided into toxicokinetic and toxicodynamic components. If credible information on toxicokinetics or toxicodynamics is available to support a lower UF than the default of 10, a UF of 3, or even 1, may be used. Conversely, credible information may be available to support a UF greater than 10, although in practice, an order of magnitude has generally been used as a plausible upper bound for each UF (USEPA 1994a).

USEPA (1994a, 2002a) recommends dividing the $UF_H$ and $UF_A$ in half, one-geometric half ($10^{0.5}$ or 3.16 rounded to 3) each for toxicokinetic ($UF_{H\text{-}k}$ or $UF_{A\text{-}k}$) and toxicodynamic ($UF_{H\text{-}d}$ or $UF_{A\text{-}d}$) differences. For example, if an inhalation dosimetry adjustment from animal to human exposure has been performed to account for toxicokinetic differences in calculating HEC, then the full $UF_H$ of 10 may be reduced to 3 (a composite value obtained on multiplying 1 for $UF_{A\text{-}k}$ and 3 for $UF_{A\text{-}d}$) (Bogdanffy and Jarabek 1995, Jarabek 1995c, USEPA 1994a).

A discussion of interspecies and intraspecies variability of response, as well as research and case studies from the USEPA and the Health Canada risk assessments that demonstrate the use of lower UFs are presented in papers by Bogdanffy and Jarabek (1995), Dourson et al. (1996), and Jarabek (1995c). In addition, when BMD modeling is conducted and a BMDL is used as the POD, Barnes et al. (1995) provide guidance on using data-based UFs rather than the default UF of 10. NRC (2001) provides a list of questions that should be addressed to support the rationale for the UF used. The TCEQ determines data-based UFs to account for interspecies and intraspecies variation on a chemical-by-chemical basis, and the rationale for application of other than default $UF_H$ or $UF_A$ values is provided in the DSD for each chemical.

#### 3.11.1.1.1 Factors Considered for $UF_A$

The factors considered when assessing the potential for interspecies differences in toxicity between laboratory animals and humans and deciding on a specific value for the $UF_A$ include: (1) the relevance and sensitivity of the laboratory animal model; (2) the animal species used in experimental studies; (3) the likely mode/mechanism of action; (4) the range of response in the animal species tested; (5) the variability of response among the species tested; and (6) toxicokinetic/toxicodynamic differences among the species tested.

#### 3.11.1.1.2 Factors Considered for $UF_H$, Including Child/Adult Risk Differences

For the $UF_H$, the factors considered in assessing the potential for intraspecies differences in toxicity among the human population and deciding on a specific value include: (1) the mode/mechanism of action, (2) the toxicological endpoint observed, (3) what is known/unknown about toxicokinetic/toxicodynamic differences among individuals, (4) the range of response among humans and subpopulations (i.e., differences due to mass or activity pattern), (5) whether toxicological (e.g., dose-response) data exist on effects in a susceptible human population, and (6) sensitivity.

The potential sensitivity of children compared to adults is an important consideration for the $UF_H$. Section 3.3.3.2.1 discusses differences, including toxicokinetic and toxicodynamic differences, between adults and children. Quantitative data regarding chemical-specific differences in toxicokinetics between adults and children are limited. However, there are some studies that have evaluated data to determine if the traditional uncertainty factors are protective of children (Renwick 1998, Ginsberg *et. al.* 2002, Bruckner 2000, Rane 1992, Skowronski and Abdel-Rahman 2001, and Calabrese 1986). Based on scientific data and an evaluation conducted on a chemical-by-chemical basis, the $UF_H$ may need to be greater than 10 in order to adequately protect children.

OEHHA (2008) and Bruckner (2000) concluded that differences between children and adults are accounted for in many cases by the $UF_H$ to protect susceptible subpopulations. Nielsen et al. (2010) found that young children frequently eliminate xenobiotics more rapidly by metabolism and excretion compared with adults, suggesting that children would be adequately protected by a 3.16-fold factor for toxicokinetics applied to the mean data for adults. A toxicodynamic $UF_H$ larger than 3.16-fold could be used if there are supporting data on a case-by-case basis.

Criteria to consider when evaluating any child/adult differences include indications or suggestions of effects on organ systems and functions that are especially vulnerable during development and maturation in early life (e.g., the nervous, reproductive, immune systems, and metabolic pathways), and evaluating experimental data on such effects in young animals. Child/adult differences will be discussed separately for acute exposures (Chapter 4) and chronic exposures (Chapter 5).

#### 3.11.1.2 Chemical-Specific Adjustment Factors

For a few chemicals, data are available to derive a CSAF to replace the default UF, thereby reducing the overall uncertainty. A CSAF is based on ratios of kinetic or dynamic values determined in animals and/or humans (e.g., ratio of peak concentration in animals divided by peak concentration in humans, if the relevant dose metric is peak concentration). Therefore, CSAFs are different than data-derived UFs (Section 3.11.1.1). For example, a data-derived UF may be based on information that shows variability in different species is small, so a smaller $UF_A$ could be used based on scientific judgment. The IPCS (2001, 2005) published a guidance document that details the data needed to develop CSAFs to account for interspecies differences and human variability in toxicokinetics and toxicodynamics. Some of the data requirements discussed by the IPCS (2001, 2005) include identification of the active chemical moiety, choice of relevant toxicokinetic parameter, consideration of the experimental data, and consideration of the endpoint. The TCEQ uses CSAFs to account for interspecies and intraspecies variation depending on the availability of toxicity information and time and resource constraints. The USEPA (2014) guidance document on data-derived extrapolation factors (DDEFs) provides an approach fairly similar to IPCS (2005) and may be useful in deriving interspecies or intraspecies DDEFs for either toxicokinetics or toxicodynamics.

### *3.11.2 LOAEL to NOAEL Uncertainty Factor ($UF_L$)*

Although the goal is to identify a POD that reflects the highest exposure level that does not cause an adverse effect (NOAEL), in some cases, only a LOAEL is available from an

experimental study. Therefore, the LOAEL should be converted to a value analogous to a NOAEL. The uncertainty in converting a LOAEL into a NOAEL can be addressed with a UF ($UF_L$). Typically, a default $UF_L$ of 10 is used to adjust the LOAEL to a NOAEL. However, multiple studies have justified use of a $UF_L$ less than 10. It is important to consider the slope of the dose-response curve in the range of the LOAEL in making the determination to reduce the size of the $UF_L$ (USEPA 2002a). Several studies have reported that the LOAELs rarely exceed the NOAEL by more than about 5-6 fold and are typically close to a value of 3 based on the ratios of LOAELs to NOAELs for a range of different chemicals and different study durations (subacute, subchronic, and chronic) (ECETOC 2003), although these findings are dependent on the dose spacing chosen in toxicity studies. Dourson et al. (1996) state the choice of $UF_L$ should generally depend on the severity of the effect at the LOAEL. If the effect at the LOAEL is severe, a larger $UF_L$ may be needed. If the effect is mild, then these effects would not require a large $UF_L$. These are important considerations in addition to the slope of the dose-response curve in the region of interest.

As described in Section 1.4, toxicity factors are set to protect the general public health, and the biological endpoint of choice for determination (i.e., critical effect) will generally be a mild effect. However, a more severe effect may be used if it is in fact the most sensitive endpoint that occurs at the lowest exposure level (for example, irreversible developmental effects), or if no data on mild effects are available. When the effect at the LOAEL is of low severity (e.g., mild local effects by inhalation), the LOAEL is likely to be relatively nearer to the NOAEL, and thus a $UF_L$ of 1-3 may be sufficient. Conversely, more severe effects indicate the likelihood of a higher LOAEL to NOAEL ratio**.**

#### 3.11.2.1 TCEQ Approach

The TCEQ uses a $UF_L$ up to 10 or develops a chemical-specific $UF_L$ if data are sufficient based on MOA analysis, slope of the dose-response curve in the range of the LOAEL, and/or severity of effect. The TCEQ uses best scientific judgment in determining the most scientifically-defensible $UF_L$ for a given chemical on a case-by-case basis, considering all of the information discussed above. Pohl and Abadin (1995) provide examples of chemicals where chemical-specific toxicity information was used to justify a $UF_L$ less than 10.

In general, the TCEQ uses the following default values of $UF_L$, for acute and chronic ReV derivations (refer to Table 4-3 in the RfC Methodology (USEPA 1994a) for information on the rank of effect levels):

- Where the observed effect level is a NOAEL or equivalent benchmark (i.e., $BMDL_{05}$ or $BMCL_{10}$), the value of $UF_L$ is 1.
- When the POD is based on a LOAEL and, the observed effect is minimal or less than mild (rank 3 or below) (USEPA 1994a), or where there is an indication that the LOAEL is close to the NOAEL, the value of $UF_L$ may be 2 to 3.
- When the POD is based on a LOAEL and, the observed effect is mild/severe (rank 4 to 5) (USEPA 1994a), the value of $UF_L$ may be 6.
- When the POD is based on a LOAEL and the observed effect is severe (rank 6 and above) (USEPA 1994a), the value of $UF_L$ is 10.

These default values are based on the criteria for determining the severity of adverse effects (Section 3.6.1) and on Table B-1 in Appendix B and may be replaced by more specific values where appropriate data are available (OEHHA 2008). USEPA (2002a) noted that data should be carefully evaluated, taking into consideration the level of response at the LOAEL and the NOAEL and the slope of the dose-response curve before reducing the size of the UF applied to the LOAEL.

#### 3.11.2.2 Other Federal and State Agency Approaches

For the purpose of comparison, the TCEQ lists default UFs including UFLs recommended by the USEPA and several other regulatory agencies and non-regulatory organizations in Table 3-6. When the less serious LOAEL approaches the threshold level (i.e., only minimal effects are observed representing an early indication of toxicity), the ATSDR (Chou et al. 1998) and the ECETOC (ECETOC 2003) recommend using a $UF_L$ of 3 and 2, respectively, for the "minimal" LOAEL. When the effects observed at the LOAEL are not considered minimal, but are less serious (mild to moderate), or serious (severe), the ECETOC recommends a $UF_L$ of 6 be used. However, the CalEPA (OEHHA 2008) recommends using a $UF_L$ of 6 and 10 for mild and severe effects, respectively, to derive its acute REL, and using a $UF_L$ of 10 for any effect to derive its chronic REL. In addition, the IPCS (1999) recommends using UFs of 3, 5, or 10 to extrapolate from a LOAEL to a NOAEL depending on the nature of the effect(s) and the dose-response relationship (Table 3-6).

### *3.11.3 Database Uncertainty Factor ($UF_D$)*

Many important considerations relevant to the $UF_D$ are discussed in this section. However, issues specifically related to the $UF_D$ used for the development of acute ReV and chronic ReV/RfD values are discussed in Sections 4.4.2 and 5.5.2, respectively. Therefore, all relevant sections should be referenced when selecting a $UF_D$ value for a particular toxicity factor.

Uncertainty introduced by database deficiencies, such as the inability of any single animal study to adequately address all potential endpoints at various critical life stages or deficiencies in the design or quality of an experimental study, can be addressed by the use of a UF (i.e., $UF_D$) (Dourson et al. 1996, USEPA 1994a). The $UF_D$ is used to account for the fact that a potential health effect may not be identified if the database is missing a particular type of study and for study quality deficiencies as well. The TCEQ also assigns a confidence level to the quality of the key study and the database, not to the ReV or RfD. The TCEQ selects $UF_D$ values based on case-by-case determinations when deriving ReVs and RfDs, and generally uses a $UF_D$ of 1 for a toxicological database with no substantial data and quality deficiencies and a $UF_D$ of up to 10 for a database with substantial database and quality deficiencies. The areas of uncertainty considered for the $UF_D$ are:

- Uncertainty associated with database deficiency (Section 3.11.3.1.1), including a lack of data on potentially sensitive subpopulations such as children (Section 3.3.3.2.1)
- Uncertainty associated with study quality (Section 3.11.3.1.2)

Prior to discussing these two areas of database uncertainty, it should be noted that there are minimum database requirements for derivation of toxicity factors which are relevant to database deficiency and the selection of a $UF_D$ value. The minimum database requirements, confidence levels, and preliminary $UF_D$ values based on the number and types of studies available for development of an acute ReV and chronic ReV/RfD are provided in Table 4-2 of Chapter 4 and Table 5-2 of Chapter 5, respectively. However, the basic summary information given in Table 4-2 and Table 5-2 may not accurately or adequately represent the completeness of the overall database for a given chemical, as many important details and considerations are not addressed. Therefore, use of these tables alone for this purpose would represent a significant oversimplification of the scientific judgment necessary for the $UF_D$ value selection process. Many of the important and relevant details and considerations not addressed by these tables are discussed below and in Section 3.11.3.2.

### 3.11.3.1 Database Deficiency and Study Quality Uncertainty and Confidence Levels

#### 3.11.3.1.1 Database Deficiency Uncertainty

As previously mentioned, the $UF_D$ is used to account for uncertainty resulting from adverse health effects that may not be identified when studies are missing from the database. Uncertainty for such database gaps or other deficiencies includes completeness (adequacy or limitations) and the size of the database. Unless a comprehensive array of endpoints (e.g., tissues, organs, systems, life stages) is addressed by the database over the exposure duration of interest, there is uncertainty as to whether the critical effect chosen for the ReV or RfD is the most sensitive and appropriate. See Section 3.11.3.2 below for other relevant considerations and questions regarding database (and study quality) uncertainty.

Of particular concern is the ability of some chemicals to affect the developing fetus or development in infants and children. Consequently, the data available for various life stages should be specifically considered. If appropriate studies to evaluate developmental effects or effects in immature animals are lacking, it may not be possible to predict if effects on developing organs and tissues occur at doses lower or higher than those which affect other endpoints. Refer to Tables 4.2 and 5.2 for recommended reproductive/developmental studies. The ideal dataset for evaluating developmental endpoints would include studies in two species in which exposure occurs during gestation (relevant for development of acute ReVs) and a two-generation reproductive study in two species (relevant to development of chronic ReVs and RfDs). When reviewing a chemical's database on developmental effects, it is important to assess (to the extent possible) the potential for systemic toxicity in neonatal animals and evaluate whether an immature metabolic system would result in increased or decreased sensitivity. In regard to the lack of data for early life stages, Nielsen et al. (2010) noted the additional 10-fold factor for infants and children called for in the 1996 Food Quality Protection Act (FQPA) is similar to the $UF_D$. It was concluded that an additional UF is not needed because the traditional factors were considered sufficient to account for uncertainties in the database from which the toxicity factors (e.g., reference values) are derived, including lack of data

on children. The rationale for application of the $UF_D$ selected will be presented in the individual toxicity summaries for each chemical.

#### 3.11.3.1.2 Study Quality Uncertainty

In addition to database deficiency, the $UF_D$ may also be used to account for less than desirable study quality of the key study or other supporting toxicity studies. Factors relevant to study quality include, but are not limited to, an appropriate number of animals per sex per group, proper use of statistics, adequate analytical techniques and instrumentation, sufficiently sensitive and objective measurement/ascertainment of adverse effects, general good laboratory practices, sufficiently detailed documentation and results, etc. See Section 3.11.3.2 below for other relevant considerations and questions regarding study quality (and database) uncertainty.

#### 3.11.3.1.3 Database and Study Quality Confidence Levels

Confidence (reliability) levels are assigned to the overall database upon which ReVs or RfDs are based. These confidence levels are assigned based on guidance in the RfC Methodology (USEPA 1994a). A dataset confidence level of high, medium, or low is assigned to the overall database as discussed in Section 4.4.2 for an acute database and Section 5.5.2 for a chronic database.

The TCEQ also assigns confidence levels to key studies. A key study of excellent quality likely receives a high confidence rating, even if its duration is not ideal (e.g., a subchronic study for a chronic ESL). A key study has a higher confidence rating if it is based on reliable human data and supported by laboratory animal data. The level of confidence in an animal study is evaluated through consideration of adequacy of study design, appropriate use of statistics, good laboratory practices, spectrum of investigated endpoints, demonstration of dose-response relationships, support from other studies, and other factors. Examples of low degree of confidence are: (1) low number of animals used, (2) conflicting results between the key study and other well conducted studies, and (3) uncertainty about the reliability of the route-to-route extrapolation (Nielsen et al. 2010). More data, either on effects or on exposure, may be needed to increase the degree of confidence.

### 3.11.3.2 Relevant Questions and Considerations

It is important to consider the adequacy of the database (i.e., the overall confidence regarding the quality, completeness, and consistency of the database) to help ensure derivation of health-protective toxicity factors. Some general questions that need to be considered in evaluating database adequacy for toxicity factor (e.g., ReV, RfD) derivation are as follows (Nielsen et al. 2010):

- How extensive is the database?
- What is the quality of the studies?
- What are the data gaps (e.g., endpoints, life stages)?

- Are both human and animal data available, and are the results consistent?
- Are there data on more than one species, and are the results consistent?
- Are data available for the relevant route of exposure?
- What are the scientific uncertainties?
- What is the overall confidence in the database?

The TCEQ also considers more specific questions (adapted from USEPA 1994a) that are useful in the overall evaluation of database adequacy, which are grouped by subject below. As the relative importance and relevance of some of these (and other) questions will vary from chemical to chemical, ultimately, sound scientific judgment is used to decide on the value for the $UF_D$ on a case-by-case basis. The primary aspect of database adequacy that each question addresses (e.g., key/supporting study quality, relevance of study results for humans, database quality) has been added in parenthesis to aid in separating study quality considerations (e.g., proper study design and statistics) from those simply pertaining to the usefulness of a study for the purpose of deriving a particular human toxicity factor (e.g., exposure route and duration, toxicokinetic similarity of laboratory animal species to humans). While the utility of a study for deriving a particular toxicity factor does not determine its quality (e.g., an intraperitoneal study may be of high quality but not particularly useful for toxicity factor development), it should be noted that the quality, number, and diversity (e.g., endpoints, life stages, and species evaluated) of studies relevant to deriving a particular human toxicity factor does determine database quality for that toxicity factor.

***Adequacy and relevance of study design***

- Is the route of exposure relevant to humans and the toxicity factor being developed (relevance of study results to humans and toxicity factor development)?
- Were an appropriate number of animals and of both sexes used for determination of statistical significance (key/supporting study quality)?
- Was the duration of exposure sufficient to allow results to be extrapolated to humans for the exposure condition/duration of interest (relevance of study results to development of the toxicity factor)?
- Were appropriate statistical techniques applied (key/supporting study quality)?
- Were the analytical techniques sufficient to adequately measure the level of the test substance in the exposure protocol, including biological media (key/supporting study quality)?
- Is the animal species and strain appropriate as a surrogate for humans (relevance of study results to humans)?
- Are the techniques for measurement of the biological endpoints scientifically sound and of sufficient sensitivity (key/supporting study quality)?
- To what degree may the biological endpoints be extrapolated (qualitatively or quantitatively) to humans (relevance of study results to humans)?

***Demonstration of dose-response relationships***

- Were sufficient exposure levels used to demonstrate the highest NOAEL for the endpoint of concern (key/supporting study and database quality)?
- Is the shape of the dose-response curve consistent with the known pharmacokinetics of the test substance (key/supporting study quality)?
- Has the dose-response curve been replicated by or is it consistent with data from other laboratories and other laboratory animal species (key/supporting study quality, human relevance)?

***Species differences***

- Are the metabolism and pharmacokinetics in the laboratory animal species similar to those for humans (relevance of study results for humans)?
- Is the species response consistent with that in other species (relevance of study results for humans)?
- Is the species from which the threshold value was derived the most sensitive, relevant species for humans (relevance of study results for humans)?

***Other factors***

- The number of biological endpoints evaluated and associated with dose-response relationships (database and key/supporting study quality).
- Sufficient description of exposure protocol, statistical tests, and results to make an evaluation (key/supporting study quality).
- Condition of animals used in the study (key/supporting study quality).
- The evaluation of effects of exposure in early life stages (database and key/supporting study quality).

### 3.11.4 Rationale for Not Using a Modifying Factor

In the past, the USEPA (1994a) recommended using a modifying factor (MF) to account for scientific deficiencies in the quality of the critical study (i.e., the one used as the basis of the POD) such as the number of animals tested or quality of exposure characterization. However, based on recent USEPA (2002a) guidance that recommends the use of the MF be discontinued, the TCEQ does not use a MF to develop toxicity factors. The USEPA (2002a) rationale for discontinuing use of the MF centers on an examination of its infrequent application in IRIS and the realization that all aspects of uncertainty considered for the MF are already explicitly addressed in the $UF_D$ or in other UFs. Essentially, the purpose of the MF is "sufficiently subsumed in the general database UF" (USEPA 2002a).

### 3.11.5 Procedures for Combining Values of Different UFs

USEPA (1994a, 2002a) recommends dividing the $UF_H$ and $UF_A$ in half, one-geometric half ($10^{0.5}$ or 3.16 rounded to 3) each for toxicokinetic ($UF_{H\text{-}k}$ or $UF_{A\text{-}k}$) and toxicodynamic ($UF_{H\text{-}d}$ or $UF_{A\text{-}d}$) differences. When multiplying these factors ($UF_{H\text{-}k}$ or $UF_{A\text{-}k}$ or $UF_{H\text{-}d}$ or $UF_{A\text{-}d}$) of "3" with each other, the product would be 10, since one geometric half ($10^{0.5}$) multiplied by another geometric half ($10^{0.5}$) is 10.

Since $UF_{Sub}$, $UF_L$, and $UF_D$ *are not based on geometric half values*, the actual value for $UF_{Sub}$, $UF_L$, and $UF_D$ will be used to form the final product of all UFs. For example, if $UF_H = 3$, $UF_A = 3$, $UF_L = 3$, $UF_D = 3$, then $UF_H$ x $UF_A$ would be 3 x 3 = 10 (i.e., since they are one-geometric half ($10^{0.5}$)), but the final product of all UFs would be 90 since the actual values of $UF_L$ and $UF_D$ are each 3, as opposed to $10^{0.5}$ (i.e., 10 x 3 x 3 = 90).

### *3.11.6 Application of Appropriate Uncertainty Factors*

The exact values of the UFs chosen should depend on the quality of the studies available, the extent of the database, and scientific judgment. For the purpose of comparison, the TCEQ lists default UFs recommended by the USEPA and several other regulatory agencies and non-regulatory organizations in Table 3-6.

## Table 3-6 Comparison of Uncertainty Factors Used by Different Organizations

| Uncertainty Factors | TCEQ | USEPA | ATSDR | OEHHA | FDA | ECETOC | Netherlands | Health Canada/ IPCS |
|---|---|---|---|---|---|---|---|---|
| Interspecies, $UF_H$ | ≤ 10 | ≤ 10 | 1, 3, or 10 | ≤ 100 | 10 | 2 – 7 (systemic effects)<br>1 (local effects) | 3 | 10 |
| Toxicokinetics, $UF_{H\text{-}k}$ | 3 | 3 | -- | 1, 3, or 10 | -- | -- | -- | 2.5 |
| Toxicodynamics, $UF_{H\text{-}d}$ | 3 | 3 | -- | 1, 3, or 10 | -- | -- | -- | 4 |
| Intraspecies, $UF_A$ | ≤ 10 | ≤ 10 | 1, 3, or 10 | ≤ 10 | 10 | 5 | 10 | 10 |
| Toxicokinetics, $UF_{A\text{-}k}$ | 3 | 3 | -- | 1, 2, or 3 | -- | -- | -- | 2.5 |
| Toxicodynamics, $UF_{A\text{-}d}$ | 3 | 3 | -- | 1,2, or 3 | -- | -- | -- | 4 |
| Subchronic to chronic, $UF_{Sub}$ | ≤ 10* | ≤ 10 | 1, 3, or 10 | 1, 3, or 10 | 10 | 2 (default)<br>1 (local effects) | 1 to 10 | 1 to 100 for $UF_{Sub}$, $UF_L$, & $UF_D$ |
| LOAEL to NOAEL, $UF_L$ | 2 – 3* (≤ mild)<br>6 *(mild/severe)<br>10* (severe) | ≤ 10 | 3 (minimal effects)<br>10 (serious effects) | 6 (mild effects)<br>10 (severe effects) | N/A | 3 (default)<br>± 3 (depends on severity) | 1 to 10 | See above |
| Incomplete database, $UF_D$ | ≤ 10* = database deficiency and key study quality, including child/adult differences | ≤ 10 | N/A | 1 or 3 | N/A | 1 ( high confidence level)<br>1-2 (medium)<br>< 2 (low) | N/A | See above |
| Modifying factor, $UF_M$ | N/A | ≤ 10 (discontinued) | 1 to 10 | N/A | N/A | 1 to 10 | 1 to 10 | 1 to 10 |

*For TCEQ, since the $UF_{Sub}$, $UF_L$, and $UF_D$ are not based on geometric half values, the actual value for $UF_{Sub}$, $UF_L$, and $UF_D$ will be used to form the final product of all UFs (i.e., use of a 3 will count as a 3 and not as $10^{0.5}$).

## 3.12 Evaluating the Reasonableness of all Risk Assessment Decisions

When default factors of 10 are used to account for each area of uncertainty (e.g., interspecies, intraspecies, LOAEL to NOAEL, incomplete database, subchronic to chronic) for a chronic toxicity value, the product of the UFs can be as high as 10,000-100,000, which may result in an overly conservative toxicity value (Swartout et al. 1998). If four UFs are used for a chronic toxicity value and the cumulative UF exceeds 3,000, the TCEQ uses a default of 3,000. Similarly, if three UFs are used for acute ReV and the cumulative UF exceeds 300, the TCEQ generally uses a maximum total UF of 300. This reduction from a higher cumulative UF is used in recognition of a lack of independence of these factors (USEPA 1994a) and to account for the interrelationships of uncertainty categories for both acute and chronic toxicity factors (USEPA 2002a). Each individual UF is generally conservative, and multiplying several areas of uncertainty likely yields unrealistically conservative toxicity factors (USEPA 1994a).

In general, the more limited the toxicity information for a chemical, the higher the product of the UFs will be in order to increase the expectation that the adjusted toxicity value is health-protective. In all cases, the DSD for each chemical discusses the basis for each component UF and the conservatism of the resulting product. The TCEQ uses criteria from the latest reference concentration/dose derivation guidance documents (USEPA 1994a, 2002a), information on the differential toxicity of chemical classes or isomers, as well as scientific judgment to determine whether the aggregate impact of all risk assessment decisions results in a toxicity factor that is unreasonable. An unreasonable toxicity factor is one that would incorporate a product of UFs generally greater than 300 or 3,000, respectively, for acute or chronic toxicity factors.

## 3.13 Identification of Inhalation Observed Adverse Effect Levels

Toxicity factors and their corresponding risk-specific concentrations are considered “safe levels” because they are set below levels where adverse health effects are expected to occur. Risk managers as well as the general public may want information on the air concentrations where health effects would be expected to occur (i.e., an air concentration observed adverse effect level). Thus, when adequate data exist for inhalation, the TCEQ will provide observed adverse effect levels in DSDs, which will include a narrative putting the observed effect levels and their associated uncertainties and caveats (e.g., data limitations, potential inter/intraspecies differences in sensitivity) into proper context. One such caveat is that exceedance of an observed effect level is meaningful only for exposure scenarios that are similar or greater in duration. Although written specifically for inhalation exposure data, analogous procedures could be used for oral data. These observed adverse effect levels are primarily for informational purposes. That is, to communicate to agency risk assessors, risk managers, the public, and other groups the air concentrations and exposure conditions (e.g., magnitude, frequency, duration) associated with observed adverse effect levels based on available dose-response data and to put into

perspective corresponding health-protective values (e.g., interval between effect levels and the ReV). Additionally, the probability of response associated with the POD used to estimate an observed adverse effect level (e.g., percent response at the $LOAEL_{HEC}$) may be informative as to the probability of response in similarly-exposed individuals, depending upon the relative sensitivities of the study population compared to the environmentally-exposed population.

### 3.13.1 Chemicals with a Threshold MOA

For noncarcinogens or carcinogens with a threshold MOA, the $LOAEL_{HEC}$ from the study that identified the critical adverse effect can be considered the lowest documented level where effects in the human population could be expected to occur in some members of the population. If BMC modeling is conducted, the central estimate $BMC_{HEC}$ corresponding to a BMR of concern for adverse effects (e.g., $BMC_{10\text{-}HEC}$ for decreased body weight) which does not require significant extrapolation below the range of the data is used as the lowest level where effects in the human population could be expected to occur.

More specifically, an $LOAEL_{HEC}$ determined from human studies, where adverse effects occurred in some individuals, represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, adverse effects are not a certainty due to potential intraspecies differences in sensitivity, depending upon the sensitivity of the study population relative to that of those exposed environmentally. Conversely, the $NOAEL_{HEC}$ from a human study is the highest concentration known (based on dose-response data) which may not be expected to result in adverse effects in humans similar to the study-exposed population (e.g., workers, adult volunteers) exposed over the same (or shorter) duration, although this is not a certainty (e.g., study power considerations). Other subpopulations could be more sensitive if the study did not use a sensitive subpopulation (assuming there is one for the endpoint in question), in which case the lowest level at which such a subpopulations would be expected to adversely respond may not be accurately predicted.

When adverse effects occur in some animals of the most sensitive species, an estimated $LOAEL_{HEC}$ extrapolated from animal studies in the most sensitive species represents a concentration at which it is possible that similar effects could occur in individuals exposed to this level (assuming there are no available data on the sensitivity of animals versus humans). This could be over the same duration as used in the study, or longer durations. However, adverse effects are not a certainty, particularly when data on potential species differences in sensitivity (i.e., the most human-relevant laboratory animal species) are lacking. If laboratory animal data are relied upon and there is no information on the sensitivity of animals versus humans, the determination of observed adverse effect levels needs to be put into the context of a discussion of relevant studies. The discussion should be on the same, and other species that did not show effects at similar or higher levels/durations, as well as the adverse effect levels demonstrated in other studies, and should be included in the broader narrative that puts the observed adverse effect levels and their associated uncertainties and caveats (e.g., potential

interspecies differences in sensitivity, applicable exposure conditions) into an appropriate context.

### 3.13.2 Application of UFs or Duration Adjustments

To the extent possible, determinations of observed adverse effect levels should have a reasonable degree of certainty associated with them. Therefore, they should be based on concentrations demonstrated to be causally associated with a probability of adverse effects occurring. That is, observed effect levels should be based on what is known (i.e., be founded in actual dose-response data). Using UFs and duration adjustments often have an unknown effect on the probability of an adverse response actually occurring (e.g., unless predictive chemical-specific "n" values, PBPK models, or CSAFs are available). The result would be a value with an unknown ability to predict the probability of an adverse response. This is contrary to the purpose of, to the extent possible based on available dose-response data, identifying a level where with a reasonable degree of certainty an adverse response in some individuals may be expected.

Consequently, UFs are inapplicable because they are based in uncertainty and applying a UF interjects uncertainty about (i.e., essentially negates) the expectation of an adverse human response occurring in some individuals based on the dose-response data. Additionally, if data are not available for an exposure duration adjustment that is predictive of toxicity (as opposed to an adjustment that is merely conservative), exposure duration adjustments will not be performed. For example, for an acute 1-h ReV, an "n" of 3 is used to perform exposure duration adjustments from a longer exposure duration study to 1-h because it is generally considered to be conservative, not because the duration adjustment accurately predicts a 1-h level associated with the same probability of an adverse response. Consequently, if duration adjustments believed to be toxicologically predictive for the chemical and endpoint in question cannot be performed to the exposure duration of interest (e.g., no chemical-specific "n" value for the endpoint is available), the estimated observed adverse effect level is tied to the exposure scenario under which adverse effects were observed. However, adjustments designed to be predictive in nature (as opposed to simply conservative) such as animal-to-human dosimetry are performed when possible as these procedures themselves should not appreciably affect the expectation of an adverse response (although, for example, interspecies differences in sensitivity may exist).

### 3.13.3 Chemicals with a Nonthreshold MOA

For carcinogenic effects (or noncarcinogens with a nonthreshold MOA), the risk-specific dose for the $^{chronic}ESL_{linear(c)}$ is set at the no significant excess risk level associated with a theoretical excess lifetime cancer risk of one in 100,000 ($1 \times 10^{-5}$ or simply $10^{-5}$). USEPA's acceptable risk range is $10^{-6}$ to $10^{-4}$ (USEPA 2000d). When tumor data are used, a POD is obtained from the modeled tumor incidences. Conventional cancer bioassays, with approximately 50 animals per group, generally can support modeling down to an increased incidence of 1–10% ($10^{-2}$ to $10^{-1}$ risk); epidemiologic studies, with larger sample sizes, may be able to support modeling to below 1% ($10^{-2}$) risk (USEPA 2005a). For a well-conducted epidemiology study with adequate number of subjects and statistical power, it may be possible to detect an increase in background cancer

incidence/mortality at the $10^{-3}$ risk level (Grant et al. 2007) or lower. Seiler and Alvarez (1994) determined that for radiation carcinogenesis, the minimum significant risk for the model is considerable larger than $10^{-3}$ and for the usual confidence limits, the minimum significant risk exceeds $10^{-2}$:

> *Whereas a more careful error analysis may yield lower limits, it is unlikely that they will lie below 1 x 10-3. Thus, even though risk values below this limit can be calculated, they are not meaningful because they are smaller than their total standard errors, and are thus not compatible with finite risks.*

Consistent with the goal of identifying "observed" effect levels (as opposed to significantly, downwardly extrapolated theoretical levels where the probability of response is uncertain), the determination of observed effect levels should focus on use of the study-specific excess risk levels and air concentrations where statistically elevated risk was observed. An air concentration corresponding to the excess risk level detected by the key epidemiological study (e.g., $10^{-3}$), preferably based on the statistical best estimate of the potency factor since this may be most predictive (i.e., central estimate or maximum likelihood estimate), can be considered the lowest level for which effects in some individuals in the human population would be expected with reasonable certainty if exposed over a similar (or longer) exposure duration than those in the epidemiological study. Alternatively, the air concentration (or range of concentrations) associated with the lowest exposure group for which statistically elevated cancer risk was observed in a well conducted epidemiological study can be used. If the lowest exposure for statistically elevated risk from an occupational study is reported in ppm-years, for example, this value may be divided by an appropriate study-specific worker exposure duration or a default worker exposure duration (e.g., 40 years) that is reasonable in the context of the study to derive the corresponding observed adverse effect level air concentration.

However, occupational-to-general population duration adjustments (e.g., Equation 5-1) are generally not appropriate for identifying observed cancer effect levels. More specifically, adjusting the exposures demonstrated to increase cancer risk in workers to continuous lifetime environmental exposure equivalents (e.g., using duration adjustments) may be inappropriate for this purpose. For example, dose rate may have at least enhanced carcinogenesis or the carcinogenic MOA in workers (e.g., the metabolic pathways responsible for carcinogenesis in workers). Such adjustments would generally not result in air concentrations representative of those where excess risk was observed. Thus, the lowest air concentration associated with statistically elevated cancer risk in a well conducted epidemiological study can be used to derive the observed cancer effect level, without duration adjustment so that the predictiveness of the values (i.e., the probability of response) is maintained (e.g., dose rate effects and dose-related changes in metabolic pathways are not potential issues).

For animal studies, air concentrations corresponding to the detected increase in cancer incidence/mortality over background (e.g., $EC_{10}$ if the study detected a 10% increase) can be used after being converted to an HEC. Alternatively, the lowest air concentration associated with a statistically significant increase may be identified. That is, the air concentration for the lowest animal exposure group (converted to an HEC) for which statistically elevated cancer risk was observed can be used. The considerations discussed

above would still apply (e.g., interspecies sensitivity, duration adjustments). For example, if there is no information on the sensitivity of animals versus humans (i.e., the most human-relevant animal model), the determination of cancer observed effect levels should be put into the context of studies in the same and other species that did not show effects at similar or higher levels/durations, as well as the effect levels demonstrated in other studies. This should be done as part of a broader narrative that gives proper context to the observed adverse effect levels (e.g., applicable conditions and caveats, associated uncertainties). Generally, whether based on animal or human data, an important caveat for observed adverse effect levels, based on endpoints such as excess cancer risk (or noncarcinogenic effects) demonstrated to result from long-term (e.g., lifetime) exposure, is that they may only be appropriately compared to a long-term average air concentration over the same or longer human equivalent exposure duration (i.e., only acute observed adverse effect levels can be appropriately compared to short-term exposure levels).

Ultimately, derivation of air concentrations where adverse effects would be expected to occur (based on dose-response data) in some individuals of the population will be based on best scientific judgment on a case-by-case basis and justified in the DSD.

## 3.14 Exposure-Response or Reference Value Arrays

Exposure arrays are a valuable graphical tool to display toxicity data regarding a chemical across toxic endpoints, species, and exposure durations (USEPA 2009a). Often a chemical has many studies that together describe the toxicity of that chemical based on duration and concentration of exposure, so exposure arrays are valuable to both toxicologists and lay persons. Importantly, exposure arrays may also provide a means by which the toxic effect(s) caused by a given duration exposure may be easily determined.

There are several ways that exposure arrays have been used by various regulatory agencies. The ATSDR regularly uses exposure response arrays to summarize toxicity data for acute, subchronic, or chronic exposure duration for chemicals. In general, the ATSDR plots exposure concentration on the y-axis and effect on the x-axis. The x-axis, in these cases, is further broken down by organ system. Symbols on these graphs represent LOAELs or NOAELs identified in critical studies. This style of representation is particularly valuable because it not only shows toxic effect or biological response induced by exposure, but also conveys a sense of the margin of toxicity, in other words what is the margin between NOAEL and LOAEL for a particular study (Figure 3-11).

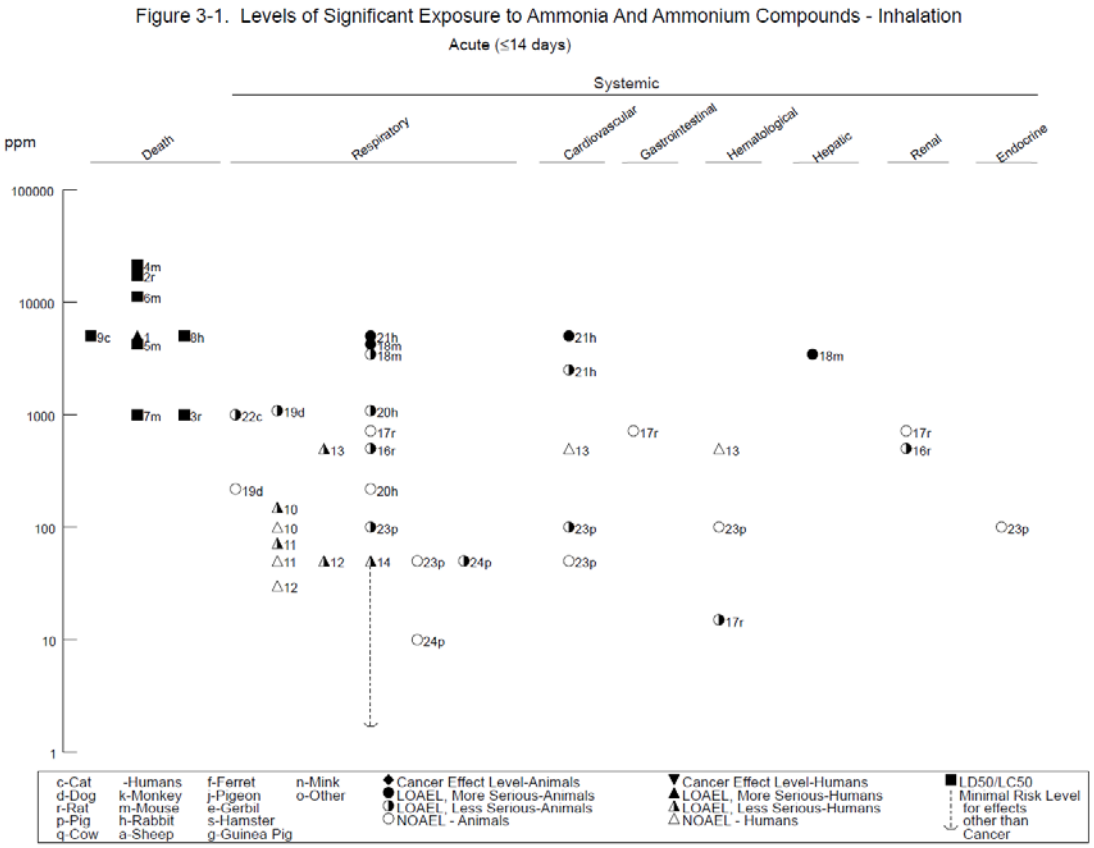


**Figure 3-11 Exposure-response array for ammonia, generated by ATSDR**

Exposure concentration (on a log scale), toxic effects for acute exposure are specified. In addition, symbols represent whether the endpoint was a NOAEL or a LOAEL and in what animal species that value was identified. Importantly, by displaying data in this way, relationships between exposure dose and effect can be observed independent from test organism. (Figure 3-1 from ATSDR 2004).

Similarly, the USEPA (2009a) has recently written guidance for the generation of exposure- response arrays, "Graphical Arrays of Chemical-Specific Health Effect Reference Values for Inhalation Exposures." That document presents duration-specific reference values developed by different federal and state organizations for a chemical as a function of exposure duration (acute, short-term, subchronic, and chronic). Thus, similar to the graphics routinely used by ATSDR, data are displayed in a comprehensive manner that allows comparison across exposure duration, species, and toxic effect. This approach does, however, display reference values rather than NOAELs and LOAELs. Thus, to have a better understanding of the margin of exposure between protective reference values and the concentrations where effects are observed would require identifying the PODs for the reference values, how the $POD_{HEC}$ values were derived, and the UFs applied (Figure 3-12).

Exposure-response arrays should be included in DSDs if sufficient data exist. Minimal data requirements for the generation of an exposure response array include at least two acute, subacute, subchronic, and chronic studies. The format for the exposure-response array may be limited by what data are available for a chemical. However, for a basic toxicity assessment, data displayed in the format of NOAELs and LOAELs may be more

informative because of the lack of adjustment via UFs. Professional judgment should be used to determine the format that is most appropriate to display summary data for a chemical.

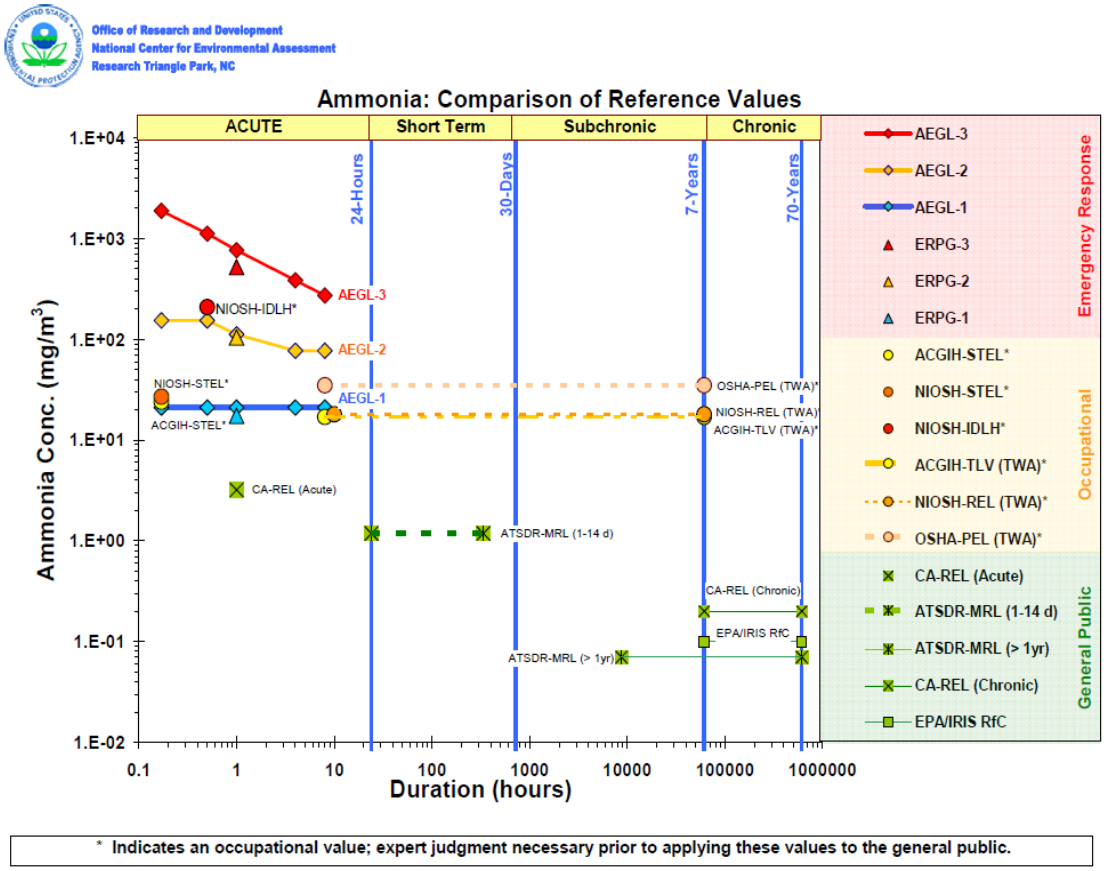


**Figure 3-12 Exposure-reference value array for ammonia, generated by USEPA**

Reference value concentration is displayed on the y-axis while exposure duration is displayed on the x-axis. Importantly, the x-axis is on a logarithmic scale to allow for display of a large range of duration exposure (Figure 2.2 from USEPA, 2009a).

## 3.15 Chemicals with Limited Toxicity Data

The TCEQ frequently evaluates chemicals with limited toxicity data (LTD). Every effort is made to obtain as much information on the chemical of interest as possible. However, when the minimum database requirements for development of an acute ReV (Section 4.3) or chronic ReV (Section 5.4) are not met, then acute or chronic generic ReVs and ESLs may be derived on an as needed basis using route-to-route extrapolation or use of relative toxicity/relative potency, if scientifically defensible (e.g., when there are final DSD values available). Other methods to derive generic ReVs and ESLs are discussed in Section 4.5 for acute inhalation exposure. Generally, URF values are not routinely developed based on a relative toxicity/relative potency approach, except in certain cases (e.g., relative potency factors for polycyclic aromatic hydrocarbons (Chapter 6)).

When the minimum database requirements for development of a chronic RfD (Section 5.4) are not met, a chronic RfD may be derived on an as needed basis, based on route-to-route extrapolation or use of relative toxicity/relative potency approach. URF and SFo values may be developed based on route-to-route extrapolation, if scientifically defensible. Generally, SFo values are not routinely developed based on a relative toxicity/relative potency approach except in certain cases (e.g., relative potency factors for polycylic aromatic hydrocarbons (Chapter 6)). Other methods to derive RfDs are discussed in Section 5.6.

### *3.15.1 Route-to-Route Extrapolation*

In the absence of human and animal dose-response data for either the oral or inhalation route of a given agent, the TCEQ may derive toxicity factors or generic ReVs and ESLs based on data from inhalation or non-inhalation (e.g., most likely oral) exposure routes, respectively, only if strict criteria are met. However, for TCEQ's purposes it is anticipated that the most likely route-to-route extrapolation will be derivation of a generic ESL from oral data. Route-to-route extrapolation for purposes of deriving a generic ESL or RfD will be performed on the $POD_{HEC/HED}$ of the critical study, not on the final toxicity factor so that appropriate UFs can be applied. Most specifically, a $UF_D$ considers and accounts for the uncertainty of deriving a toxicity factor based on route-to-route extrapolation. Route-to-route extrapolation for purposes of deriving a SFo or URF will be performed on the toxicity factor for the exposure route with carcinogenicity data as UFs are not used in the derivation of carcinogenic toxicity factors.

Extrapolation of dose-response data from one exposure route to another is accompanied by uncertainty, which is important to minimize as much as the available data and methods allow. The major factors contributing to the uncertainties associated with route-to-route extrapolation include: (1) the presence of POE effects in the lung or gastrointestinal tract and the potential for such effects for the exposure route being extrapolated to; (2) liver first-pass effects following oral dosing which would result in an expectation of adverse effects different than those due to inhalation exposure; and (3) accurate dosimetry to normalize the internal dose and biologically effective dose achieved by the compared exposure routes (i.e., pharmacokinetic differences) is unknown. USEPA states that if either a first-pass effect or POE effect is present, route-to-route extrapolation is not recommended for derivation of chronic health reference values such as the RfC (USEPA 1994a).

Oral ingestion is the most common exposure route from which toxicity is estimated for other routes, including inhalation. Data from parenteral exposure may also be considered although accurate dosimetry is still required to normalize internal and effective doses to those expected from inhalation. Honma and Suda (1998) performed a correlation of lethal doses of industrial chemicals between oral administration and inhalation exposure (i.e., oral $LD_{50}$ and $LC_{50}$ data) and between intraperitoneal administration and inhalation exposure (i.e., intraperitoneal $LD_{50}$ and $LC_{50}$ data). They demonstrated that the correlations between $LC_{50}$ and $LD_{50}$ data with intraperitoneal administration were higher than those between $LC_{50}$ and $LD_{50}$ with oral administration in both rats and mice.

Given the uncertainties associated with route-to-route extrapolation, the TCEQ does not perform route-to-route extrapolation if any of the following circumstances would be expected based on available data or information (refer to Figure 4-3 in Section 4.1.2 of USEPA 1994a):

- Different critical adverse effects are expected to result from the compared exposure routes, which can be the case for metals, irritants, and sensitizers;
- POE effects occur (e.g., irritants, sensitizers);
- Respiratory or hepatic first-pass effects are expected;
- A respiratory or oral effect is known to occur, but accurate dosimetry between the two routes is not established;
- Referenced oral/inhalation studies do not include adequate assessment of respiratory tract or gastrointestinal effects, respectively; or
- Studies are not of adequate quality to establish a toxicity factor for the exposure route from which to extrapolate.

If the above mentioned route-to-route concerns are addressed, toxicity information from other exposure routes may be used to add to the WOE, determine the MOA, or address other issues when deriving a toxicity factor for another route of exposure. For example, if a 2-generation study is available via the oral route showing no reproductive/developmental effects, and oral absorption is known to occur, then this information may be used to support the likelihood that the chemical is not a reproductive/developmental toxicant via the inhalation route (assuming no POE effects, etc., are expected).

The preferred method for route-to-route extrapolation is the use of PBPK modeling, which provides the best estimate of a toxicant's internal and biologically effective dose as a function of exposure. PBPK modeling accomplishes this by application of algorithms for physiologic factors such as ventilation/perfusion ratios, renal clearance and metabolism, as well as properties of the given toxicant (e.g., partition coefficients, reactivity). The combination of PBPK modeling and supporting toxicity data allows route-to-route extrapolation with fewer uncertainties than other methods, and the TCEQ utilizes this method whenever possible to derive toxicity factors for a constituent. When the available data are inadequate for PBPK modeling, other available mathematical dosimetry models can be used based on MOA of the chemical and whether necessary physiologic factors are available. For extrapolation of oral to inhalation, the following papers provide several case studies for different chemicals illustrating the use of mathematical models and approaches for route-to-route extrapolation that are particularly informative (e.g., chloroform, cadmium, carbon tetrachloride, and trichloroethylene) (Overton and Jarabek 1989a, 1989b; Gerrity and Henry 1990; Overton 1990; USEPA 1994a).

For deriving a generic ReV and ESL, if a more appropriate chemical-specific model is not available, the $POD_{HEC}$ can be calculated from the corresponding $POD_{HED}$ as follows (Equation 3-8):

**Equation 3-8 $POD_{HEC}$ Derived from $POD_{HED}$**

$$POD_{HEC} = \left(POD_{HED} \times BW_H \times \frac{day}{20\ m^3}\right) \times \left(\frac{A_{oral}}{A_{inh}}\right)$$

Where:

$POD_{HEC}$ = human equivalent concentration POD ($mg/m^3$)
$POD_{HED}$ = human equivalent dose POD (mg/kg-day)
$BW_H$ = human body weight (70 kg)
$A_{oral}$ = absorption via oral exposure (unitless)
$A_{inh}$ = absorption via inhalation exposure (unitless)

For deriving a RfD, the $POD_{HED}$ can be calculated from the corresponding $POD_{HEC}$ as follows (Equation 3-9):

**Equation 3-9 $POD_{HED}$ Derived from $POD_{HEC}$**

$$POD_{HED} = \frac{\left(POD_{HEC} \times \frac{20\ m^3}{day}\right)}{BW_H} \times \left(\frac{A_{inh}}{A_{oral}}\right)$$

As for noncarcinogenic effects, the appropriateness of route-to-route extrapolation of dose data for carcinogenic effects relies on a case-by-case analysis of available data (USEPA 2005a). For deriving a URF, assuming route-to-route extrapolation is considered scientifically defensible, the following equation may be used to convert the SFo (Equation 3-10):

**Equation 3-10 URF Derived from the SFo**

$$URF\ (\text{risk per } \mu g/m^3) = \left(\frac{SFo}{BW_H}\right) \times \frac{20\ m^3}{day} \times \left(\frac{1\ mg}{1{,}000\ \mu g}\right) \times \left(\frac{A_{inh}}{A_{oral}}\right)$$

Where:

SFo = oral slope factor (risk per mg/kg-day)
$BW_H$ = human body weight (70 kg)
$A_{oral}$ = absorption via oral exposure (unitless)
$A_{inh}$ = absorption via inhalation exposure (unitless)

Rearranging the equation to derive a SFo from a URF yields (Equation 3-11):

**Equation 3-11 SFo Derived from the URF**

$$SFo\ (\text{risk per mg/kg-day}) = \left(\frac{URF}{\frac{20\ m^3}{day}}\right) \times BW_H \times \left(\frac{1{,}000\ \mu g}{1\ mg}\right) \times \left(\frac{A_{oral}}{A_{inh}}\right)$$

Chemical-specific values for $A_{inh}$ and $A_{oral}$ should preferentially be used but $A_{inh}$ and $A_{oral}$ data from a structurally-related chemical or chemical-class may be used if data indicates it is relevant and scientifically defensible. Otherwise, a default absorption ratio ($A_{inh}$ /

$A_{oral}$ or $A_{oral}$ / $A_{inh}$) of 1 may be used. The TCEQ utilizes best scientific judgment on a case-by-case basis in determining whether to perform route-to-route extrapolation for derivation of a particular toxicity factor (generic ReV and ESL, RfD, SFo, URF). It is noted that the oral-to-inhalation extrapolations could result in $POD_{HEC}$ and/or toxicity factor air concentration values that are unlikely given the physical/chemical properties (e.g., low vapor pressure) of the particular chemical.

## *3.15.2 Relative Toxicity/Relative Potency Approach*

### 3.15.2.1 Background

Relative potency can be defined as a procedure to estimate the "toxicity" of a LTD chemical in relation to a reference or an index chemical(s) for which toxicity has been well defined. The concept of relative potency has been used for polycyclic aromatic hydrocarbons (PAHs) (Collins et al. 1998) and organophosphate pesticides (USEPA 2002b). PAHs are considered a class of structurally and toxicologically similar chemicals. Therefore, the concept of relative toxicity has been used to derive toxicity values for PAHs with limited toxicity information based on the toxicity information of benzo[a]pyrene, for which there is a wealth of information (Collins et al. 1998).

Various government and regulatory agencies have adopted the relative potency approach or have adopted comparable methodologies for the purpose of estimating toxicity values for chemicals with limited information. The relative potency approach was used to determine Acute Exposure Guideline Level (AEGL) values for some nerve agents based on the toxicity data of nerve gas sarin. The rationale for the relative potency approach was that other nerve gases such as tabun, soman, cyclosarin, and VX were similar in structure and toxicity to sarin gas (NRC 2003). The emergency planning and safety analysis divisions within the US Department of Energy (USDOE) complex often need to derive Temporary Emergency Exposure Levels (TEELs) for chemicals with limited toxicological information until ERPGs are available (USDOE 2008). The methodology for deriving TEELS for LTD chemicals involves comparing 50% lethality data of a structurally-similar chemical with adequate inhalation reference values to the lethality data of the LTD chemical in order to estimate values for the LTD chemical if that is the only available data (USDOE 2008).

### 3.15.2.2 Quantitative Structure Activity Relationships versus Structural Activity Relationships

Quantitative structure activity relationships (QSARs) use a mathematical model to quantitatively predict pharmacological or toxicological activity for a series of compounds from chemical structure (USEPA 1999a). While QSARs have proven to be very useful for predicting mutagenicity, their use in risk assessment is limited as they require highly trained toxicologists who are proficient in the use of the appropriate software to correlate complex molecular structures to varied health effects (e.g., acute vs. chronic, *in vitro* vs. *in vivo*, mutagenicity vs. general toxicity vs developmental toxicity). Therefore, QSARs can become time consuming, data-intensive, and expensive tools in risk assessment. In addition, there may not be a highly predictive model available for the toxicological endpoint of interest. For example, there are very few QSARs available to evaluate and predict acute inhalation toxicity. Ones that are available have not proven to be useful in

the diverse setting of regulatory toxicology. Due to these reasons, the TCEQ does not directly perform QSAR to predict acute or chronic inhalation toxicity endpoints but does use information from QSAR studies published in the scientific literature when available. Below is a list of QSAR software that may be of use to individuals wishing to apply these tools in a risk assessment:

- 3-Dimensional QSAR: www.3d-qsar.com/
- E-Dragon Software: www.vcclab.org/lab/edragon/
- OECD QSARs: www.oecd.org/env/chemicalsafetyandbiosafety/oecdquantitativestructure-activityrelationshipsprojectqsars.htm
- QSAR World: www.qsarworld.com/free-programs.php
- Toxicity Estimation Software (TEST): www.epa.gov/nrmrl/std/qsar/qsar.html
- VEGA QSAR: www.insilico.eu/use-qsar.html

Structural activity relationships (SARs) can be described as the relationship of the molecular structure of a chemical with a physical/chemical property, environmental fate, and/or specific effect on human health or on environmental species (USEPA 1999a). Both the USEPA and European Chemical Bureau have recognized the benefits of using SARs as a way to reduce the amount of testing required for chemicals with limited information. USEPA and the European Chemical Bureau define a category as a group of chemicals whose physical/chemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. The underlying premise of SARs is that members of a chemical group or class share similar physical and chemical properties and MOA, and therefore, they will tend to behave in a similar toxicological manner (USEPA 1999a, USEPA 1999b). For example, the similarities among the chemicals in the category can be based on a common functional group (e.g., aldehyde, epoxide, ester, etc.) or an incremental and constant change across the category (e.g. the dimethylene group difference between adjacent members of the alpha-olefins or the presence of homologous series as in glycol ethers) (USEPA 1999b).

The TCEQ uses the principles of SAR to choose an appropriate analog chemical or to categorize chemicals into groups or classes. An analog is defined as a chemical compound that is structurally similar to another compound but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group). In order to use the analog approach, there should be unambiguous structural and metabolic relationships between the LTD chemical and the chemical with toxicity information. A potential category can be formed by grouping a series of chemicals or using chemical categories that have been defined by USEPA such as the high production volume chemical classes (USEPA1999b).

#### 3.15.2.3 Steps to Perform Relative Toxicity/Potency

The TCEQ uses the principles of SAR coupled with the knowledge of the MOA of an index chemical or a class of chemicals in conjunction with expert judgment of trained staff to develop generic toxicity factors for LTD chemicals. Procedures used previously by others are used by TCEQ staff to estimate toxicity factors based on relative potency

(USDOE 2008, Glass et al. 1991). The TCEQ maintains the generic toxicity factors on an interim basis until additional toxicological information becomes available. The estimation process is especially valuable for estimating toxicity factors for categories of chemicals that are known to be relatively less toxic (Globally Harmonized System (GHS) Categories 3, 4 and 5; UN 2005) and for which traditional testing may not occur. Use of scientifically-valid estimation tools for the relatively less toxic chemicals allows more resources (time and resources) to be directed toward toxicity factor development for the more toxic chemicals (GHS Categories 1 and 2) which warrant a higher level of review. The following steps briefly describe the qualitative expert judgment approach that the TCEQ uses to apply the concept of SAR and relative potency for estimating generic ESLs or other toxicity factors for LTD chemicals. These steps can be employed when similar chemical categories or an analog chemical approach is used:

Step 1: Identify potential index chemical(s) for which toxicity factors have been developed.

Step 2: Gather data on physical/chemical properties, toxicity, etc. for the potential index chemical(s) and the LTD chemical.

Step 3: Construct a matrix of data for all chemicals. Table 3-7 is an example of how to organize endpoint information for a series of potential index chemicals and the LTD chemical.

Step 4: Evaluate the data to determine if there is a correlation among chemicals and the endpoints by conducting a simple trend analysis to determine whether a predictable pattern exists amongst the chemicals.

Step 5: Perform an MOA analysis and determine the relevant endpoints that can be used for a relative potency approach. Relevant endpoints should be determined using similar testing techniques, exposure durations, and species.

Step 6: Calculate the relative potency of the pertinent endpoint based on an MOA analysis of the index chemical to the pertinent endpoint of the LTD chemical (Equation 3-12):

**Equation 3-12 Relative Potency**

$$\text{Relative Potency} = \frac{\text{Relevant Endpoint}_{\text{LTD Chemical}}}{\text{Relevant Endpoint}_{\text{Index Chemical}}}$$

Step 7: Estimate the generic toxicity factor of the LTD chemical by adjusting the index chemical's value by the relative potency factor. The following equation shows this adjustment for a generic ReV and ESL, but it could also be used for a chronic generic ReV and ESL or RfD (Equation 3-13):

**Equation 3-13 Generic ReV & ESL for LTD Chemicals**

$$\text{Generic ReV}_{\text{LTD Chemical}} = \text{ReV}_{\text{Index Chemical}} \times \text{Relative Potency}$$

$$\text{Generic ESL}_{\text{LTD Chemical}} = \text{ESL}_{\text{Index Chemical}} \times \text{Relative Potency}$$

Relevant endpoint data used to ratio toxicity may be as straightforward as mortality measurements (e.g., $LC_{50}$ and $LD_{50}$ data). In addition, MOA can be used to identity other relevant endpoints whose ratio is expected to describe the difference in toxicity between the two chemicals. For example, if one needs to estimate a RfD for a limited-data organophosphate pesticide based on the RfD of another organophosphate pesticide, measurements of brain cholinesterase inhibition could be the relevant endpoint. The RfD of the index organophosphate pesticide would be multiplied by the ratio of cholinesterase inhibition of the limited-data chemical to the cholinesterase inhibition of the index chemical.

If multiple values of relative potency based on the same or different relevant endpoint are available, a geometric mean of the calculated relative potency ratios ($R_{GM}$) is obtained. The generic value for the LTD chemical can then be calculated by multiplying the $R_{GM}$ by the value of the structurally-similar index chemical. This process may be repeated if more than one chemical similar to the chemical of interest is identified.

Alternately, depending on data availability and time and resource constraints, the lowest, most conservative toxicity factor for a series of structurally-similar compounds can be used as a generic value for other structurally-similar compounds with limited toxicity information. For example, OEHHA developed a reference exposure level (REL) for metallic mercury vapor, but there was less information on mercury salts. However, OEHHA stated “Since mercury salts have no significant vapor pressure under normal atmospheric conditions, they would only be of concern as hazards if aerosolized in aqueous solution or burned. This REL is developed for metallic mercury vapor and would be an overestimate of the REL for mercury salts.” (OEHHA 1999)

**Table 3-7 Example of How to Organize Endpoint Information for a Series of Chemicals**

| Endpoint | Potential Index Chemical #1 | Potential Index Chemical #2 | LTD Chemical | Potential Index Chemical #3 |
|---|---|---|---|---|
| Category | | | | |
| Molecular weight | | | | |
| Chemical Formula | | | | |
| Chemical Structure | | | | |
| Physical Form | | | | |
| Boiling Point | | | | |
| Melting Point | | | | |
| Vapor Pressure at $25^{o}$ C | | | | |
| Partition Coefficient | | | | |
| Log $K_{ow}$ | | | | |
| Solubility | | | | |
| Odor | | | | |
| Health effects | | | | |
| Short-term ESL | | | | |
| $LC_{50}$ | | | | |
| $LD_{50}$ | | | | |
| $RD_{50}$ | | | | |
| NOAEL | | | | |
| LOAEL | | | | |
| Reproductive/ Developmental | | | | |

## 3.16 Sensitization

Sensitization is an immune process by which individuals develop an exaggerated, pathological immune response, or hypersensitivity, upon subsequent exposure to a particular antigen. Sensitization occurs in two phases: (1) induction and (2) elicitation. Induction occurs when an individual is initially exposed to an antigen. This antigen is

presented in the local lymph node and initiates clonal expansion of T lymphocytes, leading to the development of immunological memory. Immunological memory supports elicitation, an abrupt and intense cell- or antibody-mediated allergic response, upon subsequent exposure to the primary antigen.

A sensitizer is defined by OSHA as "a chemical that causes a substantial proportion of exposed people or animals to develop an allergic reaction in normal tissue after repeated exposure to the chemical" (Appendix A of 29 CFR 1910.1200). Chemical sensitization can occur through dermal, respiratory, and oral routes of exposure. Dermal sensitization causes allergic contact dermatitis. Systemic sensitization occurs via the oral route of exposure where subsequent exposure may result in gastrointestinal distress or more severe reactions such as anaphylaxis. A respiratory sensitizer is a chemical that causes the development of an allergic reaction in the airways following inhalation. The TCEQ identifies a chemical as a sensitizer if evidence exists that a chemical can induce specific hypersensitivity in humans or appropriate animal models using established scientific methods. Current established scientific methods used to determine whether a chemical is a sensitizer and guidance regarding evaluation of available *in vitro* and *in vivo* studies and human epidemiological and occupational exposure data are discussed extensively by the EPA (2003c), FDA (2002), GHS (2009), and WHO (2010). Through selection of the most sensitive endpoint and the application of UFs, short-term and long-term ESLs are designed to protect the human population, including sensitive individuals, against adverse health effects. Sensitization is typically caused by high initial doses of the chemical antigen (USEPA 1994a). Therefore, to protect against sensitization, exceedances of the short-term or long-term ESLs should be discouraged during the air permit review for chemicals identified as respiratory sensitizers. However, it should be noted that this precaution does not necessarily protect individuals who were previously sensitized. The TCEQ specifically identifies respiratory sensitizers in the DSD to inform the public and to allow previously sensitized individuals to further reduce their individual exposure to these chemicals.

## 3.17 Significant Figures and Rounding Procedures

### *3.17.1 General Procedures*

In order for the TCEQ to be consistent in the derivation process of toxicity factors, the convention of retaining significant figures used throughout the calculation process should be consistent. The TCEQ determined that it will not round numbers in intermediate equations (i.e., no rounding of numerical results will occur between separate equations). When each calculation is performed, original numerical data should be used, showing the unit conversions.

Once the toxicity factor is calculated, it will then be rounded to two significant figures. When rounding, TCEQ will use the half round down method; if the number next to the significant figure to be rounded is a 5 or less, the number will be rounded down (e.g., 13563 rounded to two significant figures = 13000). If the number next to the significant

figure to be rounded is a 6 or more, the number will be rounded up (e.g., 13623 rounded to two significant figures = 14000).

When converting toxicity factors and ESL values from µg/$m^3$ to ppb, or ppb to µg/$m^3$, the rounded value will be used. Once the conversion is complete, the converted number will then be rounded to two significant figures. A statement will be added to the DSD document informing readers of the method by which the final values were calculated. When the TCEQ shows calculations in the DSD, it will be up to the judgment of the individual toxicologist as to how many significant figures are represented in the intermediate calculations.

### *3.17.2 Air Permitting*

For air permitting, the rounded toxicity factor will then be used to determine the ESL (i.e., the ReV will be multiplied by 0.3 or the URF will be used to calculate a 1 in 100,000 extra cancer risk). The ESL will also be rounded to two significant figures.

# Chapter 4 Derivation of Acute Toxicity Factors

## 4.1 Published Toxicity Factors or Guideline Levels

The following sections discuss the database sources to which the TCEQ refers during its search for published acute values and/or data. When acute toxicity factors or guideline levels are identified in the scientific literature or databases, they are reviewed to determine whether the approach used to develop these toxicity factors is similar to the procedures used by the TCEQ to develop ReVs. If so, the TCEQ considers adoption of the published toxicity factor or guideline level, with preference given to values that have undergone an external peer review and public involvement process. Many published acute toxicity factors are not appropriate to be used as ReVs because it is likely that procedures other than those recommended in this guidance document were used to derive these values. Due to time and resource constraints, the TCEQ considers the published values and their respective key studies as a starting place for gathering toxicity information. However, because the toxicity factors or guideline levels may be outdated, the TCEQ also evaluates peer-reviewed studies available after the date these toxicity factors or guideline levels were published to ensure that the latest data are considered prior to developing an acute toxicity factor.

The TCEQ also reviews other published toxicity factors and toxicity information from organizations that specifically address susceptibility of children. Some of those organizations and factors/levels are ATSDR toxicological profiles, USEPA TEACH chemical summaries, CalEPA's RELs, USEPA Voluntary Children's Chemical Evaluation Program (VCCEP), World Health Organization (WHO), Health Canada, and ECETOC.

The following sections list the major database sources to which the TCEQ refers during its search for published acute values and/or toxicity data, although Jarabek (1995a), USEPA (2002a), and Woodall (2005) provide more extensive discussions of available acute toxicity values.

### *4.1.1 Federal and State Guideline Levels*

Cal EPA OEHHA publishes acute reference exposure levels (RELs) for chemicals identified in the Air Toxics "Hot Spots" Act (www.oehha.ca.gov/air/acute_rels/index.html). The RELs are no-effect levels used to evaluate exposures for 1 h and 8 h, except for reproductive/developmental toxicants (OEHHA 2008).

The ATSDR publishes acute (1-14 days) inhalation minimal risk levels (MRLs) for noncancer health effects for several chemicals (www.atsdr.cdc.gov/mrls/index.asp)

(ATSDR 2007). However, for some MRLs, dosimetric modeling to convert the POD from experimental animal concentrations to a $POD_{HEC}$ was not conducted.

### 4.1.2 Guideline Levels for Public Emergency Response Situations

Acute guideline levels for the general public have been developed for use in emergency response situations involving accidental chemical releases. These guideline levels are concentrations that may cause effects. These effects range from mild, transient irritation for Acute Exposure Guideline Levels (AEGL-1) to life threatening for AEGL-3 (Figure 4-1). Emergency response guideline levels and the organizations that develop them are as follows:

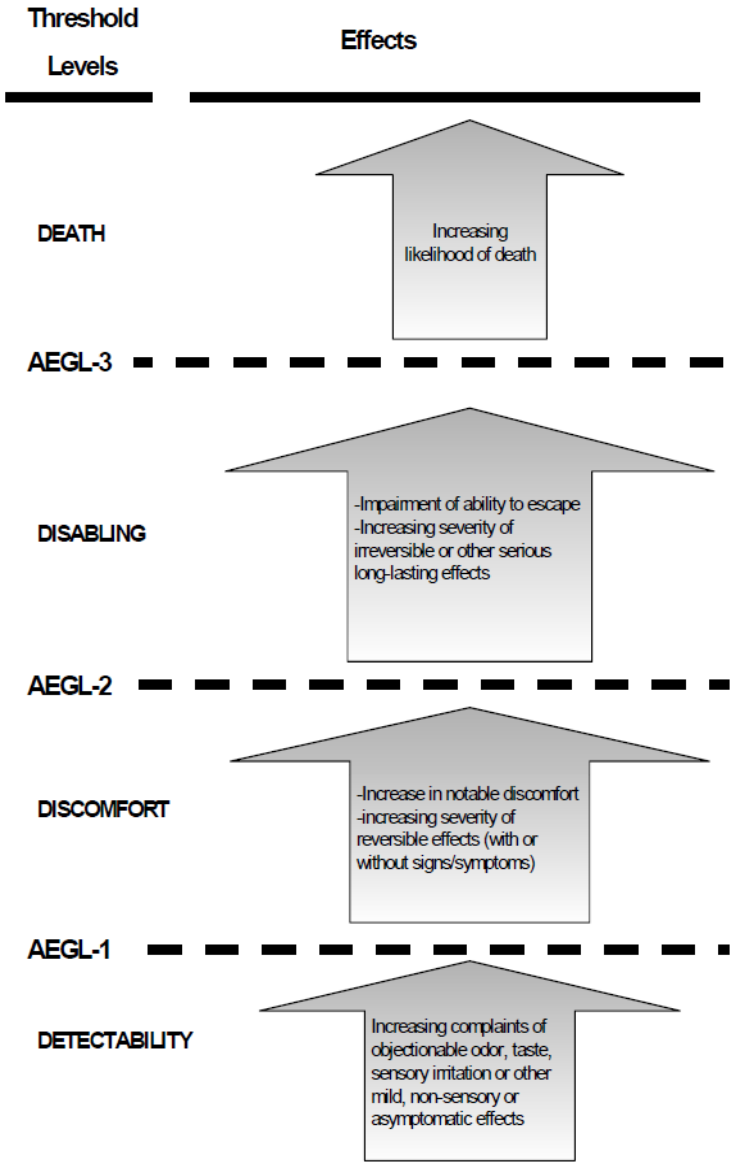


**Figure 4-1 Illustration of different effect levels for Acute Exposure Guideline Levels (AEGLs) (Figure 1-1 from NRC 2001).**

- Acute Exposure Guideline Levels (see Figure 4-1 for health effects at AEGL-1, AEGL-2, AEGL-3), National Advisory Committee for the Development of Acute Exposure Guideline Levels for Hazardous Substances (AEGL Committee), part of the National Research Council of the National Academies of Science (NRC 2001) (www.epa.gov/oppt/aegl/index.htm);
- Emergency Response Planning Guidelines (ERPG-1, ERPG-2, ERPG-3), AIHA. The health effects observed for ERPG-1, ERPG-2, ERPG-3 are similar to AEGL-1, AEGL-2, AEGL-3, respectively;
- Temporary Emergency Exposure Limits (TEEL-0, TEEL-1, TEEL-2, TEEL-3), Department of Energy (USDOE) Emergency Management Advisory Committee's Subcommittee on Consequence Assessment and Protective Action (SCAPA) (USDOE 2008). Table 2-2 of USDOE (2008) provides a comparison of the health effects observed for different levels of AEGLs, ERPG, and TEELs.

### *4.1.3 Short-Term Occupational Exposure Limits*

Data used in the establishment of the following short-term occupational exposure limits (OELs) (i.e., ceiling limits, short-term exposure limits (STELs), and immediately dangerous to life or health concentrations (IDLHs)) may also be considered; however, these values are developed for healthy workers during an 8 h work day and not for the general public. The workplace environmental exposure levels (WEELs) were developed for certain chemical and physical agents and stresses when no legal or authoritative limits exist.

- Ceiling Limits - published by OSHA, ACGIH, and AIHA. The ceiling concentrations must not be exceeded during any part of the workday;
- STELs - published by ACGIH, NIOSH and OSHA. The STEL is a 15-minute time-weighted average (TWA) exposure that should not be exceeded at any time during a workday;
- IDLHs - published by NIOSH for use in assigning respiratory protection equipment as part of the Standards Completion Program, a joint project by NIOSH and OSHA. IDLH values, as well as the basis and references for current and original IDLH values, are available in an online database maintained by NIOSH (www.cdc.gov/niosh/idlh/idlh-1.html).

### *4.1.4 Summary of Acute Reference Values*

Table 4-1 is a summary table of the acute reference values discussed above. General population guideline levels are the most applicable for adoption by the TCEQ, if procedures similar to those outlined in the Guidelines have been followed.

**Table 4-1 Summary Table of Published Acute Reference Values**

| Acute reference value | Exposure duration | Organization |
|---|---|---|
| **General population guideline levels** | | |
| MRL – minimal risk level | 1-14 day (acute) | ATSDR |
| REL – reference exposure level | 1 h and 8 h except for reproductive/developmental toxicants | OEHHA |
| ARE – acute reference exposure | 1, 4, 8, and 24 h | USEPA |
| **Public emergency response guideline levels** | | |
| AEGL – acute exposure guideline level | 10 and 30 min; 1, 4, and 8 h | NAC/AEGL Committee |
| ERPG – emergency response planning guideline | 1 h | AIHA |
| TEEL – temporary emergency exposure level | 15 min (TWA) | DOE |
| **Occupational exposure limits for healthy workers** | | |
| WEELs – workplace environmental exposure levels | 8 h (TWA) ; Ceiling or Short-Term TWA | AIHA |
| Ceiling Limit | Should not be exceeded during any part of the working exposure | OSHA; ACGIH |
| **Occupational guideline levels for healthy workers** | | |
| IDLH – immediately dangerous to life and health | Up to 30 min (immediate action) | NIOSH |
| STEL – short term exposure limit | 15 min (TWA) | NIOSH; OSHA; ACGIH |
| TLV-STEL – TLV short-term exposure limit | 15 min (TWA) | ACGIH |

### 4.1.5 Toxicologic Assessments from other Countries

If acute toxicity values or toxicity assessments are available from international agencies they are considered as sources of toxicity information and key studies (e.g., acute reference concentrations from Organisation for Economic Co-Operation and Development (OECD 2010), WHO, IARC, Health Canada or the Dutch government's National Institute for Public Health and the Environment (RIVM).

## 4.2 Acute Exposure Duration Adjustments

As discussed in Section 3.8, if an experimental study is available for the specific exposure period being evaluated, no adjustment for exposure duration is required. If the MOA of a chemical indicates the appropriate dose metric is concentration (i.e., an enhanced response is not produced by prolonged exposure), a duration adjustment is not performed. For example, odor and other mild sensory effects are typically concentration dependent (NRC 2001). Therefore, the TCEQ does not perform exposure duration adjustments for odor or mild sensory effects unless experimental data suggest odors or mild sensory effects increase in severity because of the cumulative dose over time.

As discussed in Section 3.8, if a calibrated, predictive PBPK model or other mathematical inhalation dosimetry model is available and validated for a given chemical or if chemical- and endpoint-specific values of the exponents for C and T can be determined from experimental data, then this information is used to adjust exposure concentrations. The latest version of USEPA's BMDS software (Version 2.1.2) can calculate chemical-specific values of "n" based on chemical-specific data (Section 3.8.1), or categorical regression can be used to make duration adjustments (Woodall et al. 2000).

In the absence of such information, duration adjustments are based on the relationship of the product of C and T as discussed in the following sections. The following default procedures are used to perform exposure duration adjustments for chemicals made over a limited time period. Duration adjustments for data based on reproductive/developmental effects are treated differently (Section 4.2.4).

### 4.2.1 Adjustments from a Shorter Exposure Duration to a Longer Exposure Duration

Duration adjustments are typically completed by applying Haber's rule as modified by ten Berge (1986) as discussed previously in Section 3.8. It is important to look at the mechanistic data for each chemical and determine the appropriate duration adjustment on a case-by-case basis (Woodall et al. 2000). As an example of how to perform an adjustment for a 1-h ReV, if the experimental study was conducted for a 30-min exposure duration, and concentration and duration both play a role in toxicity, then the concentration for a 1-h exposure duration would be derived as follows. Using the equation for Haber's rule, as modified by ten Berge (1986) ($C^n \times T = K$), and a default value of one for "n", the equation is expressed as (Equation 4-1):

**Equation 4-1 Adjustment from a Shorter to a Longer Exposure Duration**

$$C_1^n \times T_1 = C_2^n \times T_2$$

When adjusting from one concentration ($C_1$) for a specific exposure duration of 30 min ($T_1$) to another concentration ($C_2$) at the desired exposure duration of 60 min ($T_2$), then the TCEQ assumes that n = 1. This is generally thought to be a conservative procedure since it results in a large decrease in concentration (Woodall et al. 2000). The equation simplifies to the following:

$$C_1 \times T_1 = C_2 \times T_2$$

Solving for $C_2$:

$$C_2 = C_1 \times \left(\frac{T_1}{T_2}\right), \text{or}$$

$$C_2 = C_1 \times \left(\frac{30\ \text{min}}{60\ \text{min}}\right)$$

## *4.2.2 Adjustments from a Longer Exposure Duration to a Shorter Exposure Duration*

For adjustment from an experimental study of less than or equal to 24-h to shorter durations for the development of a 1-h ReV, the TCEQ uses MOA information as discussed in Jarabek (1995). If it can be determined that concentration and duration both play a role, then Haber's rule as modified by ten Berge (1986) with a default value of "n" = 3 will be used to adjust the concentration at a specific exposure duration of > 1-h to 1-h. This is generally thought to be a conservative procedure since it results in a small increase in concentration (Woodall et al. 2000). If it can be determined that concentration alone is the dominant determinant of toxicity or if sufficient MOA information is not available for a chemical, the TCEQ conservatively assumes there is no change in concentration (USEPA 1998b, USEPA 2002a). For example, if concentration alone plays a role in toxicity, the experimental study was conducted for a 4-h exposure duration and the POD was 30 ppm, then the POD for a 1-h exposure duration is assumed to be 30 ppm.

## *4.2.3 Adjustments for Subacute Studies*

### 4.2.3.1 Adjustments for a 1-h ReV

In some cases, toxicity information is available for a chemical from a well-conducted subacute study generally lasting from 1 day to 4 weeks. The TCEQ uses the experimental data from the subacute study when it is justified by the MOA analysis. In addition, the TCEQ uses MOA information (Jarabek 1995) to determine if concentration alone is the dominant determinant of toxicity or whether concentration and duration both play a role. If it can be determined that concentration and duration both play a role, then Haber's rule as modified by ten Berge (1986) with a default value of "n" = 3 will be used to adjust the concentration at a specific exposure duration of > 1-h/day to 1-h/day. If it can be determined that concentration alone is the dominant determinant of toxicity or if MOA

information is not available for a chemical, the TCEQ conservatively assumes there is no change in concentration in order to derive the 1-h ReV.

As an example of how to perform an adjustment if concentration and duration both play a role in toxicity, the experimental study was conducted for 4 h/day for 5 days, and the POD was determined to be 100 ppm, then the POD for a 1-h exposure duration is calculated using the procedures described below.

When adjusting from one concentration ($C_1$) at a specific exposure duration of 4 h ($T_1$) to another concentration ($C_2$) at the desired exposure duration of 1 h ($T_2$ ), then the TCEQ assumes that "n" = 3 (Equation 4-2):

**Equation 4-2 Adjustment for a 1-hr ReV**

$$C_1^3 \times T_1 = C_2^3 \times T_2$$

Solving for $C_2$:

$$C_2^3 = (100 \text{ ppm})^3 \times \left(\frac{4 \text{ h}}{1 \text{ h}}\right), \text{or}$$

$$C_2 = ((1 \times 10^6 \text{ ppm}) \times 4)^{\frac{1}{3}}$$

$$C_2 = 160 \text{ ppm}$$

## *4.2.4 Adjustments for Reproductive/Developmental Effects*

Reproductive and developmental studies are usually conducted by exposing experimental animals to repeated doses over several days (e.g., 6-h/day for gestational day 6-15). The TCEQ uses a single day of exposure from the experimental study as the exposure duration (OEHHA 2008). In doing so, we recognize reproductive and developmental effects may have been caused by only a single day's exposure that occurred at a critical time during gestation. The averaging time for ReV and ESL values based on reproductive or developmental effects is the number of hours of the single day of exposure, not a 1-h averaging time as is typical for 1-h ReVs. The TCEQ also recognizes the fact that some reproductive effects may also be considered developmental effects. The following sections provide a more detailed discussion of short-term reproductive and developmental effects in order to evaluate "critical windows of exposure."

### 4.2.4.1 Short-Term Reproductive Effects

The USEPA (1996e) defines reproductive effects as biologically adverse effects on the reproductive systems of females or males that may result from exposure to toxicants. The toxicity may be expressed as alterations to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes. In general, reproductive effects may include, but are not limited to, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence (biological aging), or modifications in other functions that are dependent on the integrity of the reproductive systems.

Reproductive difficulties due to various causes are common. According to the US Centers for Disease Control, about 10 percent of women ages 15-44 years in the United States have difficulty getting pregnant or staying pregnant. There are three main targets for reproductive effects; direct acting toxicants on the central nervous system altering secretion of hormones (e.g., the hypothalamus), direct acting toxicants on the reproductive organs (ovary and testis), and those that inhibit or alter spermatogenesis, which can lead to sterility or decreased fertility. Examples of adverse reproductive effects that can occur after short-term exposure include decreased litters, ovary weight change, testicular atrophy, vaginal bleeding, spontaneous abortions or miscarriage (loss of the embryo or fetus before full term), impaired spermatogenesis, abnormal sperm, and decreased fertility (ATSDR 2007).

To determine the critical reproductive toxicity endpoint for short-term exposure, the endpoint should be evaluated along with the MOA of the toxicant to evaluate the plausibility of the adverse effect to result following short-term exposure. In a reproductive study, discussing changes in maternal body weight gain is appropriate (ATSDR 2007). If there are not route-specific data regarding short-term reproductive effects, toxicokinetic data may be used to support the toxicant's potential to affect reproduction across routes of exposure. In those cases, it may be possible to provide qualitative information regarding the potential for reproductive effects across routes (ATSDR 2007). In addition to pharmacokinetic data relevant to the potential for distribution remote to the portal of entry (e.g., respiratory tract), route-to-route extrapolation or data from a sufficiently structurally similar compound or mixture may provide information regarding the potential for reproductive effects due to short-term exposure. For more information on reproductive and developmental effects, see WHO (2001), USEPA (1996e), and ATSDR (2007).

#### 4.2.4.2 Short-Term Developmental Effects

Developmental effects are any adverse effects to the offspring or developing organism resulting from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation (ATSDR 2007, USEPA 1991). Developmental effects can be caused by effects of the toxicant on the parents and also direct interaction of the toxicant on the offspring or developmental processes. Occasionally, it can be difficult to distinguish between the two. Exposure to the parents prior to conception can result in developmental effects in their offspring and, potentially, in subsequent generations (USEPA 1991). There are four manifestations of developmental toxicity: death, structural abnormality, growth alteration, and/or functional deficit (e.g., neurobehavioral endpoints). Examples of specific developmental effects that can occur after short-term exposure include malformations, early postnatal mortality, reduced birth weight, mental retardation, sensory loss, and other adverse functional or physical changes that are manifested after birth (USEPA 1991). Teratogenicity is a specific term used to describe permanent structural abnormalities that may adversely affect survival, development, or function (ATSDR 2007).

It is assumed that a toxicant that produces an adverse developmental effect in experimental animals will potentially pose a hazard to humans following sufficient exposure during development. This is assumed because it is difficult to determine the

most appropriate species in terms of predicting the specific types of developmental effects seen in humans. The types of developmental effects seen in animal studies may not necessarily be the same as those that may be produced in humans (USEPA 1991). Animal species differ in their critical periods, differences in timing of exposure, metabolism, developmental patterns, placentation, or mechanisms of action (USEPA 1991). Toxicokinetics and the MOA should be used to select the most appropriate animal species. Without that information, the most sensitive species should be used, based on observations that humans are equal to or are more sensitive as the most sensitive animal species tested for the majority of agents known to cause human developmental toxicity (USEPA 1991). For more information on developmental effects see USEPA (1986, 1991), Carney and Kimmel (2007), WHO 2006, Davis et al. 2009, Van Raaij et al. 2003, and Rogers et al. (2004).

## 4.3 Minimum Database Requirements for Development of an Acute ReV

The minimum toxicological database required for the development of an acute 1-h ReV is a well-conducted acute or subacute inhalation bioassay that evaluates a comprehensive array of endpoints, including an adequate evaluation of POE respiratory tract effects, and establishes an unequivocal NOAEL and/or LOAEL. Table 4-2 lists the preferred database needed to develop an acute 1-h ReV and the confidence level assigned to databases consisting of various types of studies, assuming the generation of sufficiently informative dose-response data. The TCEQ considers and evaluates developmental toxicity studies as possible key studies when developing both acute and chronic toxicity factors. Confidence in toxicological databases will vary depending on how much is known about each chemical's MOA and the quality of the experimental study (Section 3.11.3).

**Table 4-2 Minimum Database for an Acute 1-h ReV and Assignment of Confidence Levels**

| | **Acute Mammalian Database** [a] | **Database Confidence** | **Comments (*potential* $UF_D$ values)** |
|---|---|---|---|
| 1. | A. Two inhalation bioassays in different species [b] | High | Minimum database for high confidence ($UF_D$ of 1) |
| | B. Two prenatal developmental toxicity studies in different species [c] | | |
| 2. | 1A and 3D (below)<br>1B and 3C (below) | Medium to high | ($UF_D$ of 3-6) |
| 3. | C. One inhalation bioassay in one species [a] | Medium | |

| | | | |
|---|---|---|---|
| | D. One prenatal developmental toxicity study in one species [c] | | |
| 4. | One inhalation bioassay [d, e] or<br>oral data for a chemical that met the criteria for route-to-route extrapolation | Low | Minimum database for estimation of a ReV<br>($UF_D$ of 10) |

[a] Composed of studies published in refereed journals, reports that adhered to good laboratory practice and have undergone final QA/QC, or studies rated by the Office of Pesticide Programs as "core-minimum." It is understood that adequate acute or subacute toxicity data in humans can form the basis of an acute ReV and yield high confidence in the ReV without this database.
[b] Acute exposure data $\leq$ 24 h
[c] Pharmacokinetic data that indicate insignificant distribution occurs remote to the portal of entry (e.g., respiratory tract), route-to-route extrapolation of relevant results, or relevant data from a sufficiently structurally similar compound or mixture may decrease requirements for developmental data.
[d] Acute data < 24 h preferred but subacute studies generally up to 4 weeks in duration acceptable if MOA analysis indicates this is applicable.
[e] If MOA analysis indicates insignificant distribution occurs remote to the respiratory tract or the chemical does not cause developmental toxicity, the confidence in the database will be upgraded from low to medium if data on multiple toxicological endpoints are provided. In addition, reports must adhere to good laboratory practices, have undergone final QA/QC, or the studies were rated by the Office of Pesticide Programs as "core-minimum".

Studies where the data support BMCL modeling are preferred as well as studies that identify both a LOAEL and a NOAEL. However, since inhalation exposure studies are more difficult to conduct than oral exposure, inhalation studies frequently identify only a LOAEL, and these are used to derive a ReV under certain conditions. For example, for chemicals that exhibit low toxicity, some well-conducted studies only identify a NOAEL at the highest dose tested (i.e., free-standing NOAEL). In these cases, the NOAEL is conservatively chosen as the highest dose tested and a ReV is developed. In other instances, only a LOAEL is identified. A ReV is developed based on this study if studies by other investigators support the use of the LOAEL.

If the minimum database requirements are not met, or if there is great uncertainty in the toxicity assessment based on scientific judgment, then an acute ReV is not developed. For example, a study showing only effect levels for mortality or other extremely severe toxicity would not be sufficient to derive a ReV. As new data become available, this decision would be reevaluated. If an acute ReV is not developed, then a generic health-based ESL may be set based on approaches for chemicals with limited toxicity data (Sections 3.15 and 4.5).

## 4.4 Consideration of Uncertainty Factors Specific for the Development of an Acute ReV

UFs are discussed in Section 3.11 except for the $UF_H$ and $UF_D$ specific for the development of an acute ReV.

## *4.4.1 Acute Intraspecies Uncertainty Factor ($UF_H$)*

### 4.4.1.1 General Procedures

It is generally recognized that a $UF_H$ of 10 is adequate to address intraspecies variability for the majority of chemicals (Health Canada 2008). However, if credible information on toxicokinetics or toxicodynamics is available to support a lower UF than the default of 10, a UF of 3, or even 1, may be used. Conversely, a UF greater than 10 may be used because of differences in toxicokinetics or toxicodynamics of a chemical if scientific data are available to support the decision. See Section 3.3.3 on selecting key studies that include details on intraspecies variability.

## *4.4.2 Acute Database Uncertainty Factor ($UF_D$)*

### 4.4.2.1 General Procedures

As discussed in Section 3.11.3, the TCEQ uses a database UF generally up to 10 to address database deficiencies and study quality:

- Uncertainty associated with database deficiency (Section 3.11.3.1.1), including a lack of data on potentially sensitive subpopulations such as children (Section 3.3.3.2.1)
- Uncertainty associated with study quality (Section 3.11.3.1.2)

The minimum database confidence levels given in Table 4-2 for ReV derivation cannot represent the completeness of the overall database for a given chemical as many important details and considerations are not addressed, and use of Table 4-2 solely for this purpose would represent a significant oversimplification of scientific judgment necessary for the $UF_D$ value selection process. Therefore, Table 4-2 should not be the sole consideration in selecting a $UF_D$ value for a chemical. Refer to Section 3.11.3 for additional information.

### 4.4.2.2 Child/Adult Differences

In most cases, the UF of up to 10 is adequate, if appropriately applied in combination with the $UF_H$, to account for deficiencies in the database regarding child/adult differences in susceptibility (Nielsen et al. 2010). If toxicokinetic data indicate significant distribution does not occur remote to the respiratory tract, or results based on route-to-route extrapolation or a sufficiently structurally similar compound or mixture are deemed adequate by TCEQ to consider the database completion in regard to developmental studies based on best scientific judgment, then the database $UF_D$ for lack of a developmental studies is not applied. Please refer to Section 4.3 and Table 4-2 for additional information.

Identifying any chemical-specific, critical life-stage or window of susceptibility may help determine if any database deficiencies exist relevant for acute exposures (Ozkaynak et al. 2005). Information to look for in evaluating any child/adult differences regarding acute exposures includes:

- indications or suspicions of effects on organ systems and functions that are especially vulnerable during development and maturation in early life (in

particular the nervous, reproductive, and immune systems and also the metabolic pathways) and

- insufficient experimental data on such effects in young animals.

## 4.5 Chemicals with Limited Toxicity Data

On an interim basis during the air permit review process, the TCEQ frequently evaluates chemicals with limited toxicity data (LTD chemicals). Every effort is made to obtain as much information on the chemical of interest as possible, including requesting supporting information/ documentation from the facility whose permit application is under review. However, when the minimum database requirement (Section 4.3) is not met, or there is great uncertainty in the toxicity assessment, an acute ReV is not developed. Instead, a tiered approach is used to either set a default ESL or derive a generic health-based ReV or ESL depending on the availability of toxicity information and time and resource constraints (Figure 4-2).

- Tier I – Threshold of Regulation (default ESL = 2 µg/$m^3$)
- Tier II – Use of $LC_{50}$ Data (generic ESL)
- Tier III – Route-to-Route Extrapolation, or Relative Toxicity/Potency Approach (generic ReV or ESL)

When a facility requests an ESL for a LTD chemical, then a Tier I, II, or III approach is used based on time and resource constraints and judgment of TCEQ staff. The following sections discuss the procedures the TCEQ uses to set health-protective concentrations for LTD chemicals based on a tiered approach.

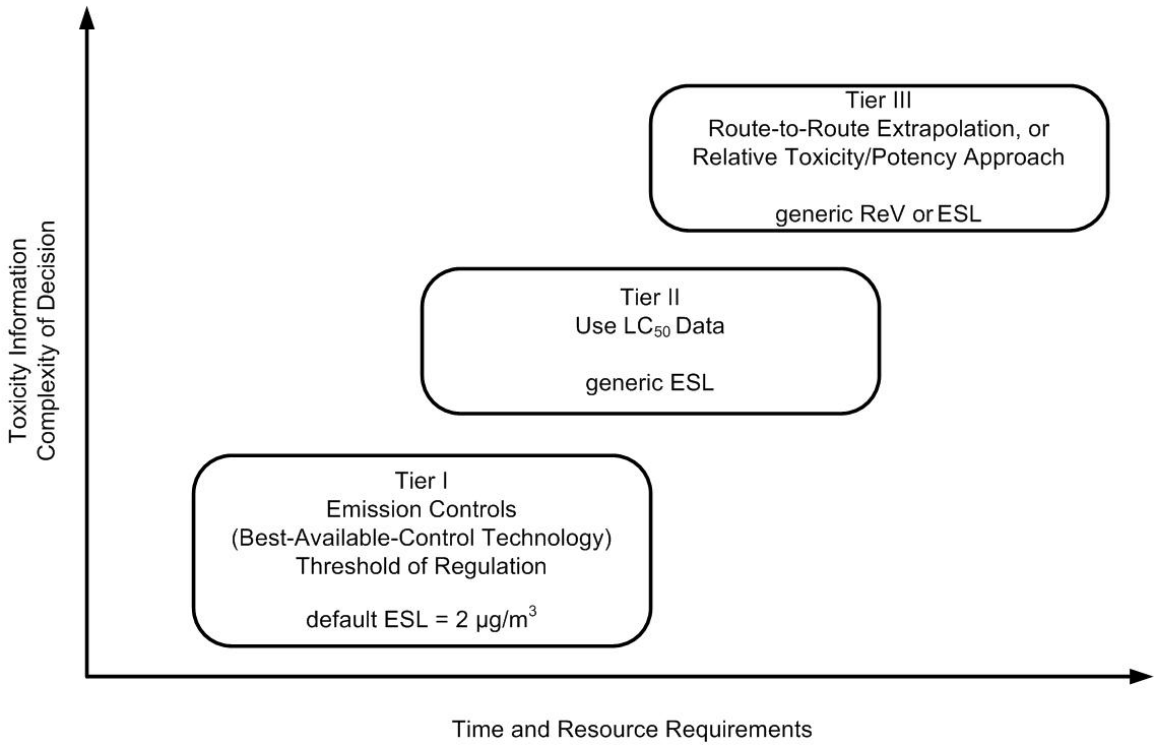


**Figure 4-2 A three-tiered approach to setting a default or a generic health-based ReV or ESL**

### *4.5.1 Tier I Default ESL: Threshold of Regulation Approach*

According to the Modeling and Effects Review Applicability (MERA) guidelines (TCEQ 2008), the applicant and/or the air permit engineer reviews the non-criteria pollutants to be emitted by the facility and assesses whether best-available-control technology has been proposed to control emissions. If the emissions from a non-criteria pollutant meet the MERA guidelines, then no ESL review is required (i.e., the emissions are deemed to be insignificant). If the emissions are deemed to be significant, worst-case emission rates are modeled to predict resulting short-term substance-specific maximum ground-level concentrations ($GLC_{max}$), which are compared to substance-specific, short-term ESLs. If an ESL is not published for a chemical, a default short-term ESL of 2 µg/m$^3$ can be used (TCEQ 2008). If the $GLC_{max}$ is below the default short-term ESL, then the potential for that chemical to cause health effects is deemed to be low, and an ESL does not need to be developed for that chemical. This approach is similar to the threshold of regulation approach used by the Food and Drug Administration (FDA) for food contact articles with limited toxicity information (FDA 1995).

If the default short-term ESL of 2 µg/m$^3$ is not attainable for an applicant for a LTD chemical, a Tier II or Tier III approach is used to estimate a generic short-term ReV or ESL.

### *4.5.2 Tier II Generic ESL: NOAEL-to-$LC_{50}$ Ratio Approach*

The evaluation of toxicity following short-term exposure to a chemical is an integral step in the assessment of its toxic potential by regulatory agencies. The TCEQ uses the

information from standard acute $LC_{50}$ toxicity tests and a NOAEL-to-$LC_{50}$ (N-L) ratio approach to estimate a Tier II generic ESL (Grant et al. 2007). In the past, a Threshold of Concern (TOC) Approach was also used to estimate a Tier II generic ESL (Grant et al. 2007). However, a study by Phillips et al. (2011) demonstrated that the N-L ratio approach was more predictive of toxicity when using acute lethality data, whereas the TOC approach was overly conservative. If inhalation or oral lethality data are available, the N-L ratio approach is used preferentially. The N-L ratio approach is discussed in detail in the following sections. However, if inhalation or oral lethality data are not available and data indicate that a chemical is corrosive or an eye or skin irritant, the TOC approach may be used. For a discussion of the TOC approach, refer to Grant et al. (2007).

#### 4.5.2.1 Criteria for Selection of Acute Lethality Data

For the N-L ratio approach, acute inhalation lethality data are multiplied by a tenth percentile composite factor N-L ratio to estimate health-protective air concentrations. The first step is selection of scientifically-defensible acute lethality data using the following criteria.

For many substances, more than one $LC_{50}$ may be identified from the literature, resulting from the fact that many substances are tested in more than one species and sex and/or at different exposure durations. This may lead, in some cases, to multiple $LC_{50}$ values for individual substances. Figure 4-3 illustrates the steps that are followed for selection of $LC_{50}$ data used for the N-L ratio approach. First, $LC_{50}$ data for all species $\leq$ 4 h are obtained (Step 1). Values are adjusted to correspond to a 4-h exposure duration because a 4-h exposure duration for $LC_{50}$ data is more commonly available than other exposure durations. Duration adjustments for $LC_{50}$ data are made using Haber's Law (Rinehart and Hatch 1964) as modified by ten Berge et al. (1986) as discussed previously in Sections 3.8 and 4.2. If all extrapolated values produce the same $LC_{50}$ data, no further action is required. If the extrapolated values produce different $LC_{50}$ data, then the lowest value is chosen although the quality of the experimental study, physical/chemical characteristics of the chemical, and other data such as eye/skin irritation, etc., can be used in the decision process. If $LC_{50}$ data $\leq$ 4 h are not available, then $LC_{50}$ data > 4 h but $\leq$ 12 h are obtained (Step 2). Duration adjustments are not performed on $LC_{50}$ data > 4 h because of the uncertainties involved with extrapolating exposure durations from longer exposure to shorter exposure durations (Jarabek 1995). If all values produce the same $LC_{50}$ data, no further action is required. If the extrapolated values produce different $LC_{50}$ data, then the lowest $LC_{50}$ data is chosen. The quality of the experimental study, physical/chemical characteristics of the chemical, and other data such as eye/skin irritation, etc., are also used to decide the chemical's $LC_{50}$. If $LC_{50}$ data $\leq$ 12 h are not available, then all other pertinent inhalation lethality data (i.e., $LC_{low}$, $LC_{33}$, etc.) are used (Step 3). This is generally a conservative approach because these values are lower than $LC_{50}$ data.

Acute toxicity testing is generally performed by the most relevant route of exposure in order to provide information on health hazards likely to arise from short-term exposure by that route. Therefore, the inhalation route may not have been evaluated for a product or chemical if the most relevant route of exposure is oral or dermal. Oral data may be used to extrapolate to $LC_{50}$ values, but only if the chemical meets the strict criteria discussed in Section 3.15.1 and is determined not to be corrosive and/or reactive (Step 4).

If inhalation or oral lethality data are not available, then information on whether a chemical is corrosive or an eye or skin irritant can be used to categorize a chemical using the TOC Approach (Grant et al. 2007) (Step 5). In order to determine whether a chemical is corrosive, available empirical data are used. If a chemical is an oxidizer, an inorganic or organic acid or base, reacts with water to form corrosive or reactive products, or is readily hydrolyzed by nasal carboxylesterases, it is more likely to be corrosive or reactive or result in POE effects. The European Union has devised a tiered testing strategy to determine whether or not compounds cause skin irritation and corrosion based on the integrated use of physicochemical properties, QSAR, and *in vitro* data (Cronin et al. 2003). If information on a chemical is derived using this tiered testing strategy, then the TCEQ uses this information to evaluate whether or not a chemical is corrosive. Information based on MOA for specific chemical classes, physical/chemical parameters, reactivity and all other available information from acute toxicity tests is used to categorize a chemical into the appropriate toxicity category if the TOC Approach is used. In addition, the facility can be contacted and additional information can be obtained.

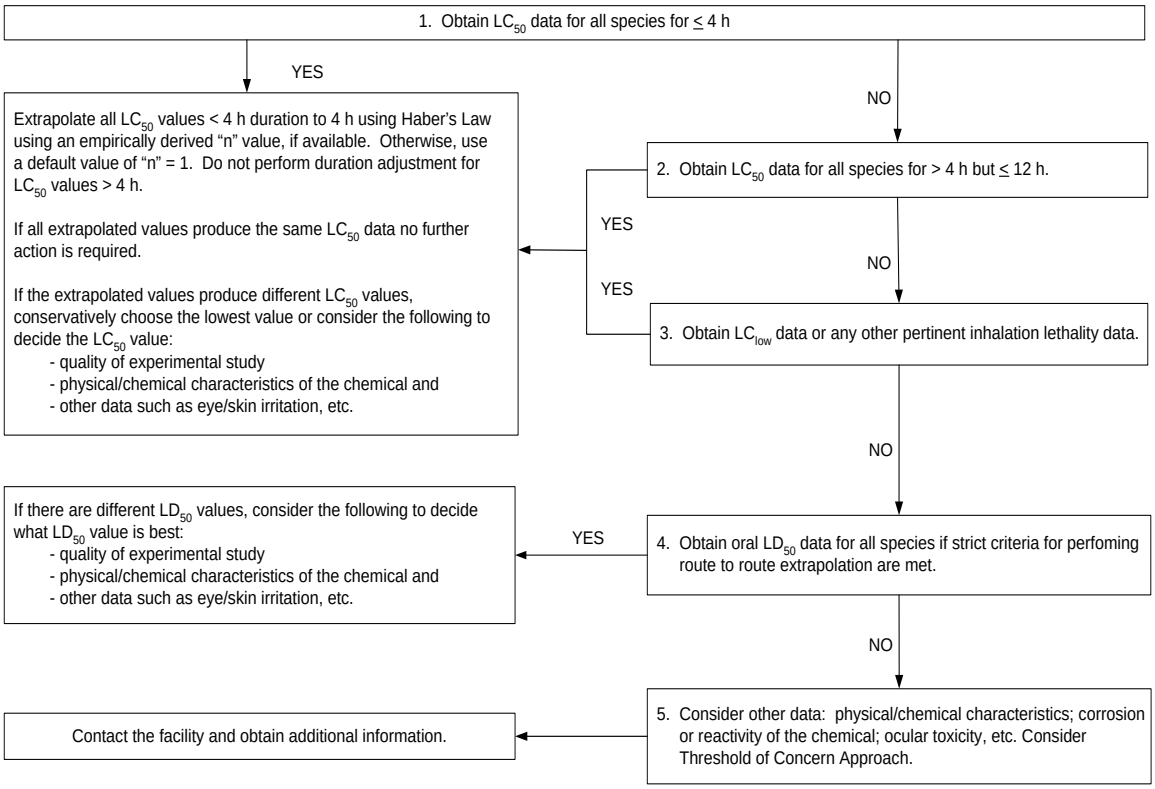


**Figure 4-3 Criteria to select $LC_{50}$ data**

### 4.5.2.2 N-L Ratio Approach

After choosing an $LC_{50}$ value for a LTD chemical as described in the previous section, an N-L ratio-based Tier II generic ESL can be determined by multiplying the $LC_{50}$ by 8.3 x $10^{-5}$. The background of the N-L ratio approach is discussed in detail in Grant et al. (2007) and is briefly discussed below.

Several investigators have suggested using readily-available acute toxicity data to estimate chronic endpoints for LTD chemicals. This procedure was proposed by Layton et al. (1987) for estimating acceptable daily intakes (ADI) for the evaluation of exposures to contaminants at hazardous waste sites. Venman and Flaga (1985) used this procedure to establish provisional ADIs for the evaluation of waste water contaminants. Both investigators calculated NOAEL-to-oral $LD_{50}$ ratios from chronic animal studies for different chemicals and determined the fifth percentile of the cumulative distributions of the ratios. The $LD_{50}$ value for contaminants with limited toxicity data was multiplied by the fifth percentile ratio to derive a surrogate NOAEL. The surrogate NOAEL was divided by an uncertainty factor of 100 in order to establish a conservative threshold dose below which no appreciable risk to human health would occur.

Grant et al. (2007) used the basic approach of Layton et al. (1987) and Venman and Flaga (1985) to establish a procedure to estimate Tier II generic ESLs for LTD chemicals using available $LC_{50}$ data. Grant et al. (2007) provides a detailed discussion of how an acute inhalation N-L ratio was calculated for the evaluation of acute inhalation toxicity, so only a brief discussion is provided here. A large reference database consisting of $LC_{50}$ data and acute inhalation NOAELs for 55 chemicals was compiled. The database consisted of acute toxicity data tested for a variety of acute inhalation endpoints where the exposure durations of the NOAEL studies were less than 24 h. The N-L ratio was calculated for each chemical and the tenth percentile of the cumulative distribution of the ratios was calculated and divided by an uncertainty factor of 100. The tenth percentile composite factor N-L ratio was $8.3 \times 10^{-5}$. For a LTD chemical, this factor is multiplied by $LC_{50}$ values which have been adjusted to 4 h or other appropriate inhalation lethality data based on criteria in Figure 4-3 to estimate a conservative generic ESL below which no appreciable risk to human health would occur (Grant et al. 2007).

TCEQ has implemented the N-L ratio approach and the TOC approach to determine Tier II generic ESLs for n-hexane (TCEQ 2007a). For n-hexane, the N-L ratio approach was deemed to be more applicable than the TOC approach. Phillips et al. (2011) conducted a validation exercise where health-based $^{acute}$ESLs derived using the guidelines were compared to Tier II generic ESLs using the N-L ratio approach and the TOC approach. For 3 of 19 chemicals, the generic ESLs derived using the N-L ratio approach were slightly higher but were within a factor of two of the health-based $^{acute}$ESLs. For 16 of the 19 chemicals, the generic ESLs using the N-L ratio approach were lower than the health-based $^{acute}$ESLs. Generally, the TOC method was more conservative than the N-L ratio approach, especially for relatively nontoxic chemicals.

#### 4.5.2.3 TOC Approach

As mentioned previously in Section 4.5.2, if inhalation or oral lethality data are available, the N-L ratio approach is preferentially used. However, if inhalation or oral lethality data are not available and data indicate that a chemical is corrosive or an eye or skin irritant, the TOC approach may be used (Step 5). For a discussion of the TOC approach, refer to Grant et al. (2007).

### 4.5.3 Tier III Generic ReV or ESL: Relative Toxicity/Relative Potency Approach

Conservative Tier I default ESLs and Tier II generic ESLs are developed on an interim basis upon request. The TCEQ will consider development of a Tier III generic ReV or ESL based on a route-to-route extrapolation or relative toxicity/relative potency approach as discussed in Section 3.15. Development of a Tier III generic ReV or ESL is more time- and labor-intensive (Figure 4-2).

## 4.6 24-Hour AMCVs

For chemicals evaluated in the TCEQ ambient air monitoring network, acute 1-h ReVs and chronic ReVs have generally been derived to evaluate 1-h measured concentrations of chemicals of interest or calculated annual average concentrations, respectively. These averaging times correspond to averaging times evaluated in air permitting. However, 24-h ambient air samples (e.g., 24-h canister samples collected every 3rd or 6th day) may be collected for special projects and also at permanent monitoring sites to calculate annual averages for comparison to chronic ReVs. A 24-h sample is an acute exposure duration significantly longer than 1-hr. Toxic effects induced by 24-h exposure may be governed by modes of action somewhat different than those influencing toxicity due to 1-h or chronic exposure. Therefore, it is not appropriate to use a short-term, 1-h ReV or long-term ReV to evaluate a 24-h ambient air sample. Thus, the development of a 24-h ReV would allow the TCEQ to fully evaluate 24-h air monitoring data for possible health concerns and could be used for risk communication purposes. In addition, this information is helpful to risk assessors for performing health effects reviews when 24-h air monitoring data exceed chronic ReVs.

A 24-h ReV is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a single 24-h exposure.

### 4.6.1 Problem Formulation

Short-term inhalation ReVs have generally been derived to evaluate 1-h reported concentrations of chemicals of interest detected by the TCEQ ambient air monitoring network (Chapter 1). In addition to 1-h ambient air samples, 5-min to 24-h ambient air samples may be collected. The use of a 1-h ReV to evaluate monitoring data collected for exposure durations less than 1 h is likely to be conservative and overestimate risk. However, a significant amount of ambient air data is collected over a 24-h duration, which is an acute exposure duration significantly longer than 1-h. It is not appropriate to use a short-term 1-h ReV or long-term ReV to evaluate a 24-h ambient air sample. This is due to the fact that while the 24-h data are an acute rather than a chronic exposure duration, toxic effects induced by 24-h exposure may be governed by modes of action

somewhat different than those influencing toxicity due to 1-h or chronic exposure. Therefore, the derivation of chemical-specific 24-h ReVs may be needed. For some chemicals, particularly those where the duration of exposure is a contributing factor in toxicity (e.g., chemicals with long clearance times, cumulative or sensitizing effects), derivation of a 24-h ReV is needed if the evaluation of 24-h air monitoring data is desired because the 1-h ReV may be much higher than the 24-h ReV. For chemicals where concentration is the primary contributing factor to toxicity, the 24-h ReV may be similar to the 1-h ReV, but the determination of a 24-h ReV is still needed.

A 24-h ReV is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a single 24-h exposure. However, exposure to chemicals may occur on an intermittent basis. The 24-h ReV would be protective of intermittent 24-h exposures at the ReV if the time period between intermittent exposures is sufficient for adequate toxicokinetic and toxicodynamic clearance such that a toxicologically significant accumulation of neither the particular causative agent nor effect is expected.

The 24-h ReV is derived to evaluate a single 24-hour exposure. In order to determine if intermittent exposures that occur frequently at or below the 24-hour ReV would cause adverse health effects, chemical-specific information such as additional dose-response data (e.g., subchronic) and toxicokinetic/toxicodynamic information would have to be evaluated in the context of the specific exposure scenario, based on actual air monitoring data.

## *4.6.2 Analytical Steps to Develop 24-h ReVs*

The same analytical steps used to derive acute 1-h ReVs and chronic ReVs are used to derive a 24-h ReV (Chapter 3, Chapter 4, and Chapter 5).The critical step in deciding whether or not to derive a 24-h ReV is the availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-h exposure duration. If there are inadequate data to derive a 24-h ReV, then a 24-h ReV will not be developed. An evaluation of the MOA, dose metric, and the toxicokinetics and toxicodynamics of the chemical of concern, as well as exposure duration adjustments that are unique for the derivation of a 24-h ReV (Figure 4-4), will be discussed in the following sections. However, animal-to-human dosimetric adjustments, as well as application of UFs to the $POD_{ADJ}$ to calculate a ReV, are similar to the development of acute 1-h ReV values (Chapter 3 and Chapter 4) and will not be discussed.

### 4.6.2.1 Availability of Toxicity Studies

Available literature should be researched to determine if data are available to guide the derivation of a 24-h ReV. Ideally, an acute study of 24-h duration would be used to develop a 24-h ReV, but such toxicity studies are rare. Many chemicals have a poor database, making the derivation of a 24-h ReV, at best, difficult. In these instances,

professional, scientific judgment must be used to decide whether sufficient data exist to support a scientifically-defensible 24-h ReV.

For a data-rich chemical, it may be possible to perform PBPK modeling or categorical regression to extrapolate from studies that are conducted at other durations than 24 h. For chemicals with limited data, a POD may need to be developed based on an acute study, subacute study, or subchronic study and appropriate duration adjustments used to develop a 24-h value. The best approach for developing a 24-h ReV is to examine all available acute and subacute studies (and possibly subchronic studies) and develop an exposure response array (Chapter 3). Then a consideration of physical/chemical parameters, MOA, toxicokinetics/toxicodynamics, etc., should be used to determine the most appropriate adverse effect relevant to humans for a 24-h exposure duration. Development of several potential 24-h ReV values based on different studies of different durations may be needed to aid in the decision-making process.

The acute key study used to develop the 1-h ReV may or may not be appropriate to develop a 24-h ReV based on the MOA, toxicodynamics, or toxicokinetics of a chemical, particularly if the 1-h ReV is based on a key study with a 1-h exposure duration or less. If data in the literature indicate that a key study other than the one used to derive the 1-h ReV is the most appropriate study to derive a 24-h ReV, which is expected to generally be the case, then a new human equivalent point of departure ($POD_{HEC\ 24\text{-}h}$) should be identified and new UFs should be applied to this value. A literature search should always be conducted to identify a key study and adverse effect that is most appropriate for a 24-h exposure duration. The following are some examples of toxicity studies that may be appropriate for derivation of a 24-h ReV:

- acute toxicity studies (exposure durations of 6-24 h) where duration adjustments are defensible;
- acute or subacute toxicity studies may be used to derive a 24-h ReV, particularly when data from subchronic and chronic studies indicate that longer exposure durations induce adverse effects unrelated to those expected to be caused by a 24-h exposure duration;
- studies using exposure durations of less than 6 h must be used cautiously, and may only be appropriate when available data indicate that the primary toxic effect induced by a chemical is irritation, the magnitude of which is generally determined by exposure concentration, and exposure to 24-h would not be expected to have additional adverse effects other than the irritation;
- subacute toxicity studies (i.e., repeated or continuous exposure to a chemical > 1 day to 1 month or less) may be of greatest value for 24-h ReV derivation, because they may be more predictive of the effects expected due to 24-h exposure when compared to acute studies of much shorter duration;
- subchronic toxicity studies may be appropriate when acute or subacute studies are unavailable. However, use of a subchronic study to derive a 24-h ReV may result in an unrealistic/unpredictive value. Section 4.6.2.4.3 below provides appropriate adjustments that may be applied to aid in the generation of more realistic values;

- chronic toxicity studies are usually not used for derivation of a 24-h ReV, since the MOA for a chronic effect would generally be different than the one governing an effect induced by 24-h exposure.

In some cases a subacute multi-day study may be more appropriate than an acute, single exposure study. Additionally, a subchronic study may be used for derivation of a 24-h ReV if MOA and toxicokinetic/dynamic information support this application (e.g., chemicals with long toxicokinetic or toxicodynamic half-lives).

#### 4.6.2.2 Toxicokinetics/Toxicodynamics

Toxicokinetics and toxicodynamics are critical determinants of the key events that occur in a chemical-specific MOA. Toxicokinetics refers to how the body acts upon a chemical; this includes absorption, distribution, metabolism, and excretion. Toxicodynamics, on the other hand, refers to how the chemical affects the body. That is, the effect the chemical has on target tissue(s), including how the chemical damages tissue and how long it takes that tissue to repair itself. Both the toxicokinetics and toxicodynamics of a chemical can cause rate-limiting steps in a MOA that lead to the toxic effect (Rozman 2000, Rozman and Doull 2000, Rozman and Doull 2001).

It is critical to carefully evaluate each step of a MOA, when known, and what the rate limiting steps may be for the toxic effects observed. An understanding of toxicokinetics and toxicodynamics of a chemical will help inform exposure duration adjustments as well as to determine whether an acute one-day exposure as opposed to a subacute repeat-dose study is more predictive of toxicity for a 24-h exposure. For example, if a chemical is known to have a long toxicokinetic half-life or cause cumulative damage, subacute studies rather than a single-day (e.g., 6-h) acute study may be more predictive of a 24 h exposure, because steady state condition may have been achieved after repeat exposures. Therefore, the POD from subacute studies may be more predictive of the toxicity expected to occur following a 24-h exposure. On the other hand, for chemicals with a short toxicokinetic half-life or chemicals that do not cause cumulative tissue damage (e.g., chemicals causing concentration-dependent POE mild sensory irritation as a critical effect), acute, or subacute studies may be appropriate to use as the key study, since intermittent exposures of the subacute studies may resemble a series of toxicologically-independent acute exposures (i.e., previous exposures may have little or no impact on the potential for current-day effects).

#### 4.6.2.3 Mode of Action and Dose Metric

An understanding of the chemical-specific MOA is critical to using available data to calculate a 24-h ReV. Briefly, some questions that should be considered in this preliminary evaluation are:

- What are the critical steps or key events in toxicity?
- How severe are the adverse effects?
- Are the adverse effects reversible given the exposure duration?

- What is the appropriate dose metric (i.e., peak exposure versus area under the curve (AUC) and are there data available on dose at the target tissue?
- What is known about the metabolism and clearance of this chemical from the body?
- Is toxicological response proportional to the chemical dose/concentration?
- Is the exposure duration a key determinant of the toxic effect?
- Are the adverse effects seen relevant to humans?
- Are the adverse effects biologically plausible?

#### 4.6.2.4 Exposure Duration Adjustments

A variety of modeling approaches are available to identify the POD upon which a 24-h ReV may be derived (PBPK or other optimized inhalation models and categorical regression). These approaches are discussed in Chapter 3 and in OECD (2010). If a PBPK model or categorical regression is used to derive a POD, these models can be used directly to perform exposure duration adjustments. Briefly, the model that may be chosen to identify the POD from a key study is dictated by the quantity and quality of the data available for a chemical of interest (Figure 4-4):

- a PBPK model may be used to identify a $POD_{ADJ}$ for a chemical based on an exposure duration of interest when such a model is available;
- exposure-response arrays may be generated as a means of estimating what a logical POD for a 24-h ReV might be (OECD 2010);
- categorical regression is a valuable tool to assess toxicity across studies and exposure durations to identify an appropriate $POD_{ADJ}$, which may be used to derive a 24-h ReV where duration adjustment is unnecessary (OECD 2010);
- when data are insufficient to apply any of the aforementioned approaches, benchmark concentration modeling or a NOAEL/LOAEL approach may be used to identify a POD. In these cases, exposure duration adjustments may be needed to calculate a $POD_{ADJ}$ for a 24-h ReV.

The approach used to identify the POD for a 24-h ReV is highly dependent on the data available for a given chemical. While several approaches may be developed, the final approach used to derive a 24-h ReV will be selected using best scientific judgment.

##### 4.6.2.4.1 Duration Adjustments for Acute Studies (< 24 hr)

If the above models are not available, there are several ways to perform exposure duration adjustments as discussed in Sections 3.8 and 4.2. Studies evaluating 24-h chemical exposures are not often available and a key study conducted for a different exposure duration may be the most appropriate key study used to derive the 24-h ReV. In this case, Haber's rule as modified by ten Berge et al. (1986) can be used to calculate a POD to be used for the 24-h ReV ($C^n \times T = K$). The same principles of performing duration adjustments discussed in Section 4.2 and used for a 1-h ReV are generally

applicable for exposure duration adjustments for a 24-h ReV. The chosen method for exposure duration adjustments for the development of a 24-h ReV should be dictated by available data and professional scientific judgment.

Haber's rule is dependent on the assumption that log concentration and log time have a linear relationship, or that a study employs experimental conditions wherein steady state toxicokinetics or toxicodynamics are achieved. This assumption, however, does not apply to chemicals that have rate-limiting critical steps in their MOA or experimental conditions that do not achieve steady state (Rozman and Doull 2001). There are many ways that a chemical's MOA may have rate-limiting critical steps, including a very short or long toxicokinetic/dynamic half-life, zero order toxicokinetics, reduced elimination due to high apparent volume of distribution caused by compound or metabolite accumulation in the study organism's body, or an MOA where tissue damage is particularly severe or irreversible, as is the case with certain neuropathies (Rozman 2000, Rozman and Doull 2001, Witschi 1999).

#### 4.6.2.4.1.1 Concentration-Dependent Defaults

In instances where the toxic effect appears to be modulated only by concentration, a horizontal line, a method called "flat-lining", from the shortest duration through the response array may be used to identify a $POD_{ADJ}$. An example of this type of chemical would be those that induce sensory irritation at the point of entry (OECD 2010).

#### 4.6.2.4.1.2 Concentration and/or Duration-Dependent Defaults

When a chemical's MOA is poorly characterized, the C exponent, "n" (see Section 3.8 regarding Haber's rule, $C^n \times T = K$), is set equal to a default value of 1, which is considered to be conservative when performing a duration adjustment from a shorter exposure duration to a longer one.

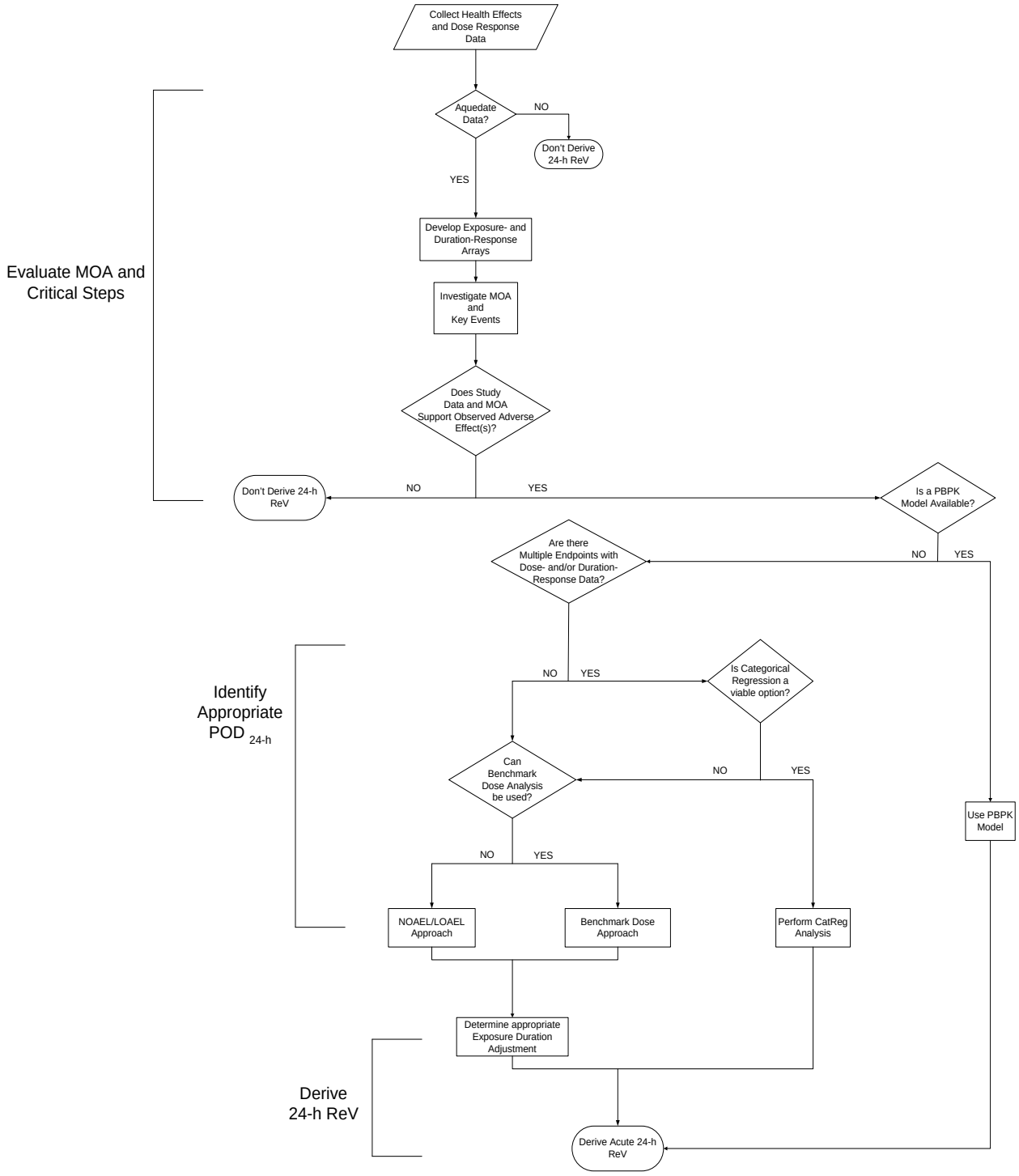


**Figure 4-4 Flowchart for Derivation of 24-h ReV**

### 4.6.2.4.2 Duration Adjustments for a Subacute Multi-Day Study

Subacute studies (> 1 day) may be used to derive a 24-h ReV if an appropriate one-day acute study is not available. Typically, subacute studies are conducted for 6 h/day for up

to 2 weeks. In these cases, the following adjustments will be made to the subacute POD to calculate a $POD_{ADJ}$ appropriate for a 24-h exposure duration.

- If it is reasonable to assume that steady state has been achieved, or toxicodynamics indicate that no additional toxic effect would be expected to occur with the subacute exposure duration, the POD from the subacute study can be used as the 24-h POD. No duration adjustments will be made.
- If the chemical has a short dynamic half-life and each new day represents a toxic effect induced by an independent exposure, then a duration adjustment can be performed to derive the 24-h ReV. The duration adjustment can be the traditional approach where a POD is derived from a key study or through an analytical method such as categorical regression.
- Alternatively, the OEHHA (2008) method for subchronic studies, which is described below, may be used to calculate a POD for a 24-h exposure duration based on a subacute study.

#### 4.6.2.4.3 Duration Adjustments for Subchronic Studies

Subchronic studies may also be used to derive a 24-h ReV if acceptable acute or subacute studies are not available or if the toxicokinetic or toxicodynamic half-life of the chemical is long. In those cases, the TCEQ uses the OEHHA (2008) default approach for a subchronic POD ($POD_{subchronic}$) to calculate a POD appropriate for a 24-h exposure duration ($POD_{24\text{-}h}$). The default approach to estimating an equivalent $POD_{24\text{-}h}$ from the $POD_{subchronic}$ is summarized as:

**Equation 4-3 Estimating an Equivalent $POD_{24\text{-}h}$ from a $POD_{subchronic}$**

$$\mathrm{POD}_{24-\mathrm{h}} = \mathrm{POD}_{\mathrm{subchronic}} \times \left(\frac{\mathrm{N\ hours}}{24\ \mathrm{hours}}\right) \times \left(\frac{\mathrm{D\ days}}{\mathrm{week}}\right)$$

Where:

$POD_{subchronic}$ = POD identified from key subchronic study
N = numbers of hour per day conducted in the key subchronic study
D = numbers of day per week conducted in the key subchronic study

#### 4.6.2.4.4 Critical Evaluation of Duration Adjustment Procedures

When performing exposure duration adjustments using default procedures outlined in the above sections, it is important to evaluate the reasonableness of the adjustment. Importantly, use of a default value of 1 for "n", where exposure concentration and duration are thought to contribute equally to the toxic effect of a chemical, may not result in a reasonable or predictive 24-h ReV, particularly when exposure durations of less than 6 h are used to calculate the 24-h ReV. This is due to the fact that the product of this calculation may result in a number that is lower than the chronic ReV.

In addition, MOA(s) governing the toxic response following a shorter exposure may be unrelated to the MOA(s) that induces a toxic effect following a 24-h exposure. To

evaluate whether a 24-h ReV derived using a default value of 1 for "n" generates a realistic value, compare where the potential 24-h ReV falls on an exposure array generated for the chemical of interest. If the value for the 24-h ReV is less than or equal to the 1-h ReV and greater than the chronic ReV, it may be a reasonable and predictive value. If the 24-h ReV appears to be an unreasonable value, a higher value for "n", such as "n" = 2 or 3, may result in a more reasonable POD for derivation of the 24-h ReV given what is known about the toxicity of the chemical. The OECD refers to this procedure as "interpolation." Exposure-response arrays may be generated as a means of interpolating the $POD_{ADJ}$ for a 24-h ReV. Alternatively, an appropriate chemical-specific "n" value may be derived via curve fitting on a log concentration versus log time plot (see Section 3.8.1). Thus, it is always advisable to use scientific judgment to identify the most scientifically defensible approach for exposure durations used to derive the 24-h ReV.

#### 4.6.2.5 Conclusions

This section describes a framework approach to derive a 24-h ReV. The steps involved in the derivation of the 24-h ReV are largely dictated by available, chemical-specific data, and include evaluation of the MOA, identification of rate-limiting steps for the resultant toxicity, selection of an approach to derive a $POD_{24\text{-}h}$ (Figure 4-4 above), and selection of UFs to apply to that $POD_{24\text{-}h}$. The OECD (2010) has proposed a similar approach for the derivation of acute reference concentrations (ARfCs) and has published a draft document wherein case studies detailing this approach may be found. Since a similar approach will be used by the TCEQ, these examples offer an illustration of how this approach can be successfully applied to model chemicals (OECD 2010).

# Chapter 5 Derivation of Chronic Toxicity Factors

## 5.1 Published Toxicity Factors

The following sections discuss the database sources to which the TCEQ refers during its search for published chronic values and/or data. When chronic inhalation (e.g., RfC, URF) or oral (e.g., RfD, SFo) toxicity factors or guideline levels are identified in the scientific literature or databases, they are reviewed to determine whether the approach used to develop these toxicity factors is similar to the procedures used by the TCEQ. If so, the TCEQ considers adoption of the published chronic toxicity factor or guideline level, with preference given to values that have undergone an external peer review and public involvement process. Many published chronic toxicity factors are not appropriate for use by TCEQ because procedures other than those recommended in this guidance document were used to derive the values. Due to time and resource constraints, the TCEQ considers the published values and their respective key studies as a starting place for gathering toxicity information to develop a DSD. However, because existing toxicity factors or guideline levels may be outdated, the TCEQ also evaluates peer-reviewed studies available after the date these toxicity factors or guideline levels were published to ensure that the latest data are considered prior to developing a chronic toxicity factor.

The TCEQ also reviews other published toxicity factors and toxicity information from organizations that specifically address susceptibility of children. Some of those organizations and factors/levels are ATSDR toxicological profiles, USEPA TEACH chemical summaries, Cal EPA's RELs, USEPA VCCEP, WHO, and ECETOC.

### *5.1.1 IRIS Toxicity Factors*

USEPA's IRIS (www.epa.gov/iris/) is often the preferred database from which to obtain existing inhalation and oral toxicity factors or to select key studies if the assessments are current. IRIS toxicity factors address both carcinogenic (i.e., URF, SFo) and noncarcinogenic (i.e., RfC, RfD) effects. The data on IRIS are accompanied by references to key and supportive studies, and the methodology and guidance used to derive the toxicity factors are provided. USEPA reviews the quality and reliability of the data and the key and supportive studies. IRIS assessments undergo an external peer review.

### *5.1.2 Cal EPA Toxicity Factors*

Cal EPA OEHHA maintains a database of peer-reviewed chronic inhalation (i.e., REL) and oral (e.g, SFo) toxicity factors, which address both carcinogenic and noncarcinogenic endpoints (oehha.ca.gov/risk/chemicalDB/start.asp).

### 5.1.3 ATSDR MRLs

ATSDR publishes chronic inhalation and oral MRLs as screening values for use in public health assessments at hazardous waste sites. For a given substance, its MRL is "an estimate of daily human exposure that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure" (www.atsdr.cdc.gov/mrls/index.asp). However, for some ATSDR MRLs, dosimetric modeling to convert experimental animal concentrations to a HEC was not conducted. Additionally, ATSDR does not include a $UF_D$ in their MRL calculations in consideration of any database deficiencies and does not derive cancer toxicity factors.

### 5.1.4 Provisional Peer-Reviewed Toxicity Values

The USEPA Office of Research and Development/National Center for Environmental Assessment (NCEA)/Superfund Health Risk Technical Support Center develops Provisional Peer-Reviewed Toxicity Values (PPRTVs) in response to requests from regional USEPA offices (USEPA 2003b), and is conducting a batch review of values listed in HEAST (USEPA 1997). PPRTVs are derived for both inhalation and oral routes of exposure, and both carcinogenic and noncarcinogenic endpoints. A chronic PPRTV value (e.g., RfC) is not derived if the toxicity factor is available on USEPA's IRIS. The TCEQ obtains the technical support documents for individual chemicals to evaluate the key and supportive studies. PPRTVs are available at hhpprtv.ornl.gov.

### 5.1.5 HEAST Toxicity Factors

USEPA's Environmental Criteria and Assessment Office last updated HEAST in 1997 (USEPA 1997). The inhalation and oral values in HEAST (carcinogenic and noncarcinogenic) are provisional but references of key studies are provided.

### 5.1.6 Occupational Data

Recommended OELs have been published for many chemicals. They include: time-weighted average threshold limit values (TWA-TLVs) published by ACGIH; permissible exposure limits (PELs) published by OSHA; recommended exposure limits published by the NIOSH; workplace environmental exposure level guides (WEELs) published by AIHA; maximum concentration values in the workplace (MAKs) published by Germany's Commission for the Investigation of Hazards of Chemical Compounds in the Work Area; and OELs published by the European Union Subcommittee on Occupational Exposure Limits. Occupational values that are strictly health-based are likely the most relevant source for environmental risk assessment. Worker exposure data used in the development of these OELs or unpublished industry worker studies may also be evaluated.

### 5.1.7 Assessments from other Countries

Chronic toxicity values available from international agencies (e.g. OECD, IARC, and WHO) or other countries (e.g. Health Canada or RIVM) are considered as sources of toxicity assessment information.

## 5.2 Duration Adjustments

Duration adjustments are commonly required for human and animal inhalation study PODs because such studies typically involve discontinuous exposure regimens, and the POD used to derive a ReV or URF should reflect continuous chronic exposure for the general human population. Such adjustments are usually not necessary for human and animal oral studies, which typically express dose in terms of an average daily dose on a body weight basis (i.e., mg/kg-day) over the chronic study duration. However, some oral studies may require other adjustments to the POD to calculate dose in the units commonly used (i.e., mg/kg-day) to derive oral toxicity factors (i.e., RfD, SFo). Therefore, as necessary, adjustments typically differ for inhalation and oral studies. Study POD adjustments are addressed separately below for inhalation and oral studies.

### *5.2.1 Inhalation Study Duration Adjustments*

Human and animal inhalation studies usually involve discontinuous exposure regimens. The inhalation data are adjusted to reflect continuous chronic exposure for the general human population. Ideally, MOA, chemical-specific, and species-specific data would be available so that PBPK models or optimal/preferred inhalation dosimetry models (Section 3.7) could be used for duration adjustments (Jarabek 1995b, Hanna et al. 2001). Otherwise, the following published default guidelines (USEPA 1994a) are used for inhalation exposures, although the TCEQ recognizes that the application of the default guidelines may not be appropriate in all cases.

According to the RfC Methodology, application of the default adjustment is appropriate only when the dosing protocol generates steady-state blood levels and follows first-order kinetics (USEPA 1994a). If detoxification or clearance occur, then exposure duration may become negligible and the product of concentration and exposure duration may not be valid (Bogdanffy and Jarabek 1995). More specifically, the default adjustment should generally not be applied when both the kinetic half-life of the putative causative chemical or metabolite and the dynamic half-life of the effect are briefly compared to the time period between doses since both the causative agent and adverse effect are effectively cleared between doses. However, the default adjustment is applicable if either the dynamic half-life of the chemical effect or the kinetic half-life is long relative to the dosing period. For example, the default adjustment is applicable if the dynamic half-life of the chemical effect is long relative to the dosing period, despite a short kinetic half-life. Sarin gas is an example of a chemical that obeys Haber's rule despite a short kinetic half-life (Rozman and Doull 2001). If data are unavailable to inform a chemical-specific duration adjustment (e.g., no validated PBPK model), the following default adjustments are used.

#### 5.2.1.1 Duration Adjustment of Human Inhalation Data

Data obtained from human occupational or controlled inhalation studies are adjusted to reflect ventilation rates and exposure durations in the general human population (Equation 5-1). This adjustment yields the HEC, as a $NOAEL_{HEC}$, $LOAEL_{HEC}$, or other relevant POD. The example that follows concerns an occupational study when average daily concentration is used as the dose metric (i.e., $mg/m^3$ or ppm); however, application

to data from controlled human studies may differ regarding the ventilation factors and exposure regimen.

**Equation 5-1 Duration Adjustment of Human Inhalation Data**

$$\mathrm{POD_{HEC}} = \mathrm{POD_{OC}} \times \left(\frac{\mathrm{VE_{ho}}}{\mathrm{VE_h}}\right) \times \left(\frac{\mathrm{days/week_{oc}}}{\mathrm{days/week_{res}}}\right)$$

Where:

$POD_{HEC}$ = human equivalent concentration POD applicable to the general public
$POD_{OC}$ = occupational time-weighted average POD
$VE_{ho}$ = default occupational ventilation rate for an eight-hour day (10 m3/day)
$VE_h$ = default non-occupational ventilation rate for a 24-hour day (20 m3/day)
$days/week_{oc}$ = occupational exposure frequency, usually 5 days/week
$days/week_{res}$ = residential exposure frequency; usually 7 days/week

If the exposure dose metric is cumulative exposure (e.g., $mg/m^3$/year) from an epidemiology study, the cumulative exposure dose metric is converted to an average daily exposure concentration by averaging cumulative exposure over an averaging time of years workers were exposed, unless MOA information is available that indicates another averaging time is more defensible. An example of the latter can be found in the silica DSD (TCEQ 2009a).

#### 5.2.1.2 Duration Adjustment of Animal Inhalation Data

The adjustment of a discontinuous animal inhalation exposure regimen to continuous exposure is similar to that used for data from human studies (Equation 5-2).

**Equation 5-2 Duration Adjustment of Animal Inhalation Data**

$$\mathrm{POD_{ADJ}} = \mathrm{POD} \times \left(\frac{\mathrm{D}}{24\ \mathrm{hours}}\right) \times \left(\frac{\mathrm{F}}{7\ \mathrm{days}}\right)$$

Where:

$POD_{ADJ}$ = POD from animal studies, adjusted to a continuous exposure scenario
POD = POD from animal studies, based on a discontinuous exposure scenario
D = exposure duration, hours per day
F = exposure frequency, days per week

USEPA recommends that this same adjustment to continuous exposure be used in calculating a chronic toxicity factor from an animal developmental toxicity study. According to USEPA (2002), duration adjustment is appropriate as the more health-protective procedure, unless there are toxicokinetic data suggesting that the adjustment to a continuous exposure equivalent is inappropriate, or MOA information suggests that a susceptible period of development is specifically targeted (which would suggest that the peak dose may represent the effective dose). For example, if a chemical is rapidly absorbed, distributed, and metabolized, duration adjustment may be less appropriate than peak exposure.

## *5.2.2 Oral Study Dosimetric Adjustments*

There is no single USEPA guidance document available for the development of oral toxicity factors (i.e., RfD, SFo). As mentioned in Section 3.1, there are numerous guidance documents available at www.epa.gov/iris/backgrd.html and other sites that are used to develop the oral toxicity factors published in IRIS.

Human and animal chronic oral studies often express dose in terms of an average daily dose on a body weight basis (i.e., mg/kg-day) over the study duration, which is the dose metric commonly used to derive oral toxicity factors (e.g., RfD). However, some oral studies may express dose in other units (e.g., mg/day, drinking water concentrations), requiring adjustments to the POD given in the study to calculate dose in mg/kg-day.

### 5.2.2.1 Adjustment of Human Oral Data to mg/kg-day

If an oral human study does not provide an average daily dose on a body weight basis (i.e., mg/kg-day) over the duration of the study, study-specific or default values (e.g., 70 kg adult body weight (BW)) may be used to convert intake into units of average daily dose on a BW basis to be used as the human equivalent dose point of departure ($POD_{HED}$) in the derivation of the RfD or SFo. The example that follows is a common calculation for oral studies to derive the $POD_{HED}$ in mg/kg-day (Equation 5-3).

**Equation 5-3 Adjustment of Human Oral Data to mg/kg-day**

$$POD_{HED} = \frac{DD}{BW_H}$$

Where:

$POD_{HED}$ = human equivalent dose POD (mg/kg-day)
DD = daily dose (average) over the study duration (mg/day)
$BW_H$ = human body weight (default of 70 kg)

### 5.2.2.2 Adjustment of Animal Oral Data to mg/kg-day

Similar to oral data from human exposure, data from animal chronic oral studies are often expressed in average daily dose on a BW basis (i.e., mg/kg-day) over the study duration. If not, study-specific or default values (e.g., animal BW, drinking water or food intake rates) may be used to convert intake into units of average daily dose on a BW basis to be used as the animal dose point of departure ($POD_{Animal}$) for derivation of the RfD or SFo. This section provides three example calculations to derive the $POD_{Animal}$ in mg/kg-day. The example that follows is a common calculation for oral studies (Equation 5-4).

**Equation 5-4 Adjustment of Animal Oral Data to mg/kg-day**

$$POD_{Animal} = \frac{DD}{BW_A}$$

Where:

$POD_{Animal}$ = animal dose POD (mg/kg-day)
DD = daily dose (average) over the study duration (mg/day)
$BW_A$ = animal body weight (kg)

Sometimes animal oral studies express dose in simple terms of chemical concentrations in drinking water or food (e.g., 100 mg chemical per liter of drinking water). In this case, study-specific or default values for intake (drinking water or food) and animal BW must be used to calculate the average daily dose on a body weight basis (Equation 5-5). While study-specific values are preferred, USEPA (1988) may be used as a source of species-specific default values.

**Equation 5-5 Adjustment of Animal Oral Data using Daily Intake Rate and Chemical Concentration**

$$\mathrm{POD_{Animal}} = \frac{\mathrm{CC} \times \mathrm{I_{Daily}}}{\mathrm{BW_A}}$$

Where:

$\mathrm{POD_{Animal}}$ = animal dose POD (mg/kg-day)
CC = chemical concentration in food (mg chemical/kg food) or drinking water (mg chemical/L water)
$\mathrm{I_{Daily}}$ = daily intake rate of food (kg food/day) or drinking water (L water/day)
$\mathrm{BW_A}$ = animal body weight (kg)

Any duration adjustment required for oral animal data will likely pertain to the days of exposure per week (e.g., exposure regimen of 5 days per week). If this exposure duration adjustment is necessary to reflect continuous chronic exposure, the following example equation may be used to calculate the $\mathrm{POD_{Animal}}$ (Equation 5-6).

**Equation 5-6 Adjustment of Animal Data for Exposure Duration**

$$\mathrm{POD_{Animal\text{-}ADJ}} = \mathrm{POD_{Animal}} \times \left(\frac{\mathrm{F\ (days\ per\ week)}}{\mathrm{7\ (total\ days\ in\ a\ week)}}\right)$$

Where:

$\mathrm{POD_{Animal\text{-}ADJ}}$ = animal dose POD, adjusted to a continuous oral exposure scenario (mg/kg-day)
$\mathrm{POD_{Animal}}$ = animal dose POD (mg/kg-day)
F = exposure frequency, days per week

As this document cannot provide equations for all possible and necessary adjustments, TCEQ staff should consult the guidance documents and chemical assessments of others agencies (e.g., USEPA) and the scientific peer-reviewed literature as needed in these cases. When chronic animal study oral data are expressed in average daily dose on a BW basis (i.e., mg/kg-day), animal-to-human dosimetric extrapolation must still be conducted.

## 5.3 Adjustment of Animal Oral Data to Humans (Animal-to-Human Dosimetric Adjustments)

Dosimetric adjustment must be performed to convert a $POD_{Animal}$ into a $POD_{HED}$. The hierarchy of preferred options for animal-to-human dosimetric adjustments is: (1) a validated, chemical-specific PBPK (or PBPK-TD) model parameterized for the species and target tissues of interest so that internal target organ doses can be calculated; (2) use of species- and chemical-specific data on toxicokinetic and toxicodynamic differences; or (3) a default procedure (USEPA 2006b, 2002a).

The most scientifically-sound approach for animal-to-human dosimetric adjustment involves use of options (1) or (2) to estimate the human external dose (mg/kg-day) that would result in the same internal dose at the target organ as in the laboratory animal, as internal dose at the target organ is the most proximate dose metric determinant of risk. However, PBPK models and sufficient species- and chemical-specific data on toxicokinetic and toxicodynamic differences frequently do not exist for the chemical of interest. Therefore, absent an acceptable PBPK model or species- and chemical-specific data that can be used, default procedures are needed to conduct these adjustments based on the administered doses cited in the oral toxicity study (USEPA 2006b).

### *5.3.1 Interspecies Scaling for Carcinogenic Effects*

USEPA (2005a) and TCEQ use body weight scaling to the ¾ power ($BW^{3/4}$) for interspecies extrapolation when deriving a carcinogenic oral toxicity factor (i.e., SFo). This animal-to-human dosimetric adjustment can be performed on the animal doses used for carcinogenic dose-response modeling or on the SFo resulting from modeling unadjusted animal doses ($SFo_A$), but should not be performed on both. The equations discussed below (Section 5.3.2) in the context of deriving RfDs can also be used to adjust the animal doses to be used in cancer dose-response modeling. Alternatively, the following equation (Equation 5-7) may be used to dosimetrically adjust the SFo resulting from modeling the unadjusted animal doses (i.e., adjusting the $SFo_A$) (USEPA 2010a).

**Equation 5-7 Interspecies Scaling for Carcinogenic Effects**

$$SFo_H = SFo_A \times \left(\frac{BW_H}{BW_A}\right)^{\frac{1}{4}}$$

Where:

$SFo_H$ = oral slope factor applicable to humans (excess risk per mg/kg-day)
$SFo_A$ = animal oral slope factor based on unadjusted doses (excess risk per mg/kg-day)
$BW_H$ = human body weight (default of 70 kg)
$BW_A$ = animal body weight (kg)

See USEPA (2011) for details regarding the derivation of the $(BW_H/ BW_A)^{1/4}$ relationship for $BW^{3/4}$ scaling.

### 5.3.2 Interspecies Scaling for Noncarcinogenic Effects

When deriving noncarcinogenic oral toxicity factors (i.e., RfDs), a $UF_A$ of 10 (3 each for toxicokinetics and toxicodynamics) has historically been used in consideration of the uncertainties associated with the extrapolation of animal data to humans (USEPA 2002a). Recent USEPA assessments continue to use this $UF_A$ (e.g., USEPA 2010a, 2010b). However, USEPA has endorsed using $BW^{3/4}$ as a scientifically-based default procedure for animal-to-human extrapolation of toxicologically equivalent doses of chronic orally administered chemicals when deriving noncarcinogenic oral toxicity factors (i.e., RfDs) (USEPA 2011a, 2006b). This adjustment is most appropriate where the area under the concentration-time curve (AUC) of the parent chemical or active metabolite is associated with toxicity, and is also recommended for POE effects (i.e., gastrointestinal) until information is developed to specifically address animal-to-human dosimetric adjustment for oral POE effects. As opposed to chronic exposures demonstrating sensitive effects where repair processes (toxicodynamics) are at work (as with RfD derivation), scaling with $BW^{3/4}$ is likely not appropriate for acute exposures causing immediate and severe effects (USEPA 2011a, 2006b). Using $BW^{3/4}$ for interspecies dosimetric adjustments for both carcinogenic and noncarcinogenic toxicity factors would harmonize the interspecies scaling factor aspect of cancer and noncancer risk assessment. However, full harmonization is prevented under current draft USEPA proposals as an additional $UF_A$ of 3 is recommended for potential interspecies toxicodynamic differences when deriving toxicity factors for noncancer effects (USEPA 2011a, 2006b, 2002a)..

While a great deal of emphasis has historically been placed on data that generally support $BW^{3/4}$ for interspecies extrapolation of important physiological determinants of toxicokinetics and of carcinogenic potency, there are also data that generally support $BW^{3/4}$ for interspecies scaling of toxicity (i.e., both toxicokinetics and toxicodynamics). For example, Schneider et al. (2004) proposed $BW^{3/4}$ for interspecies extrapolation of repeat dose toxicity evaluations in the absence of species- and chemical-specific data based on the good agreement of toxicity data for six species (including humans) with $BW^{3/4}$ predictions for 63 anti-neoplastic chemicals (e.g., see Table 6 of Schneider et al. 2004), and Figure 4B of that study shows that $BW^{3/4}$ scaling predicted the relative sensitivities of the species to toxicity relatively well. Schneider et al. (2004) also found that $BW^{3/4}$ scaling predicted reasonably well the toxicity of pesticides in long-term rat, mouse, and dog studies (Table 4 of Schneider et al. 2004). Across these species comparisons, to use an additional factor of 3 to upwardly adjust the $BW^{3/4}$ predicted sensitivity of the larger species would result in a 3.5 fold (for anti-neoplastic agents) and 3.1 fold (for pesticides) over-estimation of the actual central tendency (median) sensitivity of the larger species. The overall predictiveness of $BW^{3/4}$ shown in Schneider et al. (2004) for these noncarcinogenic effects is consistent with the overall predictiveness and use of $BW^{3/4}$ for animal-to-human dosimetric adjustment for carcinogenic potency without further adjustment (i.e., no $UF_A$ is used).

Other studies of the application of allometric scaling to toxicity data also support $BW^{3/4}$ (i.e., exponent of 0.75) as a reasonably predictive coefficient for animal-to-human dosimetric adjustment and toxicity. Krasovskii (1973, 1975, and 1976 as cited by Davidson et al. 1986) found high correlations between toxicity and BW raised to exponents between 0.62 and 0.81 for 6 to 20 mammalian species and 278 compounds of

seven chemical classes. Travis and White (1988) found the best overall slope for the combined toxicity data set of 27 anti-cancer agents across six species (i.e., the best exponent for BW) was 0.73, with 95% confidence bounds of 0.69 and 0.77, supporting $BW^{3/4}$ for animal-to-human scaling of toxicity data. These results are not surprising given that in general, important factors for interspecies correlation of toxicologic parameters such as half-life ($T_{1/2}$), AUC, clearance, hepatic enzyme activity (including the P-450 monooxygenase system), and others correlate with BW exponents of 0.67 to 0.75 (Davidson et al. 1986). Data such as those described above suggest that an additional toxicodynamic $UF_A$ is not necessary since using $BW^{3/4}$ for cross-species dosimetric adjustment is generally predictive of toxicity. This is not particularly surprising since $BW^{3/4}$ scaling addresses aspects of toxicodynamics such as many types of repair processes (e.g., cellular repair and regeneration) (USEPA 2011a).

Useful default procedures need to achieve wide applicability and generality. Therefore, it is necessary to rely on general principles and simplified broad patterns in developing default procedures predictive of overall trends while recognizing there is uncertainty with any default procedure which may lead to under- or over-estimating human risk. No default procedure can arrive at an accurate and true toxicologically equivalent dose in all circumstances, especially considering that events at high doses in animal studies (e.g., metabolic saturation of a pathway operable at environmental levels) may not be relevant to much lower human doses (i.e., the problem of high-to-low-dose extrapolation). For this reason, species- and chemical-specific data should be used for animal-to-human dosimetric adjustment when available (USEPA 1992a). Default procedures are the last option on the hierarchal framework of approaches for interspecies dosimetric extrapolation, which emphasizes the incorporation of as much species- and chemical-specific mechanistic data as feasible (see Figure 5-1 below, taken from USEPA 2011a).

***Optimal***

If available, employ PBTK (or PBTK-TD) or other biologically based modeling.

***Intermediate***

Assess available information, considering what is known about species differences, and the toxicokinetic and toxicodynamics of the chemical. Use this information to derive an appropriate cross-species adjustment (e.g., a data-supported scaling function or a different UF or combination of the two).[1] Basic issues in this consideration include

1. indications that $BW^{3/4}$ scaling or an alternate approach would be preferred for interspecies extrapolation; and
2. the best quantitative judgment of the residual uncertainty in animal-to-human extrapolation that remains after BW scaling.

Examples of intermediate approaches include the use of chemical specific adjustment factors, as described in IPCS (2005), as well as the existing IRIS assessment for boron (USEPA, 2004).

***Default***

In lieu of useful information about the chemical being considered (see intermediate approach), the default is employed.

[1] Evaluate information available for laboratory animals compared to human with respect to:

- whether the active toxicant is the parent or a metabolite,
- appropriate dose metric (e.g., $C_{max}$, AUC, TACC [time-above-critical concentration], age-related concentration x time interval),
- critical TD event(s), and
- critical effect, including consideration of portal-of-entry issues.

**Figure 5-1 Hierarchy of interspecies dosimetric extrapolation spproaches for RfD derivation (Table 6-1 from USEPA 2011a)**

Without sufficient species- and chemical-specific data, using $BW^{3/4}$ as a default for cross-species dosimetric adjustment (where AUC of the parent chemical or active metabolite is known or expected to be associated with toxicity) appears to be generally predictive of toxicity, widely applicable, eliminates the need for a $UF_A$, and limits the composite UF ($UF_L$ x $UF_H$ x $UF_D$) in most cases (except when a $UF_{sub}$ is needed) to a maximum of 1000.

As a science policy decision, TCEQ will use a $UF_A$ of 1 when $BW^{3/4}$ scaling is applied based on the following reasons:

1) as stated by USEPA (2011, 2006b), "the qualitative recognition that current scientific knowledge indicates that $BW^{3/4}$ scaling generally addresses the potential for species differences in both kinetic and dynamic processes, which the $UF_A$ had been intended to address";

2) its explicit rationale for use based on allometric variation of underlying anatomy and physiology (USEPA 1992a);
3) the use of other UFs (e.g., $UF_D$) that may account for residual uncertainty when recognizing the interrelationships of uncertainty categories for toxicity factors (USEPA 1994a, 2002a);
4) the lack of an additional toxicodynamic adjustment for carcinogenic effects;
5) the goal of truly harmonizing interspecies dosimetric adjustments for both carcinogenic and noncarcinogenic toxicity factors; and
6) the use of the most sensitive adverse effect in the most sensitive species for derivation of the RfD, regardless of whether the effect and sensitivity of the laboratory animal model are of unknown and only assumed relevance to humans.

Thus, when deriving chronic noncarcinogenic oral toxicity factors (i.e., RfDs) where AUC of the parent chemical or active metabolite is associated with toxicity, the TCEQ generally uses $BW^{3/4}$ for default dosimetry adjustments from animal-to-human with a $UF_A$ of 1 unless species- and chemical-specific data adequately support an alternative $UF_A$ value (e.g., data indicate a $UF_A$ greater than 1 is needed to account for toxicodynamic differences or that $BW^{3/4}$ scaling is inappropriate and an alternate $UF_A$ is scientifically justified). Where AUC of the parent chemical or active metabolite is not associated with toxicity (e.g., a very reactive metabolite that is removed through chemical reaction with cellular constituents at the site of formation), in the absence of sufficient PBPK modeling or species- and chemical-specific data, TCEQ does not perform a direct dosimetric adjustment when deriving an RfD but uses a $UF_A$ of up to 10 in consideration of potential toxicokinetic and toxicodynamic interspecies differences. More specifically, when appropriate in deriving an RfD, $BW^{3/4}$ cross-species scaling is used to calculate the oral dosimetric adjustment factor ($DAF_o$) (Equation 5-8).

**Equation 5-8 $BW^{3/4}$ Scaling for Calculating an $DAF_o$**

$$DAF_o = \left(\frac{BW_A}{BW_H}\right)^{-\frac{1}{4}}, \text{or rearranged}$$

$$DAF_o = \left(\frac{BW_H}{BW_A}\right)^{\frac{1}{4}}$$

Where:

$DAF_o$ = oral dosimetric adjustment factor (unitless)
$BW_A$ = animal body weight (kg)
$BW_H$ = human body weight (default of 70 kg)

Although study-specific animal body weight ($BW_A$) should be used in the equation above if available, USEPA (2002a) uses default animal body weights in the equation above to calculate the following default $DAF_o$ values found in Table 5-1.

**Table 5-1 Default $DAF_o$ (USEPA 2002a)**

| Species | Default Body Weight (kg) | Default $DAF_o$ |
|---|---|---|
| Mouse | 0.03 | 7 |
| Rat | 0.25 | 4 |
| Guinea pig | 0.5 | 3 |
| Rabbit | 2.5 | 2 |
| Human | 70 | 1 |

Once a $DAF_o$ has been determined, the following equation is used to calculate the $POD_{HED}$ (Equation 5-9).

**Equation 5-9 Calculating the $POD_{HED}$ using a $DAF_o$**

$$POD_{HED} = \frac{POD_{Animal\text{-}ADJ}}{DAF_o}$$

Where:

$POD_{HED}$ = human equivalent dose POD (mg/kg-day)
$POD_{Animal\text{-}ADJ}$ = animal dose POD, adjusted to a continuous oral exposure scenario (mg/kg-day)
$DAF_o$ = oral dosimetric adjustment factor (unitless)

See USEPA (2011) for additional information regarding use of $BW^{3/4}$ animal-to-human dosimetric scaling.

## 5.4 Minimum Database Requirements for the Development of a Chronic ReV or RfD

The USEPA (1994a) states that the minimum toxicological database component required for the development of an RfC with low confidence is "a well-conducted subchronic inhalation bioassay that evaluated a comprehensive array of endpoints, including an adequate evaluation of portal-of-entry (respiratory tract) effects, and established an unequivocal NOAEL and LOAEL." Table 5-2 is an adaptation from Table 4-1 in the RfC Methodology (USEPA 1994a), which lists different studies evaluating a certain chemical that should be available to establish an RfC with higher confidence.

Since the confidence in the database should be based on an understanding of the putative MOA for the observed effects, it varies on a case-by-case basis as discussed in the RfC Methodology. The TCEQ assigns a confidence level to the study quality of the key study and the database, not to the ReV or RfD. Although the TCEQ does not assign a confidence level to a ReV or RfD, case-specific factors could affect the database confidence category as determined under Table 5-2 and Section 3.11.3 (e.g., the available chronic studies did not examine the likely most sensitive toxic effects for a chemical,

used a poor animal model or means of exposure (gavage) dissimilar to environmental human exposure), the TCEQ generally uses the criteria in Table 5-2 for the minimum database requirements used to develop a chronic ReV and the confidence level assigned to the database. The minimum database that the USEPA has defined for derivation of low- and high-confidence RfDs is the same as for RfCs (USEPA 2002a). Thus, Table 5-2 also represents the minimum database requirements for derivation of an RfD and the confidence level assigned to the database. In order to properly evaluate reproductive effects, a two-generation reproductive study, or study that evaluates reproductive endpoints (e.g., sperm count, ovarian atrophy) from a long-term perspective, is desired.

If the minimum database requirements are not met, or if there is great uncertainty in the toxicity assessment based on scientific judgment, as discussed in this section and Section 3.11.3, then an RfD, SFo, URF, or chronic generic ReV or ESL may be developed based on route-to-route extrapolation or a relative toxicity/relative potency approach, if scientifically defensible (Section 3.15). As new data become available, this decision would be reevaluated and more reliable toxicity factors will be developed. In addition, a NOAEL-to-$LD_{50}$ (N-L) ratio approach may be used to derive chronic RfDs for LTD chemicals as discussed in Section 5.6.

**Table 5-2 Minimum Database for Both High- and Low-Confidence Chronic ReV and RfD[d]**

| | **Mammalian Database[a]** | **Confidence** | **Comments (*potential* $UF_D$ values)** |
|---|---|---|---|
| 1. | A, B, and C are needed:<br>A. Two chronic bioassays in different species [b]<br>B. One two-generation reproductive study<br>C. Two developmental toxicity studies in different species | High | Minimum database for high confidence in an RfC or RfD<br>($UF_D$ of 1) |
| 2. | The three studies in 1A and 1B above, or<br>Two of three studies in 1A and 1B above and one or two developmental toxicity studies | Medium to high | ($UF_D$ of 1-3) |
| 3. | Two of three studies in 1A and 1B above | Medium | ($UF_D$ of 3-6) |
| 4. | One of three studies in 1A and 1B above and one or two developmental toxicity studies | Medium to low | ($UF_D$ of 3-10) |
| 5. | One chronic or subchronic bioassay [c] | Low | Minimum database for estimation of an RfC or RfD<br>($UF_D$ of 10) |

[a] Composed of studies published in refereed journals, reports that adhered to good laboratory practice and have undergone final QA/QC, or studies rated by the Office of Pesticide Programs as "core-minimum". It is

understood that adequate toxicity data in humans can form the basis of a ReV or RfD and yield high confidence without this database. Pharmacokinetic data that indicate insignificant distribution occurs remote to the portal of entry (e.g., respiratory tract), route-to-route extrapolation of relevant results, or relevant data from a sufficiently structurally similar compound or mixture may decrease requirements for reproductive and/or developmental data.

[b] Chronic data.

[c] Chronic data preferred but subchronic acceptable.

[d] Adapted from Table 4-1 from the RfC Methodology (USEPA 1994a). The criteria in this table will be used to assign high to low confidence in the database used to derive the chronic ReV or RfD.

## 5.5 Uncertainty Factors Specific for the Development of a Chronic ReV or RfD

UFs are discussed in Chapter 3 except for the following UFs specific to development of a chronic ReV or RfD: $UF_H$, $UF_D$, and $UF_{Sub}$. Recognizing the interrelationships of uncertainty categories (Section 3.12 and USEPA 2002a), if the cumulative UF exceeds 3000, the TCEQ uses a default of 3000.

### *5.5.1 Chronic Intraspecies Uncertainty Factor ($UF_H$)*

The toxicokinetic UF ($UF_{H-K}$) is used in consideration of potential differences in humans in the absorption, distribution, metabolism, and elimination of the chemical. The toxicodynamic UF ($UF_{H-D}$) is used in consideration of potential differences among humans in the mode or mechanism of action. Typically, these values are up to $10^{0.5}$ each. Data are often not available to identify what toxicokinetic and/or toxicodynamic differences exist within the human population (e.g., between children and adults, age- and sex-related differences) that may affect the toxicity of a particular chemical. Likewise, data are often lacking to determine the extent to which any differences will affect sensitivity to toxicity from exposure to a particular chemical (i.e., what numerical adjustment is required to account for toxicokinetic and/or toxicodynamic differences among humans that impact the toxicity of a particular chemical). The TCEQ uses best scientific judgment on a chemical-by-chemical basis in determining the most appropriate $UF_H$ values to apply to account for potential intrahuman variability. Refer to Section 3.3.3.2.1 and Table 5-3 for using a WOE approach to evaluate the degree of concern for children.

### *5.5.2 Chronic Database Uncertainty Factor ($UF_D$)*

Uncertainty introduced by database deficiencies such as a limited number of experimental studies, animal species, or bioassays, lack of data relevant to potential age- and sex-related differences or potentially sensitive subpopulations, or deficiencies in the study design/quality can be addressed by the use of a UF (Dourson et al. 1996). The TCEQ generally applies a total $UF_D$ up to 10 to address different areas of uncertainty within the database.

In order to properly consider potential age- and sex-related differences, in the absence of relevant human data, a two-generation reproductive study is preferred (Table 5-2). Studies that evaluate reproductive endpoints (e.g., sperm count, testicular lesions, ovarian

atrophy) from a long-term perspective should also be present. If toxicokinetic data indicate significant distribution does not occur remote to the respiratory tract, or results based on route-to-route extrapolation or a sufficiently structurally similar compound or mixture are deemed adequate by TCEQ to consider the database complete in regard to developmental and/or reproductive studies based on best scientific judgment, then the database $UF_D$ for lack of developmental and/or reproduction studies is not applied.

The minimum database confidence levels given in Table 5-2 for RfD/RfC derivation cannot represent the completeness of the overall database for a given chemical as many important details and considerations are not addressed, and use of Table 5-2 solely for this purpose would represent a significant oversimplification of scientific judgment necessary for the $UF_D$ value selection process. Therefore, Table 5-2 should not be the sole consideration in selecting a $UF_D$ value for a chemical. Refer to Section 3.11.3 for additional information.

### 5.5.3 Use of the $UF_H$ and $UF_D$ to Account for Child/Adult Differences

Data from several studies indicate that in most cases, a $UF_D$ of up to 10 is adequate, if appropriately applied in conjunction with the $UF_H$ of up to 10 to account for child/adult differences in susceptibility (Nielsen et al. 2010, Dourson et al. 2002, USEPA 2002c). However, in some cases, a $UF_H$ greater than 10 may be used to account for significant toxicokinetic and toxicodynamic differences conferring increased sensitivity to children for a particular chemical that are not adequately accounted for by a $UF_H$ of 10. The need for a $UF_H$ of greater than 10 will be evaluated on a chemical-by-chemical basis, and scientific justification will be provided in the chemical's DSD for the value of $UF_H$. Please refer to Section 3.11 for additional information.

### 5.5.4 Subchronic to Chronic Uncertainty Factor ($UF_{Sub}$)

If subchronic exposure studies are the only available studies for a given chemical, then they can be extrapolated to derive chronic ReV or RfD values when the uncertainty resulting from using data from subchronic exposure studies is accounted for through use of an appropriate $UF_{Sub}$. A default $UF_{Sub}$ of up to 10 is typically applied to account for this extrapolation. The scientific defensibility of using a default $UF_{Sub}$ of 10 is debatable. Studies have been published that support a lower default $UF_{Sub}$ (e.g., Beck et al. 1993), while others support a default $UF_{Sub}$ of 10 (e.g., Pieters et al. 1998). The application of UFs should be evaluated on a case-by-case basis. In cases where toxic metabolites or damage do not accumulate (Bogdanffy and Jarabek 1995) or subchronic exposure studies indicate the chemical is relatively nontoxic, chronic effects would not be expected to differ significantly from subchronic effects and a $UF_{Sub}$ of 10 would be unnecessary. However, if the putative causative chemical or metabolite bioaccumulates and/or damage recovery (i.e., toxicodynamic half-life) is not rapid or this information is unavailable, a default $UF_{Sub}$ of up to 10 is applied. The $UF_{Sub}$ is not applied when a developmental or other shorter-duration study with a critical window of exposure is the key study. Thus, the $UF_{Sub}$ is determined and applied based on case-specific information.

ECETOC (2003) recommends that no adjustment for exposure duration is needed (i.e., $UF_{Sub} = 1$) for chemicals that have: (1) local effects (i.e., sensory irritation); or (2) a

relatively short toxicokinetic half-life, no toxic metabolite, no potential for bioaccumulation and/or cumulative toxicity, and no reactivity to tissue components. Consistent with USEPA IRIS, the TCEQ generally uses a default $UF_{Sub}$ of 1 to 10 for extrapolating from subchronic to chronic exposures when the study exposure duration was less than 10% of the study subject lifespan (e.g., 3.5 – and 7-year exposure for Rhesus monkey and humans, respectively) or $\leq$ 13 weeks for mice and rats. The average life spans for humans and experimental animals are presented in Table 5-3 below.

**Table 5-3 Average Life-Span for Humans and Experimental Animals (USEPA 1988)**

| Species | Average Life-Span (years) |
|---|---|
| Human | 70 |
| Baboon | 55 |
| Rhesus Monkey | 35 |
| Cat | 15 |
| Dog | 15 |
| Rabbit | 6 |
| Guinea Pig | 6 |
| Hamster | 2.5 |
| Mouse | 2 |
| Rat | 2 |

## 5.6 RfDs for Chemicals with Limited Toxicity Data

Occasionally, LTD chemicals are contaminants at remediation sites being addressed under the TRRP rule (30TAC§350). Since a LTD chemical may pose a potential health concern at a site that might otherwise require no remedial action due to other contaminants, it is important to calculate an RfD for the LTD chemical so that health-protective media (e.g., surface soil) concentrations may be calculated to determine if further action may be needed. In remediation programs, an RfD is especially important since the incidental ingestion of soil is the most important (i.e., media concentration limiting) exposure pathway in calculating a health-protective concentration for the vast majority of chemicals. Additionally, as exposure to site contaminants may be ongoing, it is not reasonable or prudent for the protection of public health to await possible future toxicity testing prior to using available data and procedures in the best possible effort to determine the need for remedial action. Therefore, for the protection of public health, LTD chemicals associated with remediation sites are an exception to the minimum database requirements for an RfD under Section 5.4 and the TCEQ will calculate an RfD for LTD chemicals. As discussed in Section 3.15, the TCEQ may develop an RfD based

on route-to-route extrapolation or a relative toxicity/relative potency approach, if scientifically defensible.

Another method to calculate an RfD for LTD chemicals is to use a NOAEL-to-$LD_{50}$ (N-L) Ratio Approach (e.g., Layton et al. 1987). On an as-needed basis, the TCEQ uses a NOAEL-to-$LD_{50}$ (N-L) ratio approach to estimate an RfD for an LTD chemical. After choosing the lowest $LD_{50}$ value of acceptable quality for a LTD chemical, an N-L ratio-based RfD can be calculated by multiplying the $LD_{50}$ by $6.7 \times 10^{-6}$/day. The background of the N-L ratio RfD approach is briefly discussed below.

Several investigators have suggested using readily available acute toxicity data to estimate chronic endpoints for LTD chemicals. This procedure was proposed by Layton et al. (1987) for estimating ADIs for the evaluation and management of exposures and health hazard from contaminants at hazardous waste sites. Venman and Flaga (1985) also used this procedure to establish provisional ADIs for the evaluation of waste water contaminants. Both investigators calculated NOEL-to-oral $LD_{50}$ ratios from chronic animal studies for different organic chemicals and determined the fifth percentile of the cumulative distributions of the ratios. The $LD_{50}$ value for contaminants with limited toxicity data was multiplied by the fifth percentile ratio to derive a surrogate NOEL. The surrogate NOEL was divided by an uncertainty factor of 100 ($UF_A = 10$ and $UF_H = 10$) in order to establish a conservative threshold dose (i.e., ADI) below which no appreciable risk to human health would occur.

The TCEQ used results from Layton et al. (1987) to establish a procedure to estimate interim RfDs (as needed) for LTD chemicals using available $LD_{50}$ data. Layton et al. (1987) used a fairly large dataset which included data from Venman and Flaga (1985), other prior studies, and data that the study authors assimilated themselves. The suggested multiplicative factor necessary to estimate an ADI from $LD_{50}$ data ranged from $5.0 \times 10^{-6}$ to $1.0 \times 10^{-5}$. Again, these factors are based on the fifth percentiles of various NOEL-to-$LD_{50}$ ratio datasets divided by an uncertainty factor of 100 to derive an ADI, which is similar to an RfD. The factor on the low end of the range is that associated only with use of rat $LD_{50}$ data, while that on the high end of the range is based on data for rats and other small laboratory mammals. There is no clear scientific rationale for selecting any specific value within this range. As a science policy decision, the TCEQ will use the factor of $6.7 \times 10^{-6}$/day. This value is conservative compared to central tendency factor estimates (e.g., 22 times more conservative than the multiplicative factor associated with the geometric mean of the chronic rat NOEL/$LD_{50}$ ratio database ($1.5 \times 10^{-4}$) from three prior studies and 27 times more conservative than the geometric mean of the chronic NOEL/$LD_{50}$ ratio database ($1.8 \times 10^{-4}$) for rats and other small laboratory mammals). Additionally, the selected factor of $6.7 \times 10^{-6}$/day is:

- on the conservative end of the range of fifth percentile factors calculated from the datasets of three prior studies used by Layton et al. (1987);
- likely to result in an adequately health-protective RfD since the lowest scientifically-acceptable $LD_{50}$ value across species will be used by TCEQ and additional toxicity testing would likely result in higher ADI values (Layton et al. 1987); and

- likely to result in health-protective media cleanup concentrations as it is combined with conservative exposure assumptions (e.g., long-term, daily simultaneous exposure to surface soil through incidental ingestion, dermal exposure, consumption of vegetables homegrown in the soil, and the inhalation of vapor/particulate emanating from the soil).

For LTD chemicals needing an RfD, the $LD_{50}$ value is multiplied by the factor of 6.7 x $10^{-6}$/day to calculate an RfD (Equation 5-10). This RfD will be used until toxicity information that is more informative of potential chronic effects is available to derive an RfD.

**Equation 5-10 Calculating an RfD for LTD Chemicals**

$$\text{RfD} = \text{LD}_{50} \times \frac{6.7 \times 10^{-6}}{\text{day}}$$

Where:

RfD = chronic oral reference dose (mg/kg-day)
$LD_{50}$= lowest $LD_{50}$ value of acceptable quality (mg/kg)

Similar to the discussion in Section 4.5.2.1 for the selection of $LC_{50}$ data, the TCEQ may use study quality considerations to select the $LD_{50}$ value used for RfD derivation if significant quality differences exist between experimental studies, or conservatively select the lowest $LD_{50}$ value. An RfD calculated using this procedure will be replaced when and if sufficient toxicity information becomes available to calculate a more scientifically-defensible RfD.

## 5.7 Nonthreshold Carcinogens and Threshold Carcinogens

This section describes the approach used by the TCEQ to determine whether a toxicant warrants consideration for possible carcinogenic endpoints. The same analytical approach discussed in Section 3.2 is used to derive toxicity factors for carcinogens as well as to evaluate carcinogenic toxicity factors derived by other scientists or regulatory agencies (i.e., review essential data including physical/chemical properties and select key studies; conduct an MOA analysis; choose the appropriate dose metric; determine the POD for each key study; conduct appropriate dosimetric modeling; select critical effect and extrapolate from the adjusted POD to lower exposures based on MOA analysis). If the dose-response is determined to be nonthreshold in the low-dose region (based on data or science policy default assumptions), inhalation URFs or oral SFos are derived whereas if the dose-response is determined to be threshold, then inhalation ReVs or oral RfDs are derived.

In March 2005, USEPA issued an updated version of the *Guidelines for Carcinogen Risk Assessment*, hereafter referred to as the 2005 Cancer Guidelines (USEPA 2005a) as well as a supplemental guidance document entitled *Supplemental Guidance for Assessing*

*Susceptibility from Early-Life Exposure to Carcinogens* (USEPA 2005b), hereafter referred to as the 2005 Supplemental Guidance. The purpose of the 2005 Supplemental Guidance is to address the potential for an increased susceptibility to cancer due to early-life exposure to carcinogenic compounds. The 2005 Cancer Guidelines and the 2005 Supplemental Guidance reflect knowledge concerning the carcinogenic process gained in recent years and have undergone an extensive peer-review and public comment process. Therefore, the TCEQ uses these guidance documents as the main source of information to derive carcinogenic URFs/SFos and ReVs/RfDs. However, if new information, scientific understanding, or science policy judgment become available, the TCEQ may conduct cancer risk assessments differently than envisioned in the cancer guidelines. The following sections briefly summarize key features of the 2005 Cancer Guidelines and the 2005 Supplemental Guidance which are found at the following website: www.epa.gov/iris/backgrd.html.

### *5.7.1 Hazard Assessment and Weight of Evidence*

The 2005 Cancer Guidelines contain a detailed discussion of hazard identification based on a chemical's MOA using a WOE approach so a detailed discussion is not included here (Chapter 2 of USEPA 2005a). Briefly, hazard assessment determines whether a chemical may pose a carcinogenic hazard to humans and under what circumstances an identified hazard may be expressed (NRC 1994). A variety of data ranging from observations of tumor responses to analysis of SARs are examined in order "to construct a total analysis examining what the biological data reveal as a whole about carcinogenic effects and MOA of the agent, and their implications for human hazard and dose-response evaluation" (USEPA 2005a).

The 2005 Cancer Guidelines recommend that a hazard narrative be used instead of the classification system suggested in the 1986 Cancer Guidelines. The following standard hazard descriptors are used as part of the hazard narrative to summarize the WOE for potential human carcinogenicity:

- Carcinogenic to Humans
- Likely to Be Carcinogenic to Humans
- Suggestive Evidence of Carcinogenic Potential, but Not Sufficient to Assess Human Carcinogenic Potential
- Data Are Inadequate for an Assessment of Human Carcinogenic Potential
- Not Likely to be Carcinogenic to Humans.

Additional information is included in the narrative, such as whether a chemical appears to be carcinogenic by certain routes of exposure but not others, is expected to be carcinogenic only under certain conditions based on the MOA (e.g., doses inducing regenerative cell proliferation as a key event), or whether exposure during potentially sensitive life-stages of development may increase the carcinogenic potential of a chemical. Thus, the WOE carcinogenic descriptor may be route- and/or dose-specific, and the descriptor for one exposure route should not be viewed as automatically relevant to another route as there may be important route-specific considerations (e.g., significant differences in absorption or response at the POE). For example, when a chemical produces tumors only at the POE, the descriptor generally applies only to that exposure

route (unless the MOA is also relevant to other routes) (USEPA 2005a). The narrative may also summarize uncertainties and key default options used in the assessment. The entire range of information included in the narrative should be considered instead of simply focusing on the descriptor.

Hazard identification for carcinogens by organizations other than USEPA is typically approached using a WOE classification system. These systems may be numeric, alphabetic, or alphanumeric, depending on the organization that publishes them. In the United States, organizations that classify carcinogens by WOE classification systems include NTP, OSHA, ACGIH, and NIOSH. In Europe, the German MAK classification scheme is used, and internationally, IARC publishes a WOE classification.

The TCEQ uses all of the aforementioned sources as well as other peer-reviewed research when considering the carcinogenic potential of a toxicant based on a WOE approach. Generally, the TCEQ only performs carcinogenic dose-response assessments for chemicals considered by the TCEQ to be "Carcinogenic to Humans" and "Likely to Be Carcinogenic to Humans" and for which available data adequately characterize the dose-response curve. Additionally, it should be known or biologically plausible that the putative carcinogenic MOA operates at environmentally-relevant exposure levels, and if based on laboratory animal data, the tumors observed must be of known or biologically-plausible relevance to humans.

### *5.7.2 MOA*

The 2005 Cancer Guidelines emphasize that a critical analysis of all relevant information be used as a starting point to assess carcinogenic risk of a compound rather than using default options. In fact, the use of MOA information is a main focus of the guidelines. Section 2.4 of the 2005 Cancer Guidelines discusses how to evaluate and accept a carcinogenic MOA. MOA information can be used to make decisions about the relevance of animal data to humans, assist in identifying sensitive subpopulations, model tumor incidence or key precursor event data (i.e., curve fitting), and decide upon approaches of high-dose to low-dose extrapolation in dose-response assessment. However, extensive experimentation is needed to support a hypothesis as to MOA for a specific tumor response, or to decide whether other or multiple MOAs are plausible.

An initial process in the cancer dose-response assessment is to examine the MOA and dose-response for each tumor type with a significant increase in incidence. This includes an analysis of the following information on all tumor types that are increased in incidence by the chemical: the number of sites; their consistency across sexes, strains and species; the strength of the MOA information for each tumor type; the anticipated relevance of each tumor type to humans; and the consistency of the means of estimating risks across tumor types. For each tumor type, the MOA and other information may support one of the following dose-response extrapolations: 1) nonthreshold (typically a linear extrapolation to zero); 2) threshold (typically choosing a POD and applying UFs; or (3) both.

## *5.7.3 Dose-Response Assessment*

Different dose-response assessments may be conducted when tumor data is based on animal studies or whether human epidemiology studies are available. Dose-response assessment for each tumor type is performed using the following steps: derivation of a POD based on observed data, dosimetric adjustments to the POD, followed by extrapolation to lower concentrations. The following sections discuss basic principles common to both. Chapter 7 will discuss dose-response modeling for data obtained from human epidemiology studies.

### 5.7.3.1 Derivation of a POD based on observed data

Derivation of a POD is discussed in Section 3.6, although the terminology used for a carcinogenic assessment is different. For inhalation exposure, the term "effective concentration (EC)" is the central estimate and is analogous to the term "BMC" and the term "lower bound of EC (LEC)" is the lower 95% confidence limit and is analogous to the term "BMCL". When the POD is determined from an oral exposure study, the term "effective dose (ED)" is the central estimate and is analogous to the term "benchmark dose "BMD" and the term "lower bound of ED (LED)" is the lower 95% confidence limit and is analogous to the term "benchmark dose level BMDL" as shown in Figure 5-2. When using BMD modeling to derive a POD, the estimated values (e.g., $EC_{10}$) are compared with the empirical dose-response data and values that significantly conflict with empirical data will generally not be used because of uncertainties associated with extrapolations beyond the experimental data (NRC 2001). Additionally, if the POD is to be used for linear low-dose extrapolation, the TCEQ may consider how the resulting slope compares to the low-dose slope on the modeled dose-response curve if sufficiently informed by empirical data in the low-dose region. The TCEQ evaluates potential PODs and determines the most appropriate POD for use on a case-by-case basis using best scientific judgment.

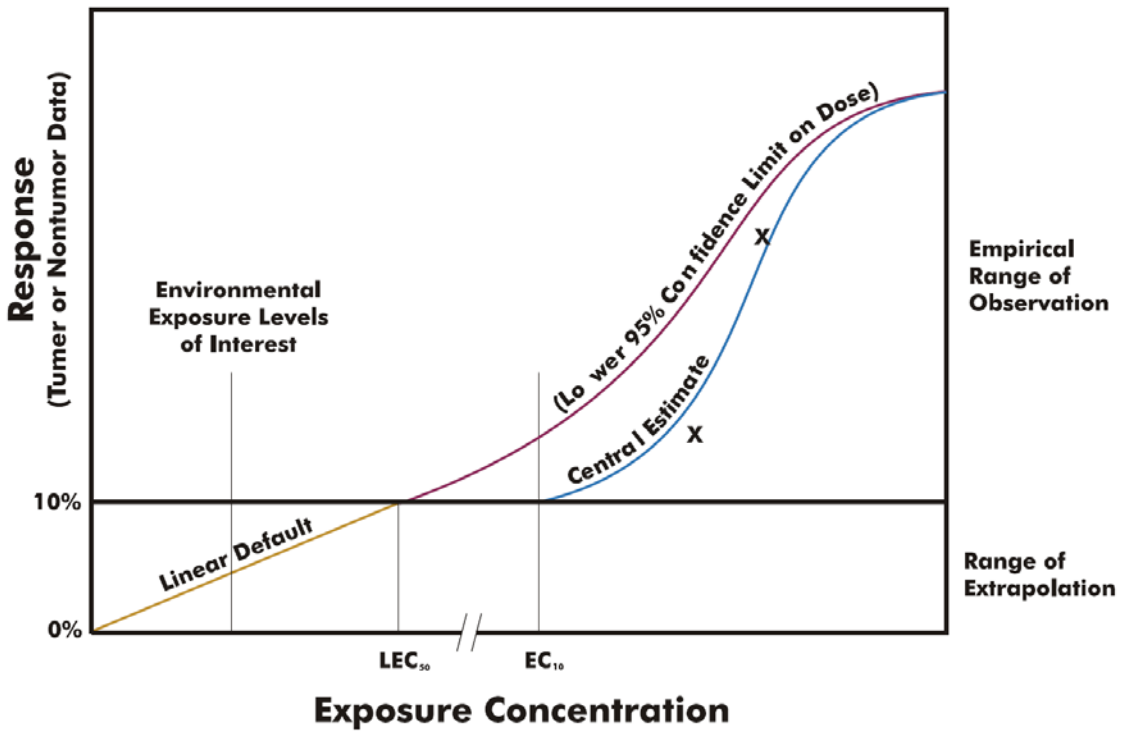


**Figure 5-2 Example of a linear approach to extrapolate to lower exposures**

The terms "EC and LEC" refer to concentration but are analogous to the terms "ED and LED", respectively, which refer to dose (Exhibit 12-3A of USEPA 2004a).

Typically for animal studies, the EC or ED is at a 10% response level ($EC_{10}$ or $ED_{10}$) as the limit of detection of studies of tumor effect in animal studies is about 10%. Since the POD alone does not convey all the critical information present in the data from which it is derived, it is suggested that a POD narrative be included in a cancer assessment. Section 3.2.5 of the 2005 Cancer Guidelines discusses several key factors to consider for characterizing the POD. These factors include:

- nature and level of the response,
- nature of the study population,
- slope of the observed dose-response curve at the POD,
- relationship of the POD with other cancers, and
- extent of the overall cancer database

For epidemiological studies, the type of study and how dose and response are measured in the study determine how the data in the range of observation are modeled. The 2005 Cancer Guidelines refers to the Science Advisory Board who stated "it may be appropriate to emphasize lower statistical bounds in screening analyses and in activities designed to develop an appropriate human exposure value, since such activities require accounting for various types of uncertainties and a lower bound on the central estimate is a scientifically-based approach accounting for the uncertainty in the true value of the $ED_{10}$ [or central estimate]." The LEC/LED or the $EC_{10}$/ $LED_{10}$ may be appropriate for certain datasets based on human epidemiological data. When TCEQ staff develop a

toxicity value for a carcinogen based on a human epidemiological study, the following types of uncertainties of the human study are considered in order to determine whether to use the EC/ED or the LEC/LED as the POD (Section 3.2.1 of USEPA 2005a):

- when estimates of mortality are available rather than incidence because survival rates for different cancers vary;
- when the chemical has discernible competing or additive interactions with other agents and epidemiologic studies cannot adequately estimate the contribution of each agent as a risk factor for the effects of the other;
- when control groups have been exposed to the chemical, risk estimates may be biased toward zero (analysis is improved if background exposures in the exposed and control groups are taken into account);
- when a well-conducted meta-analysis based on several epidemiologic studies is performed, the risk calculation can be done with greater precision thereby decreasing uncertainty;
- when MOA analysis indicates that the carcinogen acts on multiple stages of the carcinogenic process, all periods of exposure including study subjects who were exposed near the end of the study should be considered. However, if MOA indicates there may be a latency period, then study subjects who were exposed near the end of the study need to be analyzed differently. Their data may be similar to analysis of data for those who were not exposed;
- when studies investigate only one effect (typical of many case-control studies), include only one population segment (e.g., male workers or workers of one socioeconomic class), or include only one lifestage

USEPA (2005a) states "risk assessors should calculate, to the extent practicable, and present the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) to inform decision makers." This applies for both animal studies and human studies.

In addition to using BMC/BMD modeling to derive an $EC_{10}$/$LEC_{10}$ or $ED_{10}$/$LED_{10}$ for extrapolation to lower exposures as discussed in Section 3.6.3, specific dose-response modeling and a BEIR IV life-table analysis (NRC 1988) may be used to calculate these values for use as the POD for low-dose extrapolation as discussed in Chapter 7. Briefly, a BEIR IV analysis accounts for age-specific noncancer mortality and cancer mortality for the cancer endpoint of interest in estimating excess lifetime risk as a linear function of dose. Cancer potency factors (β and 95% UCL β values) are estimated through fitting a linear model to study cancer data (e.g., maximum likelihood estimates of β from Cox or Poisson regression of cancer mortality against dose fit by maximum likelihood estimation). Then, a cancer potency factor is input into the BEIR IV analysis and the lowest POD adequately supported by data (e.g., $LEC_{10}$ or $LED_{10}$) is calculated for extrapolation to lower exposures. That is, the BEIR IV methodology is used to calculate the lifetime daily inhalation or oral dose (mg/kg-day) corresponding to the lowest excess cancer BMR supported by data (e.g., $LEC_{10}$ or $LED_{10}$) for use as the POD for low-dose extrapolation, with the end result being a URF (risk per $\mu g/m^3$) or a SFo (risk per mg/kg-day). See Chapter 7 for additional information on using these types of analyses with data from epidemiological studies to derive a POD.

### 5.7.3.2 Dosimetric Adjustments to the POD

All approaches for performing dosimetric adjustments to the POD to account for animal-to-human differences and exposure duration discussed in Chapter 3 and Sections 5.2 and 5.3 are used to perform adjustments to the POD for both threshold and nonthreshold cancer assessment when average daily concentration is used as the dose metric (i.e., $mg/m^3$ or ppm). If the exposure dose metric is from a worker epidemiology study to be used in a BEIR IV life-table analysis, the dose metric is converted to an average daily environmental concentration for the general public consistent with procedures in Chapter 7.

### 5.7.3.3 Extrapolation to Lower Exposures

After a $POD_{ADJ}$ or $POD_{HEC/HED}$ has been determined, extrapolation to lower dose levels is conducted. In a few cases, detailed MOA information may be available that allows the formulation of a toxicodynamic or biologically-based model for extrapolation to lower exposures (USEPA 2005a, Moolgavkar and Knudson 1981, Chen and Farland 1991, Portier 1987). If substantial MOA information is available, the extrapolation is based on an extension of a biologically-based model. If not, any information on the proposed MOA(s) of the chemical can be used to decide whether the extrapolations should assume a nonthreshold or threshold response for the dose-response relationship, or both. Examples of factors supporting a nonthreshold (i.e., linear) approach, threshold approach, or both approaches are discussed in Section 3.3 of the 2005 Cancer Guidelines.

When the MOA information supports nonthreshold, as is the case for a carcinogen operating via a mutagenic MOA, or when the MOA is not understood for a chemical, the default is to use a nonthreshold (i.e., linear low-dose extrapolation) approach (Figure 5-2). This approach utilizes a straight line extrapolation from the POD to the origin (zero incremental dose, zero incremental response) (USEPA 2005a). For example, if the $LEC_{10}$ is used as the POD, then the slope of the line from the $LEC_{10}$ to the origin of the dose-response curve yields the inhalation URF, 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 (Equation 5-11):

**Equation 5-11 Inhalation URF Using the $LEC_{10}$**

$$\text{URF} = \frac{0.10}{\text{LEC}_{10}}$$

See Section 1.5.2.2 for the equation to use this URF to calculate the air concentration at a 1 in 100,000 excess cancer risk (i.e., ${}^{\text{chronic}}\text{ESL}_{\text{nonthreshold (c)}}$).

In regard to oral exposure, the same equation as above may be used to derive a SFo where the $ED_{10}$ or $LED_{10}$ is in units of mg/kg-day (i.e., average daily dose over a lifetime). In this ED/LED approach to low dose extrapolation and SFo derivation, the standard procedure is to calculate the ED or LED (lower 95% confidence bound on the ED) with the BMR typically set at 10% extra risk (i.e., calculate an $ED_{10}$ or $LED_{10}$). The SFo is then calculated by dividing the BMR by the $ED_{10}$ or $LED_{10}$. Although the $LED_{10}$ is typically used as the POD for both animal and epidemiological carcinogenicity studies, see Section 5.7.3.1 for a discussion of the human study uncertainties considered in

determining whether to use the $ED_{10}$ or $LED_{10}$. For example, if the $LED_{10}$ is used as the POD, the resulting SFo represents upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at an intake of 1 mg/kg-day (i.e., SFo units are excess risk per mg/kg-day) (Equation 5-12):

**Equation 5-12 SFo Using the $LED_{10}$**

$$\text{SFo} = \frac{0.10}{\text{LED}_{10}}$$

If based on animal carcinogenicity data, see Section 5.3 regarding the method to convert the $SFo_A$ to a human equivalent $SFo_H$.

If sufficient evidence is available to support a threshold MOA for the general population and any subpopulations of concern, the default approach changes to a determination of a POD and application of UFs in order to derive a ReV or RfD protective of carcinogenic effects. The POD is generally the LEC (i.e., BMCL), LED (i.e., BMDL), NOAEL, or LOAEL depending on the quality and nature of the data as discussed in Chapter 3 and illustrated in Figure 3-11.

Chloroform is an example of a carcinogen where available evidence indicates that the carcinogenic response is secondary to another toxicity that has a threshold (USEPA 2001a). Chloroform-induced carcinogenicity appears to be secondary to cytotoxicity and regenerative hyperplasia. Accordingly, doses below the RfD do not result in cytolethality and hence are unlikely to result in increased risk of cancer. The RfD developed for protection against noncancer effects (including cytolethality and regenerative hyperplasia) can also be considered protective against increased risk of cancer. Formaldehyde-induced respiratory cancers and dioxin carcinogenicity are also likely to be threshold phenomena.

The POD for threshold carcinogens can be based on precursor responses if MOA information indicates that precursor responses are key events in the development of tumors or tumor incidence. Precursor events can often be detected with greater sensitivity (i.e., prior to tumor development and at lower doses). The TCEQ will exercise best scientific judgment in determining what response may constitute a precursor event in the MOA appropriate for use as a POD in a threshold carcinogen assessment (e.g., cytotoxicity-induced cell proliferation for formaldehyde-induced respiratory tract cancers). Using a POD based on precursor events actually represents a “no effect level” with respect to tumor formation. An example of a chemical where a consideration of precursor effects is warranted is vinyl acetate (Bogdanffy and Jarabek 1995). Acetic acid produced within sustentacular cells of olfactory epithelium due to exposure to vinyl acetate initiates cytotoxicity. Tissue proton burdens that overwhelm the natural cellular buffering and proton transport mechanisms leads to cell death. Based on this MOA analysis and the observation that nasal tumors were observed at the highest concentration only, USEPA derived an RfC for vinyl acetate, not a URF.

If the dose-response can be adequately described by both a linear and a nonlinear (e.g., threshold) approach, then the default is to present both the linear and nonlinear analyses. The results of both analyses are considered by the TCEQ. It is helpful to present the data

on both the linear or nonlinear assessment in a form that allows an informed decision to be made, such as a data array mentioned in Chapter 3. Carcinogenic MOA data may ultimately suggest which approach is likely more biologically plausible and predictive of human risk at environmentally-relevant exposure levels. It is possible that some mutagenic or genotoxic chemicals exhibit nonlinearity in cancer response at very low doses or perhaps even a threshold (e.g., due to robust DNA repair at low doses), which could result in significant overestimation (e.g., by several orders of magnitude) of low-dose risk using linear low-dose extrapolation (Bailey et al. 2009, Pratt and Barron 2003, Kirsh-Volders et al. 2003, Bolt 2003, Elhajouji et al. 2011). A linear low-dose relationship has historically been assumed for direct acting genotoxic agents. However, DNA damage thresholds have been demonstrated for some direct-acting genotoxic carcinogens (e.g., ethyl and methyl methanesulphonate), which may occur at doses of genotoxins (direct-acting or metabolically-activated) which do not overwhelm the several tiers of protection against DNA damage in humans (Jenkins et al. 2010). Utilizing available data, the TCEQ evaluates the scientific-defensibility of potential low-dose extrapolation procedures (e.g., linear, nonlinear/threshold) on a chemical-by-chemical basis.

A list of options for presenting results when multiple estimates can be developed is presented in Section 3.3.5 of the Cancer Guidelines (e.g., multiple risks estimated from several different tumor types) (USEPA 2005a):

- Adding risk estimates derived from different tumor sites
- Combining data from different datasets in a joint analysis
- Combining responses that operate through a common MOA
- Representing the overall response in each experiment by counting animals with any tumor showing a statistically significant increase
- Presenting a range of results from multiple datasets (in this case, the dose-response assessment includes guidance on how to choose an appropriate value from the range)
- Choosing a single dataset if it can be justified as most representative of the overall response in humans
- A combination of these options

### *5.7.4 Uncertainty*

Uncertainty analyses are an essential part of a risk characterization and are needed for decision makers to understand the confidence in cancer risk estimates (USEPA 2005a, NRC 1990, NRC 1999). Uncertainty can be categorized into model uncertainty, parameter uncertainty, and human variation. Refer to USEPA (2005a) for a discussion of issues relating to these different categories of uncertainties. The components of an uncertainty analyses are numerous and variable and should be done on a case-by-case basis. Uncertainties when using animal data to determine cancer risk estimates are different from uncertainties using human epidemiological data (Section 7.13).

## 5.7.5 Evaluating Susceptibility from Early-Life Exposure to Carcinogens

The USEPA issued a 2005 Supplemental Guidance document (USEPA 2005b) at the same time as the 2005 Cancer Guidelines to address the potential for an increased susceptibility to cancer due to early-life exposure to carcinogenic compounds compared with adult and whole-life exposure. Additional supplements are expected to be issued in the future. The TCEQ closely monitors emerging issues in evaluating susceptibility from early-life exposure to carcinogens and will revise the ESL development guidance as appropriate.

If carcinogens act through a mutagenic MOA, the 2005 Supplemental Guidance provides specific guidance on potency adjustment for early-life exposures. A mutagenic MOA is one that produces cancer via irreversible changes to DNA, a determination that is to be reached by a WOE approach as described below and in additional detail in Section 2.3.5 of the Cancer Guidelines (USEPA 2005a).

### 5.7.5.1 Mutagenic MOA

A draft mutagenic MOA framework proposed by the USEPA considers all relevant evidence (e.g., genotoxicity data, structural alert information, pharmacokinetic data) to determine if a chemical or its metabolite causes cancer via a mutagenic MOA (USEPA 2007). The framework outlines a multi-step process for assembling, characterizing, and evaluating data to judge whether or not an agent has a mutagenic MOA for carcinogenicity.

In evaluating the carcinogenic MOA, USEPA (2007) emphasizes:

> *The determination that a chemical carcinogen is capable of producing mutation is not sufficient to conclude that it causes specific tumors by a mutagenic MOA or that mutation is the only key event in the pathway to tumor induction."* *"For a chemical to act by a mutagenic MOA, either the chemical or its direct metabolite is the agent inducing the mutations that initiate cancer. This is contrasted with a MOA wherein mutagenicity occurs as an indirect effect of another key event in carcinogenesis occurring later in the process.*

The TCEQ agrees with these statements and will use them as guiding principles in evaluating the carcinogenic MOAs for chemical carcinogens. The TCEQ interprets these principles as setting a reasonably scientifically-rigorous standard for demonstration of a mutagenic MOA. Most specifically, the WOE of scientific information must sufficiently support that, "either the chemical or its direct metabolite is the agent inducing *the* mutations that initiate cancer [emphasis added]." Thus, since the determination that a carcinogen is capable of producing mutation is insufficient alone to conclude that it operates via a mutagenic MOA, to demonstrate a mutagenic MOA the WOE must further indicate that it induces an early mutation in target tissue that causes cancer (i.e., the ability to produce mutagenicity alone or mere genotoxicity does not lead to a presumption of a mutagenic MOA as this only supports that mutagenesis might be an MOA). This requires scientific judgment regarding the WOE of information relevant to:

(1) linking the chemical or a metabolite to mutations; and (2) linking those mutations induced by the chemical to the initiation of cancer in target tissues.

Two key WOE determinations are involved in applying the USEPA (2007) framework. They generally concern the critical underlying questions of interest:

1) Does the carcinogen demonstrate mutagenic activity?
2) Is the carcinogen operating via a mutagenic MOA in the cancer target tissue?

The results of these determinations are combined into an overall WOE regarding the likelihood of an affirmative answer to the ultimate question in regard to a possible mutagenic MOA for carcinogenicity: Does the carcinogen (or its metabolite) cause mutagenicity in viable cells of the target tissue (at relevant doses) which is key in initiating the carcinogenic response? Considerations for each of these WOE determinations are discussed below.

#### 5.7.5.1.1 WOE Approach to Determine if the Chemical has Mutagenic Activity

Mutagenicity and genotoxicity have not been defined in the draft mutagenic MOA framework proposed by the USEPA (2007). Generally, mutagenicity refers to the ability of agents to cause permanent and heritable changes in DNA (e.g., gene mutations in the base sequence of DNA), while genotoxicity refers to the ability of agents to damage DNA directly or indirectly (e.g., effects on DNA repair or DNA polymerases adversely affecting genome fidelity) and includes all adverse effects on genetic information but is not necessarily associated with mutagenicity (Eastmond et al. 2009). Within the context of these definitions, agents that are mutagenic are also genotoxic (directly or indirectly) but not all agents that are genotoxic are mutagenic. Examples of assays designed to detect genotoxicity include: sister chromatid exchange, unscheduled DNA synthesis, DNA strand breaks, or DNA adducts (McCarroll et al. 2010). However, while genotoxicity can result in mutation (e.g., DNA adducts may result in mutation if DNA replication takes place before repair and replication results in an error), gentoxicity is not necessarily predictive of mutagenicity (the key initiating event in a mutagenic MOA). For example, genotoxicity (e.g., chromosome aberration) assays may not measure cytotoxicity properly and the damage may be lethal and thus only present in cell populations with significant cell death (Klein et al. 2007).

As there should be a reasonably scientifically-rigorous standard for demonstration of a mutagenic MOA, genotoxicity alone (e.g., in nontarget cells, in cells exposed to irrelevantly high (environmentally or to the carcinogenicity study) doses, in dead cells (cell populations with low survival) that will never replicate (no heritability), or otherwise) does not provide adequate support for mutagenicity in target cells at relevant doses much less a carcinogenic MOA where mutagenicity is the key initiating event in target cells. As opposed to genotoxicity (e.g., DNA adducts, strand breaks), which may be repaired, mutations (at either the gene or the chromosome level) are irreversible changes in DNA structure that alter its genetic information content. Mutations cannot be repaired and are heritable in the progeny of the originally mutated cell (Swenberg et al. 2008).

Because of the wide variety of possible genetic events that can occur, no single test is able to detect the entire spectrum of chemically-induced genotoxicity and/or mutagenicity. Accordingly, assays and test batteries have been developed to assess effects on three major endpoints of genetic damage associated with human disease (Cimino 2006, USEPA 1986a):

- Gene mutation (i.e., point mutations that affect single genes or blocks of genes),
- Clastogenicity (i.e., structural chromosome aberrations such as deficiencies, duplications, insertions, inversions, and translocations), and
- Aneuploidy (i.e., numerical chromosome aberrations as gains or losses of whole chromosomes (e.g., trisomy, monosomy) or sets of chromosomes (i.e., haploidy, polyploidy)).

Table 5-4 summarizes the common mutagenicity and genotoxicity tests and the endpoints they evaluate based on information provided in USEPA (2007), Eastmond et al. (2009), and Dearfield et al. (2011). Refer to the original articles for strengths and limitations for each assay. Other endpoints of interest for an MOA include gene amplification and epigenetic effects (which may be mistaken for mutagenesis). This information may be useful in organizing and summarizing study results in a WOE approach emphasizing mutagenicity (i.e., heritable changes).

**Table 5-4. Mutagenicity and Genotoxicity Assays and Endpoints**

| Type of Assay | Endpoint Evaluated |
|---|---|
| Bacterial reverse gene mutations | Point mutation, oligonucleotide insertion or deletion |
| *In vitro* mammalian gene mutations (e.g. MLA[a]) | Point mutation, oligonucleotide insertion or deletion, allele loss, small and large chromosome alteration, and aneuploidy (varies by the reporter genes and cell systems selected) |
| Chromosome aberrations | Large chromosome alteration[b] |
| Micronucleus | Large chromosome alteration and aneuploidy[c] |
| Comet or single cell gel electrophoresis | single strand breaks (strand breaks and incomplete excision repair sites), DNA adducts, crosslinks and oxidative damage |
| DNA adduct analysis | DNA damage |
| Sister chromatid exchanges | Inter-chromatid exchange |
| Unscheduled DNA synthesis | DNA synthesis occurs other than S-phase in the cell cycle (usually associated with DNA repairs in response to DNA damage) |
| Transgenic animal models | Gene mutation (mostly point mutation, deletions in some models), can be applied to many tissues and |

| Type of Assay | Endpoint Evaluated |
|---|---|
| | gene specific |
| The rodent dominant lethal assay (*in vivo*) | Dominant lethal mutation in germ cell |
| Hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay (*in vivo*) | Gene mutation |

[a] Mouse Lymphoma Assay (MLA) uses L5178Y Mouse Lymphoma cell for thymidine kinase gene forward mutation.
[b] May be lethal, proper evaluation of cytotoxicity is essential.
[c] Aneuploidy may result from mitotic spindle inhibition and exhibit a threshold.

Some important considerations for the mutagenic potential WOE include, but are not limited to, the following (USEPA 2007, Nielsen et al. 2010):

- Positive effects in multiple test systems for different genetic endpoints, particularly heritable gene mutations and structural chromosome aberrations.
- Mutagenicity tests are of greater significance, especially when genotoxicity test results differ.
- Mammalian cell tests are generally of greater significance than nonmammalian cell tests when results differ, although differences may be explained by differences in metabolism or the organization of genetic material.
- *In vivo* tests are generally of greater significance than *in vitro* tests if results are contradictory.
- Positive *in vivo* results (particularly for mutagenicity) in target cells and/or multiple organs/tissues, species, and by multiple routes of exposure (for systemic mutagens).
- Positive *in vivo* results for highly reactive chemicals (or metabolites) at the POE or site of metabolism (e.g., target cells).
- Positive *in vitro* tests are supporting data for positive *in vivo* tests.

Additionally, several guidelines (USEPA 1986a, 2007, ICH 2008) and scientific literature articles (Dearfield et al.1991, Dearfield and Moore 2005, Elespuru et al. 2009, Kirkland et al. 2007, Thybaud et al. 2010) may be useful in using a WOE approach for determining the ability of an agent to damage DNA and/or produce mutations or chromosomal alterations. Within the overall WOE approach for determining the likelihood of a mutagenic MOA for carcinogenicity, emphasis should be on evidence of mutagenicity being the initating event in target cells at relevant doses (environmentally or to the carcinogenicity study).

It is important to recognize that the *in vitro* assays were designed to optimize the possibility of detecting a response. The bacterial reverse mutation test uses a series of different bacterial strains, all altered in different ways to be very sensitive to genetic

damage. The *in vitro* mammalian assays (both for mutation and for cytogenetic analysis) are conducted in cell lines well adapted for growth in culture (with the exception of cytogenetic analysis conducted in primary human lymphocytes) and with exposure concentrations that cause considerable cytotoxicity to the cells (Dearfield and Moore 2005). A number of recent analyses demonstrated an extremely high false positive rate for *in vitro* genotoxicity tests (in particular, tests in mammalian cell lines) when compared with rodent carcinogenicity results (Kirkland et al. 2007). Additionally, it is possible that some genotoxic chemicals (e.g., ethyl methanesulphonate or EMS), mutagenic chemicals (e.g., dibenzo[a,l]pyrene), and indirectly genotoxic chemicals (e.g., aneuploidy-inducing mitotic spindle inhibitors, agents interacting with DNA modifying enzymes) may exhibit a threshold for such effects (e.g., due to robust DNA repair mechanisms at low doses) (Bailey et al. 2009, Pratt and Barron 2003, Kirsh-Volders et al. 2003, Bolt 2003, Elhajouji et al. 2011). For example, Jenkins et al. (2010) demonstrated DNA damage thresholds for two direct-acting genotoxic carcinogens (EMS and methyl methanesulphonate).

Positive *in vivo* data (especially in the carcinogenic target tissue) are of greater significance than positive *in vitro* results, as they better reflect the genetic consequences of exposure in intact laboratory animals. However, a negative *in vivo* assay does not automatically negate positive *in vitro* assay results. Similarly, the WOE for genotoxicity and/or mutagenicity (much less the WOE for a mutagenic MOA) is not determined simply by the number of positive or negative study results. TCEQ uses best scientific judgment, considers applicable guidance and scientific literature (e.g., USEPA 2007, 1986b), and emphasizes heritable changes in determining the WOE that a chemical has mutagenic activity potentially relevant to the cancer target tissue of interest.

#### 5.7.5.1.2 WOE Approach to Determine if a Carcinogen is Operating via a Mutagenic MOA in the Cancer Target Tissue

Because USEPA (2005) guidance on potency adjustment for early-life exposure only applies to carcinogens which act through a mutagenic MOA, it is insufficient to simply conclude that a carcinogen has mutagenic activity/potential (i.e., carcinogens which exhibit some type of genotoxicity and/or mutagenicity in some cells/tests do not necessarily induce cancer through those same effects in target tissues *in vivo*). Whether the carcinogenic MOA is likely mutagenicity must be determined.

The carcinogenic MOA encompasses a sequence of key events and processes, starting with the interaction of a chemical with a cell, proceeding through functional and structural changes, and resulting in cancer formation. See Table 1 of Preston and Williams (2005) for an example of key events and processes leading to cancer formation for DNA-reactive carcinogens. For a mutagenic MOA for cancer, mutagenicity induced by the chemical is an obligatory early action (i.e., generally a very early key event for the MOA of the chemical or its metabolite). This is contrasted with other MOAs wherein mutations are acquired subsequent to other key events (e.g., cytotoxicity-induced regenerative cell proliferation). Consequently, for a mutagenic MOA for carcinogenesis, the chemical is expected to interact with DNA early in the process and produce changes in the DNA that are heritable (USEPA 2007).

It is well established that mutations in somatic cells play a key, early role in cancer initiation and may also affect other stages of the carcinogenic process (e.g., promotion, progression). Since all cells acquire multiple mutations during malignant transformation, mutation induction or acquisition can be key events at some stage in all cancers. However, there are several important considerations in assessing evidence for a mutagenic MOA for cancer once a carcinogen has been determined to have mutagenic potential: (1) whether there is evidence that the action of the carcinogen as a mutagen is a key event in the sequence of key events in the chemical's carcinogenic process; (2) whether the chemical-induced mutation occurs prior to the initiation of the carcinogenic process (i.e., early in relation to the key events that lead to cancer) in the target tissue (i.e., site and temporal concordance between mutagenicity and carcinogenicity) as opposed to a mutation that was secondary in tumorigenesis ; and (3) if the chemical-induced mutation is THE key event that initiates the carcinogenic process in the target tissue (USEPA 2007).

Consistent with the guiding principles mentioned above, a positive WOE for mutagenic activity is not at all deterministic for the WOE for a mutagenic MOA. The WOE for a mutagenic MOA is focused on the evaluation of data (if any) which indicate that a chemical's mutagenic activity is critical to the induction of the specific tumors in question. For a mutagenic MOA, mutation is the first step which initiates a cascade of other key events (e.g., cytotoxicity or cell proliferation) that are critical to the carcinogenesis process. There is no default carcinogenic MOA, even for chemicals demonstrating mutagenic activity (USEPA 2007). The burden of scientific proof lies in demonstrating a reasonably robust WOE for a mutagenic MOA based on available scientific data for the specific chemically-induced tumors, even if data on other possible carcinogenic MOAs are lacking (i.e., the carcinogenic MOA may ultimately be judged simply to be unknown). Simply demonstrating plausibility is not sufficient for adequately supporting a mutagenic MOA, which requires a WOE that in fact mutagenicity is the MOA. Additionally, since there may be dose-dependent changes in MOAs, the contribution of the key events of a particular carcinogenic MOA may vary with conditions of exposure and delineating the contributions of these events may be important for guiding dose-response analysis, low-dose extrapolation, and risk characterization. USEPA (2007) provides a hierarchy of evidence for determining a mutagenic MOA (listed in decreasing order of relevance/importance):

1) Cancer relevant oncogene/tumor suppressor gene mutations can be detected in the target tissue following chemical exposure.
2) Surrogate gene mutations can be detected in the target tissue following chemical exposure.
3) DNA adducts (known to be mutagenic adducts) can be detected in the target tissue following chemical exposure.
4) Primary DNA damage can be detected in the target tissue following chemical exposure.
5) Gene mutations and/or DNA adducts or other measures of primary DNA damage can be detected in vivo.

6) Evidence that the chemical can induce mutation, cytogenetic damage, DNA adducts and/or primary DNA damage *in vitro*.

In general, the types of evidence to evaluate whether a chemical acts through a mutagenic MOA include, but are not limited to, the following (USEPA 2007):

- Initially, evidence that the carcinogen or a metabolite is DNA-reactive and/or has the ability to bind to DNA (in a manner that causes mutations) as demonstrated with in vivo or in vitro short-term testing results for genetic endpoints (i.e., evidence of such DNA reactivity triggers further evaluation of the carcinogenic MOA as possibly mutagenicity).
- For chemicals that can induce mutation, assess the evidence as to whether mutation is THE key event in the induction of the specific tumors induced by the chemical (see the hierarchy of evidence listed above; Note: any evidence under this hierarchy, particularly lower tier evidence, does not necessarily constitute sufficient evidence of a mutagenic MOA).
- Positive in vivo results (particularly for mutagenicity) early in the exposure regimen (as compared to time to tumors) in the carcinogenic target tissue at doses relevant to those producing carcinogenesis are especially pertinent.
- Mutagenic/genotoxic effects in the target tissue known to be caused by the chemical significantly precede the occurrence of tumors in the target tissue based on an examination of their dose-response-temporal relationships (i.e., the absence of chemical-specific induced mutagenicity at doses lower than those that cause cancer or its presence after tumorigenesis suggest that the chemical-specific mutagenicity is a secondary effect).
- Early termination of exposure does not prevent the carcinogenic effect.
- Tumors appear early in chronic studies at multiple sites, in multiple species, and by multiple routes of exposure.
- Mutations shown to be caused by the chemical (or its metabolite) in genes that affect carcinogenesis (e.g., tumor suppressor p53, Rb) soon after exposure, especially in the target tissue (not in the tumors).
- The carcinogen has similar properties and SAR to a carcinogen or chemical group that a consensus of the scientific community has identified as operating via a mutagenic MOA.
- All data should be evaluated using criteria for acceptable quality (see Section 2.2 of USEPA 2007).

In considering the evidentiary hierarchy and types of evidence mentioned above, emphasis should be placed on mutagenic (i.e., heritable) changes, especially in the target tissue, as there should be a reasonably scientifically-rigorous standard for demonstration of a mutagenic MOA. A WOE determination for a mutagenic MOA may be precluded if these types of evidence are lacking and/or an alternative MOA is well supported (e.g., receptor binding mediated MOA for dioxin, cytotoxicity-induced regenerative cell proliferation for formaldehyde-induced respiratory tumors (Meek 2008)).

It is noted that chemicals that are capable of causing genotoxicity or even mutations do not necessarily cause cancer through a mutagenic MOA, especially if testing conditions and/or tissues differ significantly from those associated with carcinogenesis. For example, the conditions under which such chemicals may have caused genotoxicity (e.g., carcinogenic study-irrelevant or environmentally-irrelevant high doses with dose-related changes in metabolic pathways, non-target cells or tissues, *in vitro*) may not necessarily be predictive of mutagenic effects in the carcinogenic study laboratory animal target tissues or the target tissues of humans exposed to environmentally-relevant doses. For example, although hexavalent chromium is capable of genotoxicity in certain test systems, cells/tissues, and conditions (e.g., high doses) (USEPA 2010a), mutagenicity may not be a carcinogenic MOA operable at environmentally-relevant oral doses, which would be expected to be within gastrointestinal reductive capacity to reduce hexavalent chromium to trivalent chromium and prevent hexavalent chromium absorption and cellular uptake (Thompson et al. 2011). A chemical may cause other effects which lead to carcinogenicity but do not constitute a mutagenic MOA (e.g., cytotoxicity-induced cell proliferation). DNA damage induced by reactive oxygen species (ROS) and cell proliferation are thought to be two of the primary MOAs for carcinogenesis by nongenotoxic environmental chemicals, but they may also be important MOAs for genotoxic chemicals (Swenberg et al. 2008). Additionally, positive genotoxicity and/or mutagenicity results in tissues that do not subsequently develop tumors certainty do not explain why those non-target tissues do not experience carcinogenesis (in fact they would suggest a real potential for carcinogenesis in those non-target tissues), much less explain with any certainty how the chemical or its metabolite causes cancer in target tissues, although they warrant further evaluation of a potentially mutagenic MOA. Mutagenicity results in cancer target tissues are the most relevant evidence for evaluating the likelihood of a mutagenic MOA (e.g., genotoxicity does not necessarily result in mutagenicity).

Lastly, a key issue is whether the observed dose-response relationships of the initial mutagenic events correspond with the dose-response relationship for tumors. Therefore, if possible, a comparison of the dose-response-temporal relationships between the occurrence of tumors and mutagenic/genotoxic effects known to be caused by the chemical (and perhaps even known to be present in the tumors) would be beneficial. Refer to Moore et al. (2008) and Allen et al. (2005) for detailed discussion and chemical-specific examples. Relevant genomics information and new genetic toxicity testing results may also be useful as part of the WOE (Benton et al. 2007, Dix et al. 2005, Lynch et al. 2011). The TCEQ uses best scientific judgment and considers applicable guidance and scientific literature (e.g., USEPA 2007) in using WOE to determine whether a chemical is likely carcinogenic via a mutagenic MOA.

#### 5.7.5.2 Carcinogens Acting Through a Mutagenic MOA

As mentioned previously, the 2005 Supplemental Guidance provides specific guidance on potency adjustment for early-life exposure for carcinogens that act through a mutagenic MOA. When data are available for assessment of early life susceptibility (e.g., laboratory animal carcinogenicity studies incorporating early-life stage exposure), they should be used directly to derive the cancer potency value(s) for that chemical on a case-by-case basis. Vinyl chloride is an example where age-dependent default adjustment factors are not applicable because chemical-specific data on early life susceptibility are

available and were used by USEPA in deriving the slope factors (USEPA 2000b). The emphasis is to rely on analyses of data, rather than general defaults. Age-dependent default adjustment factors (ADAF) are meant to be used only when chemical-specific data are not available to directly assess cancer susceptibility from early-life exposure to a carcinogen operating via a mutagenic MOA. The following ADAFs (from EPA 2005b) are recommended for such chemicals, using estimates from chronic studies (i.e., URFs, SFos) with appropriate modifications to address the potential for differential risk due to early-lifestage exposure:

- For exposures before 2 years of age (i.e., spanning a 2-year time interval from the first day of birth up until a child's second birthday), a 10-fold adjustment
- For exposures between 2 and <16 years of age (i.e., spanning a 14-year time interval from a child's second birthday up until their sixteenth birthday), a 3-fold adjustment
- For exposures after turning 16 years of age, no adjustment.

Note that the two ADAFs greater than 1 (ADAFs of 10 and 3), which upwardly adjust carcinogenic potency, apply only to certain age ranges (0<2 and 2<16 years) for early-life exposure from 0-16 years of age. An additional factor to account for susceptibility due to early-life exposure is only applied to carcinogens that have been identified by the scientific community as acting through a mutagenic MOA. A general acceptance of the mutagenic MOA should be established based on an independent peer review and assessment by the scientific community or the development of a large body of research information and characterization of the mutagenic MOA.

#### 5.7.5.3 Calculation of an ESL and SFos for Carcinogens Acting Through a Mutagenic MOA

For inhalation carcinogens operating via a mutagenic MOA, the inhalation risks associated with each of the three relevant time periods are as follows, where both E and URF are expressed in the same units, although the URF is in reciprocal units to E (i.e., $\mu g/m^3$ and $(\mu g/m^3)^{-1}$, respectively) (Equation 5-13, Equation 5-14, and Equation 5-15):

**Equation 5-13 Risk for Birth Through < 2 Years for Inhalation Carcinogens Acting Through a Mutagenic MOA**

$$\text{Risk for birth through} < 2\ yr = E \times URF \times 10 \times \frac{2\ \text{yr}}{70\ \text{yr}}$$

**Equation 5-14 Risk for Ages 2 Years and < 16 Years for Inhalation Carcinogens Acting Through a Mutagenic MOA**

$$\text{Risk for ages 2 yr and} < 16\ yr = E \times URF \times 3 \times \frac{14\ \text{yr}}{70\ \text{yr}}$$

**Equation 5-15 Risk for Ages 16 Years Until 70 Years for Inhalation Carcinogens Acting Through a Mutagenic MOA**

$$\text{Risk for ages 16 yr until 70 yr} = \text{E} \times \text{URF} \times \frac{54\ \text{yr}}{70\ \text{yr}}$$

The inhalation risks associated with each of the three relevant time periods are summed to produce the lifetime risk for a population with average life expectancy of 70 years (Equation 5-16):

**Equation 5-16 Lifetime Risk Level as a Sum of the Three Relevant Time Periods for Inhalation Carcinogens Acting Through a Mutagenic MOA**

$$\begin{aligned}\text{Lifetime Risk Level} &= (\text{Risk for birth through} < 2\ yr) \\ &+ (\text{Risk for ages 2 yr and} < 16\ yr) \\ &+ (\text{Risk for ages 16 yr until 70 yr})\end{aligned}$$

$$\begin{aligned}\text{Lifetime Risk Level} &= \left(\text{E} \times \text{URF} \times 10 \times \frac{2\ \text{yr}}{70\ \text{yr}}\right) + \left(\text{E} \times \text{URF} \times 3 \times \frac{14\ \text{yr}}{70\ \text{yr}}\right) \\ &+ \left(\text{E} \times \text{URF} \times \frac{54\ \text{yr}}{70\ \text{yr}}\right)\end{aligned}$$

This equation can be simplified as follows

$$\text{Risk Level} = \text{E} \times \text{URF} \times \frac{(10 \times 2\ \text{yr}) + (3 \times 14\ \text{yr}) + 54\ \text{yr}}{70\ \text{yr}}$$

This equation can be rearranged to solve for E (exposure concentration in μg/m$^3$) for a chronic exposure period that corresponds to a specified target risk level:

$$\text{E} = \frac{\text{Risk Level}}{\text{URF}} \times 0.6$$

For inhalation carcinogens operating via a mutagenic MOA, the comparison level of a chemical that corresponds to a target risk level of 1 x $10^{-5}$ for a chronic exposure period ($^{\text{chronic}}\text{ESL}_{\text{nonthreshold(c)}}$) specific to the situation of constant (unchanging) exposure concentration throughout a lifetime is calculated as follows (Equation 5-17):

**Equation 5-17 Chronic ESL for Nonthreshold Carcinogens Operating Via a Mutagenic MOA**

$$^{\text{chronic}}\text{ESL}_{\text{nonthreshold(c)}} = \frac{6.0 \times 10^{-6}}{\text{URF}}$$

As an alternative to the above methodology, ADAFs may be incorporated into a BEIR IV life-19 table analysis approach (NRC 1988) to account for early-life exposure and produce the resulting $^{\text{chronic}}\text{ESL}_{\text{threshold}}$(c) as discussed in Chapter 7.

For oral carcinogens operating via a mutagenic MOA, the adjustment of oral risk calculations using ADAFs in conjunction with SFo values must be accomplished within exposure route-specific equations (e.g., soil ingestion, dermal) on a receptor-specific basis (e.g., child, age-adjusted adult), consistent with applicable rules (e.g., TRRP; 30TAC§350). Generally, this requires that exposure parameters be divided into the relevant ADAF age groups (0≤2 years, 2<16 years, ≥16 years) within the exposure route-specific equation so that the relevant ADAF may be applied to the SFo in each age group-

specific portion of the equation. These equations may be used to calculate health-protective environmental media (e.g., soil) concentrations at a given excess risk level or be rearranged to calculate risk for a given exposure scenario. As such equations are beyond the scope of this document, USEPA example calculations may be found at www.epa.gov/oswer/riskassessment/sghandbook/prgs.htm.

#### 5.7.5.4 Carcinogens Acting Through a Nonmutagenic or Unknown MOA

USEPA (2005b) concluded that the data for carcinogens not acting through a mutagenic MOA (i.e., nonmutagenic MOA carcinogens) or for carcinogens where the MOA is unknown were too limited and the MOAs too diverse to apply a general default potency adjustment for early-life exposures. For carcinogens where the MOA is unknown, USEPA recommends that a linear low-dose extrapolation methodology be used, based on the procedures in the 2005 Cancer Guidelines, "since use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life sensitivity." USEPA expects to produce additional supplemental guidance for carcinogens acting through MOAs other than a mutagenic MOA as data from new research and toxicity testing become available.

# Chapter 6 Assessment of Chemical Groups and Mixtures

## 6.1 Overview

Guidelines for the Health Risk Assessment of Chemical Mixtures (USEPA 1986b) and Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (USEPA 2000c) provide procedural guides for evaluating data on the health risks from exposure to chemical mixtures. Briefly, if a dose-response assessment is developed for a mixture of compounds or a mixture that is judged similar, the TCEQ uses these data to develop an inhalation toxicity factor (e.g., ESL) for that mixture. The TCEQ typically does not derive oral toxicity factors for mixtures as oral toxicity factors (i.e., RfDs, SFos) are used in remediation programs (e.g., TRRP) that usually analyze and address chemical contamination on an individual-chemical basis (although there are cumulative risk/hazard considerations). However, similar procedures may be followed in the event that derivation of an oral toxicity factor for a mixture is needed (e.g., various Aroclors). Examples of pollutant mixtures for which a dose-response has been evaluated are gasoline, coke oven emissions, diesel exhaust, and various Aroclors (Aroclor 1016, 1248, 1254) (USEPA 1996b, 1996c, 1996d). During air permit reviews, an ESL may need to be developed for a chemical product. If a dose-response assessment for the chemical product is not available, a component-by-component approach is employed as discussed below in Section 6.4. Specific approaches are used for mixtures of carcinogenic polycyclic aromatic hydrocarbons (PAHs), laterally-substituted dioxins/furans, and dioxin-like polychlorinated biphenyls (PCBs).

## 6.2 Carcinogenic Polycyclic Aromatic Hydrocarbons

Relative potency factors (RPFs) have been developed by USEPA and other organizations for carcinogenic PAHs, since these classes of chemicals possess toxicologically similar properties. An RPF is the ratio of the toxic potency of a chemical of interest to that of an index chemical. NCEA has calculated an inhalation URF for benzo(a)pyrene, the index chemical for carcinogenic PAHs, from which a $^{chronic}ESL_{linear(c)}$ can be developed. Applicable RPFs can be used to derive $^{chronic}ESL_{linear(c)}$ values for specific PAH compounds. RPFs for seven carcinogenic PAHs have been published in *Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons* (USEPA 1993a). Additional RPFs for other potential carcinogenic PAHs have been published by Collins et al. (1998). Similarly, USEPA has derived a SFo for benzo(a)pyrene which can be used to derive SFo values for other PAHs with RPFs consistent with applicable rules (e.g., §350.76(f) of TRRP).

## 6.3 Dioxins/Furans and Dioxin-Like Polychlorinated Biphenyls

The USEPA has developed an inhalation URF for 2,3,7,8- tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD or dioxin) from which a chronicESLlinear(c) can be developed. For other laterally-substituted dioxins/furans and dioxin-like PCBs, toxicity equivalency factors (TEFs) have been developed to relate their toxicities to that of 2,3,7,8-TCDD. The TCEQ uses TEFs from Van den Berg et al. (2006) to develop chronicESLlinear(c) values for these other laterally-substituted dioxins/furans. For non-planar dioxins/furans, the TCEQ will use the most current scientifically-defensible guidance. Scientifically-defensible chronic oral toxicity factors (e.g., SFo, nonlinear cancer-based RfD, RfD) for 2,3,7,8-TCDD could be derived under applicable sections of this guidance (e.g., Chapter 5) to be used consistent with applicable rules (e.g., toxicity equivalent quotient approach in TRRP).

## 6.4 Product Formulations

If a chemical product contains two or more components and the ESLs for all components are known, the TCEQ derives an ESL for the product based on the percent composition (by weight) of the product. The effects of the different components are considered additive, and the sum of ground-level concentrations (GLCs) divided by their respective ESLs (i.e., $GLC_1/ESL + GLC_2/ESL_2 + ..... GLC_n/ESL_n$) should not exceed unity. The TCEQ also assumes that the dispersion characteristics of the product are similar to those of its components. Accordingly, an ESL of the chemical product can be derived by the following formula where $f_n$ equals the fractional quantity of component 'n' in product X, and $ESL_n$ equals the ESL for component 'n' (Equation 6-1):

**Equation 6-1 ESL for a Chemical Product**

$$X = \frac{1}{\frac{f_a}{ESL_a} + \frac{f_b}{ESL_b} + \frac{f_c}{ESL_c} + \cdots\cdots + \frac{f_n}{ESL_n}}$$

Example: Product X consists of 20% chemical A (ESL of 100 µg/m$^3$), 30% chemical B (ESL of 60 µg/m$^3$), and 50% chemical C (ESL of 200 µg/m$^3$).

$$\text{ESL for Product X} = \frac{1}{\frac{0.2}{100} + \frac{0.3}{60} + \frac{0.5}{200}} = \frac{1}{0.0095} = 105\ \mu g/m^3$$

Except in limited cases (e.g., §350.76(g) of TRRP), a mixture procedure based on individual components is not used in TCEQ remediation programs. Therefore, this section is generally irrelevant to oral toxicity factors as used by the TCEQ.

# Chapter 7 Hazard Characterization and Exposure-Response Assessment Using Epidemiology Data

## 7.1 Objectives

This chapter provides guidance for conducting a quantitative hazard characterization and exposure-response assessment using epidemiology data. It is neither an exhaustive text on epidemiology nor a guide to the conduct of an epidemiology study. Rather, it is a guide to the methods for performing quantitative hazard characterizations and exposure-response assessments using existing epidemiology studies that focus on chronic toxicity rather than acute toxicity. The main body of this epidemiology cancer section concerns general guidelines, with specific mathematical models included in Appendix D - Linear Multiplicative Relative Risk Models:

- D.1 Overview of Poisson Regression Models
- D.2 Summary Estimates of Standardized Mortality/Incidence Rates
- D.3 Adjustments for Possible Differences Between the Population Background Cancer Rate and the Cohort's Cancer Rate in the Relative Risk Model
- D.4 Estimating the Slope Parameter, $\beta$, in the Relative Risk Model Adjusting for Differences in Background Rates
- D.5 Estimating the Asymptotic Variance for the Slope Parameter in the Relative Risk Model

Exposure-response and dose-response are used synonymously throughout this chapter. Exposure-response is a term preferred by epidemiologists whereas dose-response is commonly used by toxicologists. Special emphasis is placed on deriving carcinogenic inhalation unit risk factors and oral slope factors based on human epidemiology studies. Consequently, the discussion is in terms of a dichotomous response such as the presence or absence of a specified carcinogenic response or development of a specific type of cancer.

In this chapter, epidemiology is considered to be the study of diseases in specified populations of humans. The science of epidemiology was first developed to discover and understand possible causes of contagious diseases such as smallpox, typhoid and polio among humans. It has expanded to include the study of factors associated with non-transmissible diseases like cancer, and of potential adverse health effects caused by environmental exposures. Some epidemiology studies are mostly qualitative, primarily descriptive, and focus on determining what factors are associated with diseases (risk factors) and the associated distribution of the disease among the members of the population. More quantitative epidemiology studies attempt to quantify the exposure and

the relationships between exposure characteristics (duration, intensity, timing, co-exposures, etc.) and response characteristics (frequency, probability, standardized mortality rates (SMRs), relative risk rates (RRs), odds ratios (ORs), timing, severity, etc.). Some of these more quantitative epidemiology studies can be used for exposure-response modeling and may provide useful information for extrapolating from relatively high exposure scenarios to lower environmental exposure scenarios.

Properly conducted epidemiology studies (i.e., a proper study design, confounding factors accounted for, Bradford Hill Criteria considered, etc.) can be useful tools. Epidemiology studies can provide evidence (sometimes strong evidence) concerning risk factors; however, they cannot "prove" that a specific risk factor actually causes the disease being studied. In contrast to a cohort or case-control study, an ecological study is an epidemiology study wherein the unit of analysis is a group rather than an individual and, as such, is not suitable for TCEQ's dose-response modeling. The "ecological fallacy" occurs because statistics that accurately describe group characteristics are not necessarily applicable to individuals within that group (e.g., Pearce 2000). Please refer to Appendix D Glossary for definitions of terms used in these guidelines.

## 7.2 Published Hazard Characterizations and Exposure-Response Assessments

It is generally recognized that human epidemiology data are preferred over data from animal studies as the basis for dose-response modeling. Although the TCEQ does not conduct epidemiology studies, the TCEQ does review such studies and any dose-response modeling therein. If the study is of suitable quality and the necessary data are available, the TCEQ may perform its own dose-response modeling following these guidelines. When quantitative hazard or exposure-response characterizations using epidemiology data are identified in the scientific literature or databases, they are reviewed by the TCEQ to determine whether the approach used to develop these characterizations (and resultant toxicity values) is appropriate. Many published characterizations are not appropriate for use by the TCEQ because procedures other than those recommended in this guidance document were used to derive toxicity factor (e.g., URF, SFo) values. Due to time and resource constraints, the TCEQ considers the published values and their respective key studies as a starting place for gathering information on hazard or exposure-response characterizations. However, because the characterizations may be outdated, the TCEQ also evaluates peer-reviewed studies available after the date these characterizations were published to ensure that the latest data are considered prior to developing a hazard or exposure-response characterization. The TCEQ also reviews other published hazard or exposure-response characterizations from organizations that specifically address susceptibility of children. In addition, the TCEQ considers adoption of a published hazard or exposure-response characterization when the risk assessment procedures used to develop such factors are similar to those described in this guidance. Preference will be given to values that have undergone an external peer review and public involvement process.

The evaluation and selection of suitable epidemiology studies (especially for the purposes of exposure-response modeling) is discussed in the scientific literature (e.g., Federal Focus 1995, Graham 1995, Hertz-Picciotto 1995, WHO 2000b, Meek et al. 2003, IPCS 2005 and 2006, Goldbohm et al. 2006, Boobis et al. 2008, USEPA 2011a). Important topics include study designs other than the typical occupational cohort with retrospective follow-up such as case-control and cross-sectional designs, evaluating weight-of-evidence that a chemical causes a specific cancer(s), estimation of exposure-response regression models, estimation of uncertainty introduced by potential biases, confounding, and missing information, calculation of excess lifetime risk through a life table to take into account competing risks, and sensitivity analyses focusing on the impact of assumptions made and the variability of the underlying data.

## 7.3 Components of the Exposure Response Assessment

Whereas Section 7.2 addresses the quality of epidemiology studies, Sections 7.4 to 7.13 focus on a selection of the most important components of the exposure-response assessment and addresses them from a top-down perspective. The purpose of the discussions in the following subsections is to guide TCEQ staff in determining the utility of specific components of an epidemiology study for the purposes of TCEQ's exposure-response assessment.

## 7.4 Endpoint Selection

The toxicity endpoint for hazard characterization and exposure-response assessment using epidemiology data needs to be explicitly specified *a priori* or after a carefully conducted WOE demonstrating causality based on the Bradford Hill Criteria (Hill 1965, Höfler 2005, Howick et al. 2009, Phillips and Goodman 2006, Ward 2009). If a common name for the toxicity endpoint is specified (e.g., leukemia), then the intended diseases should be more precisely defined (e.g., specific International Classification of Diseases (ICD) codes for mortality) in the epidemiology study. If ICD codes are specified, the ICD revision should also be noted in the study as well as how earlier revision codes can be transformed to the specified revision.

The USEPA 2005 Guidelines for Carcinogen Risk Assessment (USEPA 2005a) discuss the role of the mechanism of action and MOA in the dose-response models. EPA clarifies the difference between mechanism of action and MOA by stating the following:

> *The term 'mode of action' is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A 'key event' is an empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element. Mode of action is contrasted with 'mechanism of action,' which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action. The toxicokinetic processes that lead to formation or*

> *distribution of the active agent to the target tissue are considered in estimating dose but are not part of the mode of action as the term is used here. There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.*

Mechanistic or biologically-based exposure-response models are most appropriate when there is an identified, well understood mechanism of action or at least an identified, well understood MOA for the specified toxicity endpoint. There are limitations to assessments of toxicity endpoints that involve multiple MOAs. For example, lymphohematopoietic cancers can have multiple MOAs so that, the appropriate method for low-exposure extrapolation cannot necessarily be defensibly determined (e.g., Sielken et al. 2007 and 2011). Thus, the TCEQ takes special care when the toxicity endpoint involves grouping of responses with possibly multiple target tissues, mechanisms of action, MOAs, and severities.

There are also other important issues that the TCEQ considers when selecting the toxicity endpoint:

- Potential confounding (e.g., cigarette smoking) should be addressed and avoided if possible.
- Potential double counting of individuals with the toxicity endpoint should be addressed and avoided if possible.
- While data derived from death certificates can provide invaluable information, the usefulness of such data depends on the completeness of records, the accuracy in assigning underlying causes of death, etc. (e.g., Bonita et al. 2000, Manos et al. 2008). Thus, there are limitations of death certificates or other means of identifying the presence or absence of a specified toxicity endpoint in the epidemiology study.
- Epidemiology studies usually are based on mortality or incidence data. Mortality is a good surrogate for incidence for tumors (or other endpoints) that have low survival rate. However, mortality is a poor measure of cancer incidence for some tumors with high survival rates (e.g., skin cancer, and some other types). The severity of the response (e.g., mortality, incidence) should be clearly defined and should be the same severity for both the exposure-response modeling and the risk characterization.

## 7.5 Exposure Characterization

Exposure characterization is performed by the epidemiologist. The manner in which an individual's exposure is characterized is important and should be discussed in the epidemiology study. The exposure metric used in the exposure-response model is also important and is discussed in the next section. The TCEQ considers the following potential exposure characterization issues (the relative importance of which varies from

case to case) when reviewing epidemiology studies for potential use in deriving toxicity factors:

- temporality,
- measurements,
- models,
- reasonableness of underlying modeling assumptions,
- exposure estimation errors,
- grouped versus continuous exposure values, and
- biomonitoring.

Exposure in epidemiology studies generally occurs over a period of time and has a temporal profile. Exposure characterizations that capture the changes in this profile over calendar years and changes in the epidemiology setting (e.g., occupational setting) generally support age-dependent, exposure-response modeling and calculation of excess risk (i.e., BEIR IV modeling discussed in Section 7.6) and are generally preferred. For example, exposure histories in an occupational epidemiology study can be generated from job/task histories combined with calendar-year and job/task specific exposure characterizations (job-exposure matrices (JEMs)). Macaluso et al. (2004) provides a good example for the characterization of 1,3-butadiene in the styrene-butadiene-rubber cohort.

Ideally, the exposure concentrations in an exposure history are based on accurate analytical measurements (e.g., biomonitoring where the relationship between the exposure concentration and the biomonitored value is known) with personal measurements being better than area measurements (Hays et al. 2007). Sometimes, measurements (e.g., industrial hygiene measurements) are designed for a different purpose than individual exposure measurements and, thus, have limitations (e.g., unrepresentative sampling, changing analytical methods, incomplete documentation, and sparseness over jobs, times of the day, and/or calendar years) (e.g., Hewett 2001 and Stewart 1999). Examples using analytical methods are discussed in Moseman and Oswald 1980, Paustenbach 2006, and Hays et al. 2008. The ACGIH Biological Exposure Indices (BEI) documentation (ACGIH 2011) provides useful information on many topics related to the potential BEIs for each chemical covered, including specificity of the biomarker, and whether the biomarker reflects short-term or chronic exposure (all of which should be considered in determining whether biomonitoring data can be used to reflect exposure).

Biomonitoring can be useful as either an indicator of the presence or absence of exposure or as a quantitative measure of the magnitude of exposure. In addition, biomonitoring may also be useful as a means of creating a relative ranking of exposures and as a tool for validating other exposure characterizations. However, there are some potential limitations associated with biomonitoring such as its relation to dose and temporal integration (Hays et al. 2007). For example, the relationship between the dose at the target tissue and the amount in the biomonitoring medium (e.g., blood or urine) may be unknown. It may also be unclear as to how the observed biomonitoring value has integrated the preceding exposures over time. For example, did the urine concentration reflect exposures over the

last 3 hours, 24 hours, 48 hours, etc. For such reasons, some current biomonitoring data may be of limited value to retrospective epidemiology studies.

By necessity, exposure concentration estimates from exposure models are frequently used as alternatives to analytical measurements. Numerous individuals and groups (including academics and federal and state agencies) have created exposure models (e.g., USEPA Center for Exposure Assessment Modeling (CEAM), USEPA Office of Pollution Prevention and Toxics (OPPT), Calendex™ (www.exponent.com/practices/foodchemical/calendex.html), Cumulative and Aggregate Risk Evaluation System (CARES™) (cares.ilsi.org), LifeLine™ (www.thelifelinegroup.org/lifeline/index.htm), McKone 1987, Little and Chiu 1988, Paustenbach 1989, Kim et al. 2004, Ott et al. 2007). An example where estimates from exposure models were used is the characterization of 1,3-butadiene in the styrene-butadiene-rubber cohort (Macaluso et al. 2004 and Sielken and Valdez-Flores 2011). Because not all exposure models are created equal but some are useful when implemented by epidemiologists in the context of their study, the TCEQ considers the reasonableness of the exposure models when evaluating the usefulness of the study for the TCEQ's purposes.

The evaluation of an exposure model's utility should be based on the quality of the information incorporated into the model and the reasonableness of underlying modeling assumptions. Also, some models may seem to include multiple aspects of exposure (e.g., exposure duration, intensity, formulation, method of use, and personal protective equipment) but are really primarily functions of only one input (duration). For example, duration (e.g., years or days) frequently dominate time-dependent exposure models.

All exposure estimates have errors associated with them, and a discussion of these errors should be made available in the published epidemiology study and included in the uncertainty section of the DSD. Two examples of such errors are measurement errors of a continuous variable and misclassification errors of a categorical variable (e.g., classifying a job's exposure into a lower category than it should be). It may be important to use sensitivity analyses (where possible) to determine whether these errors may be leading to a directional bias (e.g., over- or under-estimation of exposure). Measurement errors of a continuous variable (the difference between the actual value of a quantity and the value obtained by a measurement) may be random errors that are unbiased (e.g., for additive errors their expected value is zero). However, even these unbiased random errors may lead to a biased estimator depending on what characteristic of the exposure is being estimated. For example, if the estimator is estimating the 95$^{th}$ percentile of a distribution, then, because the random errors tend to make at least some of the larger sample values larger than they would normally be, the 95th percentile of the sample values with errors is expected to be an over-estimate of the 95th percentile of the sample values without errors (e.g., Chaisson et al. 1999). Thus, knowing the directional bias of an exposure estimator may guide the interpretation and use of that estimator by an epidemiologist.

A random variable is a function that associates a unique numerical value with every outcome of an experiment. A continuous variable is a random variable that can take on any value between its minimum value and its maximum value. Continuous variables typically correspond to measurements. For example, body weight is a continuous variable

if the weight can be measured to as many decimal points as desired and is not restricted to be a whole number of units. Random variables that are restricted to a countable number of possible values are discrete variables. For example, if body weight is restricted to a whole number of pounds (or kilograms), then body weight is discrete. Variables that are restricted to a finite number of values are categorical variables. Categorical variables are usually names or labels such as gender, health status, and type of job. Categorical variables may also be labels for groups of discrete or continuous variable values. For example, body weight under 100 pounds might be labeled 1; body weight between 100 and 200 pounds might be labeled 2; and body weight over 200 lbs might be labeled 3; in which case this label would be a categorical variable.

The TCEQ will evaluate how any continuous variables (e.g., cumulative ppm-years) in the epidemiology study have been grouped or partitioned into categories and how the categories are characterized quantitatively (e.g., by the mean or median in a given category) with particular attention to unbounded categories. Categorizing continuous exposure variables can cause several problems (Shaw et al. 1987, Altman et al. 1994, Schulgen et al. 1994, Figueiras and Cadarso-Suárez 2001, Hollander at al. 2004, Richardson and Loomis 2004, Royston et al. 2006, Wainer 2006, Fedorov et al. 2009). For example, categorizing can cause loss of power and loss of precision of estimated means, odds, hazards, etc. This is due to the fact that categorization assumes that the relationship between the predictor (e.g., dose) and the response (e.g., cancer endpoint) is flat within each exposure interval, which is an assumption far less reasonable than a linearity assumption in most cases. There are other potential issues as well. For example, researchers seldom agree on the choice of category cutpoints. Thus, there is a potentially severe study interpretation problem among researchers and across studies. Also, because of sample size limitations in the very high range of the exposure variable, there will be significant heterogeneity of subjects within those intervals and residual confounding. Categorization assumes that there is a discontinuity in response as interval boundaries are crossed, and categorization that is not blinded to the response variable (i.e., when response is considered in deriving categories) can result in biased effect estimates. For example, cutpoints are arbitrary and can be manipulated, which can result in either positive or negative associations within the same study depending upon the choice of cutpoints. If a confounder is adjusted for by data categorization, there may be residual confounding that can be explained away by inclusion of the continuous form of a predictor (e.g., dose) in the model in addition to the categories. Confidence in results based on categorization can be increased if the author conducts a sensitivity analysis of the impact on the ultimate result of various cutpoints for the categorization.

## 7.6 Exposure Metric

The exposure metric, used in exposure-response modeling or as dose in dose-response modeling, is a critical component of both the modeling and the risk characterization. As mentioned previously, epidemiologists prefer the term exposure metric versus dose metric. The exposure metrics used for exposure-response modeling are evaluated by the TCEQ along with the following information when reviewing epidemiology studies for potential use in deriving toxicity factors.

The most commonly reported exposure metric, which is frequently the only reported exposure metric, in epidemiology studies is cumulative exposure (e.g., cumulative ppm-years). Cumulative exposures can either incorporate or not incorporate simple lags where exposures in a specified number of preceding years are excluded. Cumulative exposures can also be restricted to an exposure window where exposures in a specified number of preceding years are excluded as well as excluding exposures that occurred more than a specified number of years into the past. Simple lags and/or exposure windows have been included in the risk assessment of several substances (Shore et al. 1992, Steenland et al. 1998, Steenland et al. 2001, Crump et al. 2003, Agalliu et al. 2005). Cumulative exposures may also be weighted. Weighted cumulative exposures are an alternative to unweighted cumulative exposures. For example, the exposure in a year can be weighted on the basis of its relative importance with respect to age or distance into the past. The TCEQ evaluates whether the specific form of the cumulative exposure is biologically and statistically defensible. In addition, when evaluating the appropriateness of specific exposure metrics, the TCEQ considers the sensitivity of the derived toxicity factors to the exposure metrics.

It is important to note that the use of the simplest form of cumulative exposure (i.e., without lags, windows, weights, etc.) as the exposure metric makes several implicit assumptions. It assumes that cumulative exposure is more biologically relevant than other aspects of exposure such as duration and intensity. Cumulative exposure also does not differentiate between high intensity exposures for short durations and low intensity exposures for long durations. In other words, cumulative exposure assumes that the temporal pattern of exposure magnitudes within a specified exposure duration is not important to the toxic response. For example, the cumulative exposure by age 50 could be the same numerical value if all of the exposure occurred between ages 20 to 30, all of the exposure occurred between ages 40 and 50, or the exposure was at a constant level for 50 years - ignoring the temporal pattern of exposure levels. As another example, using cumulative exposure as the exposure metric assumes that a 10 ppm exposure has the same impact on the likelihood of a response today if it occurred yesterday, 5 years ago, or 50 years ago. Limitations of cumulative exposure have been widely discussed in the literature (e.g., Copes et al. 1985, ten Berge 1986, Checkoway et al. 1992, Cox et al. 1996, USEPA 1998c, Weller et al. 1999, Murdoch et al. 1992, Goddard et al. 1995, Miller et al. 2000, Evans et al. 2002, Buchanan et al. 2003, Collins et al. 2003, Ginsberg 2003, Boyes et al. 2005, and Shusterman et al. 2006). After reviewing the limitations of cumulative exposure, USEPA's 2005 Carcinogen Risk Assessment Guidelines (page 3-4) concludes that cumulative exposure or potential dose may be replaced by a more appropriate dose metric when indicated by the data.

Some alternatives to cumulative exposure are those based on metrics that place greater emphasis on intensity or duration, such as $(C-C_0)^n \times (T-T_0)^m$ where C is the concentration intensity, $C_0$ is a concentration threshold, T is exposure duration, and $T_0$ is a duration threshold, and n and m are parameters (specified or estimated) (e.g., ten Berge 1986, Vacek et al. 1991, Smith 1992, Schnatter et al. 1996, Rozman 2000, Blankenship and Stefanski 2001, Bunce et al. 2003, Kriebel et al. 2007). Such metrics can also be weighted as discussed above. Extensive additional discussion and examples are in the

Summary of the USEPA Workshop on the Relationship between Exposure Duration and Toxicity (USEPA 1998c).

Additionally, exposure metrics do not necessarily have to be cumulative. For example, the exposure concentration at the time the observation is made, the exposure duration, years since hire, and the average exposure intensity are non-cumulative exposure metrics.

It is important that exposure metric reflects the chemical's MOA and is as biologically relevant as possible. This may mean that an exposure metric reflecting the number (or duration) of exposure events above some specified exposure level (e.g., high intensity tasks), peak exposure, or some other less frequently used exposure metric may be useful and should not *a priori* be discounted.

With several possibly relevant exposure metrics available for exposure-response assessment and because a single exposure metric (e.g., cumulative exposure) captures only one part of the exposure scenario, an epidemiologist may evaluate more than one exposure metric, either separately or together. For example, it may be worthwhile to consider other characteristics of the exposure to the toxicant under consideration as well as other potentially confounding co-exposures to other toxicants. Many of these exposure metrics may be correlated or otherwise dependent upon one another. However, their individual or joint impacts may still be worth investigating by the epidemiologist and should not be ignored *a priori*. When several exposure metrics are available to characterize exposure-response, the TCEQ will evaluate the relevance of each exposure metric being considered for selection in terms of the specified toxic response, the chemical, and its mechanism(s) and mode(s) of action.

In addition to the considerations discussed above, the TCEQ evaluates the implications of the differences between the exposure metric that is biologically relevant in the epidemiology study and the exposure occurring in the inference scenario (i.e., the exposure scenario being extrapolated to which is the exposure to the general population). For example, the exposures in the modeling scenario might be sporadic, high-intensity exposures and the inference scenario might be continuous, low-intensity exposures.

Ultimately, *the exposure metric used in the dose-response modeling discussed in the next section must be an exposure metric reported in the epidemiology study.*

## 7.7 Dose-Response Models

As mentioned previously, mechanistic or biologically-based dose-response models are most appropriate when there is an identified, well understood mechanism of action or at least an identified, well understood MOA for the specified toxicity endpoint. Care should be taken when the toxicity endpoint involves grouping of responses with possibly multiple target tissues, mechanisms of action, MOAs, and severities.

The USEPA (2005a) recognizes that there is rarely sufficient information about the MOA to scientifically justify a specific detailed model for that chemical. In the absence of a scientifically defensible and biologically-based dose-response model or sufficient MOA information indicating a nonlinear dose-response relationship at low doses, the TCEQ

makes reasonable health-protective assumptions about the relationship between exposures and toxicologic endpoints in epidemiology data including the assumption that the extrapolation of estimated dose-response relationship conforms to linearity at low doses of exposure. That is, linear in the exposure metric and not necessarily linear in the administered dose or exposure concentration.

Epidemiology data can be analyzed in diverse ways and for several different purposes. The analyses of epidemiology data for the purpose of risk assessment requires that the data be modeled in such a way that the model can be used to evaluate the risk for a target population different than the population included in the epidemiology study. A model based on epidemiology data describes the mathematical relationship between the observed mortality or disease incidence and the exposures. The form of the dose-response model should enable the separation of the effect of the agent being evaluated on the toxicity endpoint from the effects that other factors may have on that endpoint. For example, the effect of background hazard rates and co-exposures in the epidemiology data should be part of the dose-response model when fitting or describing the epidemiology data but should be excluded from the model when evaluating risks for a target population with different background hazard rates and not exposed to other agents.

Obviously, the models that can be used for epidemiology studies depend on the availability of the data. The following subsections discuss various models and then provide guidelines indicating the different alternative models that can be used for different epidemiology data, depending on the type of data that were collected, evaluated, and reported. The TCEQ uses these guidelines to identify possible modeling approaches to investigate available, chemical-specific epidemiology data.

### *7.7.1 Individual Epidemiology Data*

The full potential and best use of dose-response modeling of epidemiology data are possible only when the information is available at the individual (person) level rather than a group level. Information such as time-dependent exposure history, demographic characteristics (e.g., gender, race), lifestyle habits (e.g., smoking) relevant to the health endpoint under investigation, time-dependent co-exposures history to other potential agents that cause or may affect the health endpoint, etc., allow the researcher to use exposure-response models to best describe the relationship between health endpoints and potential explanatory variables. The TCEQ rarely has access to this type of data and relies on published results from epidemiologists (e.g., modeling for 1,3-butadiene by Cheng et al. 2007) or dose-response modelers who have been able to obtain the raw data (e.g., modeling for 1,3-butadiene by Sielken and Valdez-Flores 2011).

Ideally, a dose-response model should be such that the relationship between the health endpoint and the explanatory variables are biologically defined. Most biological processes that give rise to health endpoints, however, are complex in nature and generally not fully understood or developed and cannot be summarized via simple mathematical models. Researchers usually must rely on statistical methods to fit mathematical exposure-response models to the observed epidemiology data. As indicated above, in the absence of scientific justification to use a biological-based dose response model, the

TCEQ makes the reasonable health-protective assumption that the extrapolation of the estimated dose-response relationship conforms to linearity at low doses of exposure, i.e., linear low-dose risk.

### 7.7.2 Multiplicative Background Hazards Models

The risk of a specified health endpoint increases proportionally to the background rate for a specified value of the dose metric and values of the covariates in multiplicative background hazards models. These models are also known as relative risk, proportional hazards, or multiplicative background risk models. The multiplicative background models have been used extensively in modeling epidemiology data because of their flexibility, robustness and the assumption that the increase in risk is proportional to the background hazard rate.

Multiplicative background hazards models have been useful in modeling the incidence of cancer in humans exposed to radiation (Törnqvist and Ehrenberg 1994). According to Törnqvist and Ehrenberg (1994), a multiplicative model for cancer incidence is expected if the agent is an initiator and cause irreversible damage. The validity of multiplicative background hazards models is supported by analyses of epidemiology data of cancers related to ethylene oxide (Törnqvist and Ehrenberg 1992). Multiplicative background hazards models have been used by USEPA (e.g., 1986d, 2001b, 2006d); TCEQ (e.g., 2007c, 2008); and several others (e.g., Harris, 1983, Crump 1994, Cheng et al. 2007, Sielken and Valdez-Flores 2009 and 2010). The National Research Council (NRC 1990) adopted the multiplicative background hazards model for radiation-induced cancers.

### 7.7.3 Additive Background Hazards Models

In additive background hazards models, the risk of a specified health endpoint increases by the same amount, regardless of the size of the background rate, for a specified value of the dose metric and values of the covariates. These models are also known as absolute risk models. Additive background models have not been used as often by USEPA as multiplicative background models in epidemiological risk assessment.

Additive background hazards models have been used only in limited occasions. Oftentimes additive models have been used in conjunction with multiplicative background hazards models (e.g., USEPA 1986d). Publications comparing additive and multiplicative models have not made any recommendations for using one model over another (e.g., Stayner et al. 1995), while some others have recommended using the multiplicative model (e.g., Törnqvist and Ehrenberg 1994).

### 7.7.4 Adjustment of Background Hazard Rate

The multiplicative or additive background hazards models discussed in Sections 7.7.2 and 7.7.3, respectively, used to model epidemiology data usually include a factor to account for the potential differences between a target population background rate and the

underlying background rate in the cohort of the epidemiology study. For example, if the models were linear in the dose (i.e., the hazard rate in the dose-response model is a linear function of the dose), then they would be as follows (Equation 7-1 and Equation 7-2):

**Equation 7-1 Adjustment of Background Hazard Rate for the Additive Background Rate Model**

$$\text{Additive Rate } \lambda(d) = \lambda_0 + \alpha + \beta \times d$$

**Equation 7-2 Adjustment of Background Hazard Rate for the Multiplicative Background Rate Model**

$$\text{Relative Rate } \lambda(d) = \lambda_0 \times \alpha \times (1 + \beta \times d)$$

Where:

$\lambda_0$ = the reference population's estimated background hazard rate of the endpoint being analyzed
d = the dose measure (e.g., cumulative exposure in ppm-years)
$\beta$ = the slope (i.e., the change in the rate per unit increase in the dose)
$\alpha$ = reflects the study cohort's departure from the reference population's background hazard rate

The reference population's background hazard rate and the study cohort's departure from that rate are relevant during the modeling. As discussed further in Section 7.9, during the excess risk calculation for the target population, the target-population specific background hazard rates substitute for the estimated $\lambda_0+\alpha$ in the additive models and the $\lambda_0 \times \alpha$ in the multiplicative models in the evaluation of risks. For example, if a model is fit to the mortality of lung cancer in an epidemiology cohort, the risks for the population of Texas based on the model should be calculated using the Texas population background hazard rates of lung cancer mortality instead of the background hazard rate and adjustments estimated for the cohort. Age- and calendar-year- dependent background hazard mortality and incidence rates are regularly published by federal and state agencies (e.g., Surveillance Epidemiology and End Results of the National Cancer Institute at www.seer.cancer.gov).

### *7.7.5 Cox Regression*

The Cox regression model fits a family of multiplicative background hazards models to epidemiology data. Cox regression is the preferred modeling methodology for health endpoints of epidemiology studies because of its statistical properties and widespread availability in software packages. Cox regression, as opposed to other methods, is more robust and does not require any assumptions about the underlying background hazard rates of the health endpoint. In addition, Cox regression can readily incorporate time-dependent covariates as well as fixed covariates (Cox 1972, Allison 2010). The covariate effects in Cox regression can be modeled as parametric or nonparametric effects. A parametric model assumes a specified functional form (e.g., linear or log-linear), and a nonparametric model does not assume a specified functional form. For example, regression models assume specified functional forms (e.g., linear or polynomial) and

hence are parametric models. The magnitudes of the independent variable (e.g., dose) have an impact on the estimation of the model parameters. On the other hand, nonparametric models do not assume a functional relationship between the independent variable (e.g., treatments) and the response. The labels for the different treatments do not have a numerical significance and do not have an impact on the results.

Nonparametric modeling of covariate effects in Cox regression is especially useful when the effects do not have a clearly defined functional form (which happens frequently). The effects of fixed covariates can also be included by using stratified Cox regression whereby different strata are formed for each combination of the values of the stratifying covariates.

Cox regression has several other advantages. For example, because age is usually the main factor in the increased incidence of carcinogenic endpoints, it is of paramount importance to closely control the effect of age on health endpoints of epidemiology studies. Cox regression uses age as the index variable, adjusting for age in an optimal way. Also, Cox regression has an advantage over other methods in that exposure and other time-dependent covariates are treated as continuous variables that can take on any real value and do not have to be discrete values or group values. This feature of the Cox model avoids making extra assumptions that may increase the uncertainty of exposure estimates and of other measured or estimated covariates.

### *7.7.6 Poisson Regression*

The Poisson regression methodology fits either multiplicative or additive background hazards models to epidemiology data. Poisson regression models require that individual person-years at risk be partitioned into different risk groups because these models operate on grouped data (Crump and Allen 1985). The effect of dose, for example, has to be modeled by creating dose intervals where the background hazard rates are approximately constant through the interval. These models (as opposed to the Cox proportional hazards models that use continuous measures of exposures or other time-dependent covariates) use groups of person-years at risk, grouped averages of exposure, and groupings of other time-dependent covariates to fit dose-response models. Poisson regression models assume that the hazard rate in any specific group is a constant through the intervals of time defining the group.

The number of observed individuals with the health endpoint under investigation in each group of person-years and each combination of time-dependent and fixed covariates characteristics is assumed to follow a Poisson distribution with a group-specific rate. Specifically, the number of responses occurring in a particular group of exposure and a particular group of other covariates is assumed to take the values of r=0, 1, 2, …, with the probability given by (Equation 7-3):

**Equation 7-3 Probability for Poisson Regression**

$$p(R = r) = (\lambda n)^r \times \frac{e^{-\lambda n}}{r!}$$

Where:

p(R=r) = the probability that r is observed
r = the number of responses occurring in the group
n = the number of person-years in the group
λ = the unknown rate of occurrence of the response per person-year at risk (i.e., λn is the expected number of responses in the group)

The parameter λ can be modeled using an additive or multiplicative background hazard dose-response model that depends on the dose and the covariates defining the different groups. For example, if each group of person years were defined by a dose interval, an age group and sex, a multiplicative model could be (Equation 7-4):

**Equation 7-4 Multiplicative Model for Person Years Defined by Dose Interval, Age Group, and Sex**

$$\lambda = \lambda(\mathrm{d}, \mathrm{age}, \mathrm{sex}) = \lambda_0 \times \text{Effect of Age} \times \text{Effect of Sex} \times (1 + \beta \times \mathrm{d})$$

Where:

the rate λ depends on the dose d, the age, and the sex of the group

The "Effect of Age" can be represented by a parametric function or nonparametric estimates. The "Effect of Sex" is a nonparametric estimate and accounts for the difference between males and females in the response rate. The parameters $\lambda_0$, "Effect of Age", "Effect of Sex" and β are unknown and need to be estimated from the data. (See Appendix D for more details.)

The form of the group-specific rate λ is given by the specified model, and its numerical value is the expected number of responses observed in each group. The expected number of responses in a group is the product of the group-specific rate and the group-specific number of person-years at risk.

When individual (person) data are available, Cox regression methods are preferable over Poisson regression methods. When only grouped data are available, Cox regression methods cannot be used, but Poisson regression models can be used.

## *7.7.7 Parametric Dose-Response Models*

Dose-response models for epidemiology studies usually incorporate a parameter that estimates the underlying background hazard rate for the unexposed individuals included in the study. Epidemiological dose-response models used for risk assessment are a parametric function relating the health endpoint being investigated and a measure of the dose from the carcinogenic agent being evaluated. As discussed in Section 7.7.4, for the calculation of excess risks, the underlying background hazard rate estimated for the epidemiology study is replaced by the underlying background hazard rate in the target population for whom risks of the health endpoint are to be estimated (e.g., the general public). The same exposure-response relationship estimated from the epidemiology study

is used in the estimation of risks for the inference population (e.g., the Texas population, the US population, etc.).

Regardless of whether the data are individual or grouped or the background hazards are additive or multiplicative, the dose-response model is of paramount importance because it defines the shape of the curve that describes the relationship between a dose metric and a health outcome. The shape of the dose-response model has an important impact on the estimation of risks at low doses.

#### 7.7.7.1 Linear Dose-Response Models

Generally, the dose-response model can be assumed to be a polynomial function of the dose metric. In the absence of mechanistic information about the carcinogen and the health endpoint, the linear exposure-response model is the most parsimonious and simplest polynomial that should be used to fit epidemiology data. There are at least three reasons for using linear exposure-response models for epidemiology data (Crump and Allen 1985):

1) A linear model is biologically plausible for carcinogens, particularly for genotoxic carcinogens or those acting at a site where cancers occur spontaneously (i.e., in the absence of the carcinogen of interest; Crump et al. 1976).
2) A linear model is considered to be conservative in the sense that other biologically plausible dose-response models would generally imply lower risks.
3) A linear model usually fits data adequately.

The TCEQ believes interpreting "genotoxic carcinogens" in reason 1 above as "carcinogens acting though a mutagenic MOA" to be more appropriate and consistent with current terminology and the rationale being applied. In reason 1, the idea of dose additivity is being referred to by Crump and Allen. That is, the idea that the new dose adds onto a background dose (of the specific chemical or a similarly acting substance) and thus the dose-response curve is locally linear – like a tangential approximation. However, it is also true that spontaneous cancers and dose-related cancers may not necessarily be linear and dose additivity may not be present even if there are spontaneous cancers.

Although some authors have used more sophisticated exposure-response models for epidemiology data, there has not yet been any statistical evidence showing any superiority of these models over the linear model in describing the relationship between exposure or dose and cancer endpoints. Biological justification for nonlinear models and models that include thresholds may exist on a case-by-case basis.

The linear dose-response multiplicative background hazard rate model can be written as follows (Equation 7-5):

**Equation 7-5 Linear Dose-Response Multiplicative Background Hazard Rate Model**

$$\lambda = \lambda_0 \times \text{Covariate Effects} \times (1 + \beta \times \text{d})$$

Where:

$\lambda_0$ = the background hazard rate
d = the value of the dose-metric
"Covariate Effects" = can be parametric functions or nonparametric estimates that describe the effect of variables other than the dose metric on the hazard rate

The rate ratio compares the rate of events at a dose to the corresponding rate when the dose is zero. The dose-response model is said to be linear because the rate ratio is equal to (Equation 7-6):

**Equation 7-6 Rate Ratio for Linear Dose-Response Models**

$$\text{Rate Ratio} = \frac{\lambda}{\lambda_0 \times \text{Covariate Effects}} = 1 + \beta \times d$$

### 7.7.7.2 Log-Linear Dose-Response Models

An alternative model that has been used extensively in modeling epidemiology data is the log-linear model. The log-linear dose-response model has very similar characteristics, advantages, shape, and statistical behavior as the linear models do, especially at low doses. The functional form of the log-linear model is such that the logarithm of the hazard rate of the health endpoint is linearly related to the dose metric. The log-linear model can be used in conjunction with Poisson regression but is especially useful in conjunction with Cox regression.

The log-linear dose-response multiplicative background hazard rate model can be written as follows (Equation 7-7):

**Equation 7-7 Log-Linear Dose-Response Multiplicative Background Hazard Rate Model**

$$\lambda = \lambda_0 \times \text{Covariate Effects} \times e^{\beta \times d}$$

Where:

$\lambda_0$ = the background hazard rate
d = the value of the dose-metric
"Covariate Effects" = can be parametric functions or nonparametric estimates that describe the effect of variables other than the dose metric on the hazard rate

The dose-response model is said to be log-linear because the logarithm of the rate ratio is linearly related to the logarithm of the product of the slope and the dose; that is (Equation 7-8):

**Equation 7-8 Rate Ratio for Log-Linear Dose-Response Models**

$$\text{Ln}(\text{Rate Ratio}) = \text{Ln}\left(\frac{\lambda}{\lambda_0 \times \text{Covariate Effects}}\right) = \text{Ln}(\beta \times d)$$

Where:

Ln(x) = the natural logarithm of x

The above equation can also be written as:

$$\text{Rate Ratio} = \frac{\lambda}{\lambda_0 \times \text{Covariate Effects}} = e^{\beta \times d}$$

### 7.7.7.3 Log-transformed Dose and Supra-Linear Models

As indicated by Crump and Allen (1985), linear exposure-response models are "considered conservative in the sense that other biologically plausible dose-response models would generally imply lower risks." Some researchers have published dose-response models that are inherently supra-linear at low exposures (e.g., Steenland et al. 2003 and 2004). The increase of the hazard rate or relative risk of a supra-linear exposure-response model is faster at lower exposures than at higher exposures. These types of models are generally not biologically plausible and tend to grossly exaggerate the estimation of risks at low exposures (Crump 2005, Valdez-Flores et al. 2010, Ginevan and Watkins 2010). A power model is another name used for a log-transformed dose model.

An example of a multiplicative hazard background log-transformed dose model is given as follows (Equation 7-9):

**Equation 7-9 Multiplicative Hazard Background Log-Transformed Dose Model**

$$\lambda = \lambda_0 \times \text{Covariate Effects} \times e^{\beta \times \text{Ln}(1+d)}$$

or, equivalently:

$$\lambda = \lambda_0 \times \text{Covariate Effects} \times (1+d)^{\beta}$$

The value of 1 (or some other positive value) is usually added to the value of the dose d to avoid having an undefined logarithm when the dose is equal to zero.

Unrealistic supra-linear exposure-response models oftentimes result from exposure transformations that automatically render a supra-linear shape of the relationship between cancer incidence and dose measures. Inappropriately, dose metric transformations like the square root of cumulative exposure or the logarithm of cumulative exposure have sometimes been used in modeling epidemiology data even though linear dose-response models fit the data as well as models with transformed doses. Crump (2005) showed that even when the true dose-response relationship is linear in dose, the models based on log-transformed doses fit the data as a supra-linear function of dose in the presence of random error in the estimation of exposure. Using supra-linear exposure-response models can only be justified if there is sufficient biological or mechanistic data to support their application.

### 7.7.7.4 Splines and Nonparametric Estimates

Splines and nonparametric estimates of health endpoint incidences and exposure are useful techniques for purposes of preliminary evaluation or exploration of epidemiology data (e.g., Steenland and Deddens 2004). However, the TCEQ will typically not use these two techniques as exposure-response models for risk characterization based on the following reasons.

There has been some recent research promoting the use of splines in modeling epidemiology data (e.g., Steenland and Deddens 2004). Splines are mathematical functions that try to provide a piecewise description of the shape and behavior of observed epidemiology data. There are several assumptions that have to be made when fitting a spline to epidemiology data and the resulting spline depends on these assumptions. The simplest splines are given by piecewise linear dose-response models but could include piecewise polynomial models of any order. Splines, although useful, can be misinterpreted and misused as a guiding tool in model selection and model formulation. Splines should not be used as surrogates for biological or mechanistic interpretations of exposure-response relationships. For example, a threshold in a dose-exposure relationship should be included only if there is evidence that exposure below a specific value does not increase the risk of the incidence of the health effect being investigated.

A more basic technique than splines, but frequently just as useful as splines, is nonparametric estimation of the relationship between exposure and incidence, which also helps in inferring the shape of the exposure-response relationship. Also, model selection can be guided by the models ability to reflect the nonparametric estimates. Both splines and nonparametric estimates cannot be used for risk characterization and are useful only as tools in the exploratory analyses of epidemiology data sets.

### *7.7.8 Grouped Epidemiology Data*

Individual worker information in epidemiology studies published in the literature is not available in most cases. Information for groups of person-time at risk, however, is sometimes reported for epidemiology studies in the open literature. Depending on the level of detail of summary epidemiology data published, exposure-response models can be fit to these summary data using Poisson regression. For example, if the number of individuals observed with a specified health endpoint and the corresponding standardized mortality ratio (SMR) for several intervals of an exposure metric are reported, a multiplicative exposure-response model can be fit using Poisson regression. If the information is further split into other categories (e.g., sex, race, plant, year of hire, smoking, etc.), then these data can be used to adjust for the effect of those factors on the incidence of the health effect. For example, the DSD for Arsenic and Inorganic Arsenic Compounds (TCEQ 2012, Erraguntla et al. 2012) fit multiplicative relative risk models adjusting for year of hire to summary epidemiology data of arsenic exposures.

There are instances when odds ratios (ORs) or rate ratios (RRs) are reported (instead of SMRs) for the number of individuals with the health endpoint for groups of workers exposed to different exposure intervals. These data cannot be used for exposure-response modeling using Poisson regression because ORs and RRs do not include sufficient information to estimate the expected number of individuals with a specific health effect in each exposure interval. If there are no better epidemiology data, the ORs can be used as surrogate estimates of the rate ratios or relative risks (RRs) and fit an exposure-response model using least squares methodology. For example, the DSD for Nickel and

Inorganic Nickel Compounds (TCEQ 2011) fit a least squares linear dose-response model to summary epidemiology RRs of lung cancer (in addition to other analyses).

It is important to note that the OR and the RR are, by definition, equal to one for the reference or "control" group. The reference or "control" group may or may not be exposed to any agent causing the health effect under investigation. In addition, the underlying background hazard rate for the health effect in the epidemiology study is likely different than the background hazard rate for the health effect in the target population for whom the risks are to be estimated (e.g., the general public). It is thus important, when fitting a dose-response model to RRs or ORs, to include an intercept in the model with a parameter to estimate the underlying background hazards rate of the health endpoint being investigated. The estimate of the intercept (the estimate of the underlying background hazards rate in the epidemiology cohort) is replaced by the age-dependent and population-specific background hazards rate in the target population for the characterization of risks. For example, the DSD for Nickel and Inorganic Nickel Compounds (McCant et al., 2009) fit a least squares linear dose-response model with a multiplicative intercept to summary epidemiology RRs of lung cancer.

### *7.7.9 Limited Epidemiology Data*

Sufficient epidemiology data to fit a dose-response model to the observed health endpoint of interest are not always available. Oftentimes only minimal summary data are reported in published articles. When only limited information is available, the researcher has to make the best use of these limited data to develop a dose-response relationship. Regulatory agencies have often relied on simple linear regression models whenever there are only limited data (e.g., USEPA 1986d). One such example is when results (e.g., SMRs) are published only for the epidemiology group as a whole and hopefully an estimated average exposure for the whole group is given. A simple linear model that goes through one at zero exposure and through the SMR at the average exposure can define the linear exposure-response. This limited estimate of a model is justified only if there are no better data that can be obtained. The maximum likelihood estimate of the slope would just be equal to the SMR divided by the average of the exposure. The slope of the linear multiplicative dose-response model is then equal to (Equation 7-10):

**Equation 7-10 Slope of Linear Multiplicative Dose-Response Model**

$$\beta = \frac{SMR - 1}{d}$$

Where:

d = the average value of the dose metric for all the individuals in the epidemiology study
SMR = the ratio of the hazard rate in the individuals in the epidemiology study and the hazard rate of a reference population , such as the U.S. or Texas population

This type of model has been referred as an average relative risk model because is based on an average estimate of risk (SMR) and an average estimate of the dose.

### *7.7.10 Covariate Effects*

Dose-response modeling of health endpoints in epidemiology studies should be adjusted by the epidemiologist for the effects of any relevant factors. These factors are usually called covariates because they vary from one individual to another. The epidemiologist should provide a discussion of covariate effects in the published paper, and covariate effects should be discussed in the uncertainty section of the DSD (see Cheng et al. 2007 for an example). Ideally, the covariates included in the model should be selected based on biological or mechanistic arguments. However, if there is no biological or mechanistic information that dictates which covariates should be included in the dose-response model, the impact of the covariates in the health effect being investigated can be assessed using statistical methodology. Likelihood ratio tests can be used to determine whether a covariate contributes significantly to the explanation of the relationship between exposure and incidence of a health endpoint.

The covariates can be time independent (e.g. race, gender) or time dependent (e.g. age, years since hire, co-exposures to other agents, jobs, or plants). The effect of the covariates on the model fit to the data can be evaluated, with the one covariate with the most significant impact on the likelihood included first. This process can be repeated including one covariate at a time until all covariates that make a significant improvement in the likelihood of the fit are included in the exposure-response model. Sielken and Valdez-Flores (2011) provide an example of this type of analysis for 1,3-butadiene. There are additional procedures for selecting which covariates to include.

Statistically-based criteria to include covariates lead to more robust and less subjective modeling. However, if there is any biological or mechanistic indication that a covariate should be part of the dose-response model, then the covariate should be included in the analysis. It is better to risk increasing the uncertainty in the estimate of the dose-response relationship by adding potentially unnecessary covariate effects than to introduce the bias resulting from excluding important covariate effects (Checkoway et al. 1989, Rothman 1986, Breslow and Day 1980 and 1987).

The estimates of the underlying background hazard rate and of the covariate effects and other adjustments to the underlying background hazard rate are replaced by the age-dependent background hazard rates observed in the target population for purposes of risk characterization. In the risk characterization step of the risk assessment, only the dose-response component of the model is used because the target population's underlying age-dependent background hazard rates are intrinsically adjusted for any other relevant factors, or are not part of the target population's experience of the health endpoint being studied. For example, if the following multiplicative background dose-response model were used:

$$\lambda = \lambda_0 \times \text{Covariate Effects} \times (1 + \beta \times \text{d}),$$

then only the slope parameter (β) estimated from the model is needed for the characterization of risks in a specified population. In addition, the estimated background hazard rate ($\lambda_0$×Covariate Effects) is replaced by the target population hazard rate in the characterization of risks for such population. Sielken and Valdez-Flores (2009a, 2009b) are examples of how to calculate population risks from parameters of dose-response models fitted to epidemiology data.

### *7.7.11 Goodness of Fit*

Goodness of fit of dose-response models fit to epidemiology study data involve groupings of the numbers of individuals with the health endpoint under investigation (e.g., Breslow and Day 1980 and 1987). The goodness of fit of the model is then judged by the lack of fit of the model that compares the likelihood of the model's fit to the data with the likelihood of the observed data. The difference in likelihoods is then compared with a chi-square distribution with the appropriate degrees of freedom.

Because Poisson regression requires data to be grouped, goodness of fit tests for models based on Poisson regression are usually easy to perform. Methods similar to assessing the goodness of fit based on Poisson regression models can be used in assessing the goodness of fit based on other models but the data has to be grouped first in order to perform the test. One procedure that has been used is to group the data into risk groups based on the risk predicted by the model and then compare the number of predicted cases with the number of observed health endpoint cases in each group (Lemeshow and Hosmer 1982).

Graphical display of ORs and RRs cannot be used to judge goodness of fit or to compare alternative models fit to epidemiology data. Nonparametric estimates of ORs and RRs are relative to an estimate of the underlying background hazard rates and oftentimes are adjusted for covariate effects. The estimated background hazard rates and estimated covariate effects for nonparametric ORs and RRs are different than the estimated background hazard rates and estimated covariate effects for parametric dose-response models. Thus, plots of nonparametric estimates of ORs and RRs cannot be compared to fitted dose-response models.

## 7.8 Quantitative Cancer Exposure-Response Characterizations

The TCEQ derives URF and SFo values consistent with the following information. Some definitions of quantitative exposure-response characterizations in the context of the presence or absence of a response like cancer (either cancer mortality or cancer incidence) are as follows (although the following sections refer to effective concentration for calculation of an inhalation URF, it is also applicable for effective dose for calculation of an oral SFo).

URFs express cancer potency in terms of risk per unit air concentration (e.g., risk per $\mu g/m^3$) assuming continuous environmental lifetime exposure. They are calculated using

linear low-dose extrapolation when the carcinogenic MOA is mutagenic or the MOA is unknown. When a dose-response curve is modeled for tumor or cancer mortality data (Figure 7-1), the URF is the slope of a straight line from the POD to the origin, with the POD being the lowest tumor response or cancer mortality response supported by the study data. (Specifically, the curve is a graph of the frequency (or probability) of the specified response versus exposure concentration.)

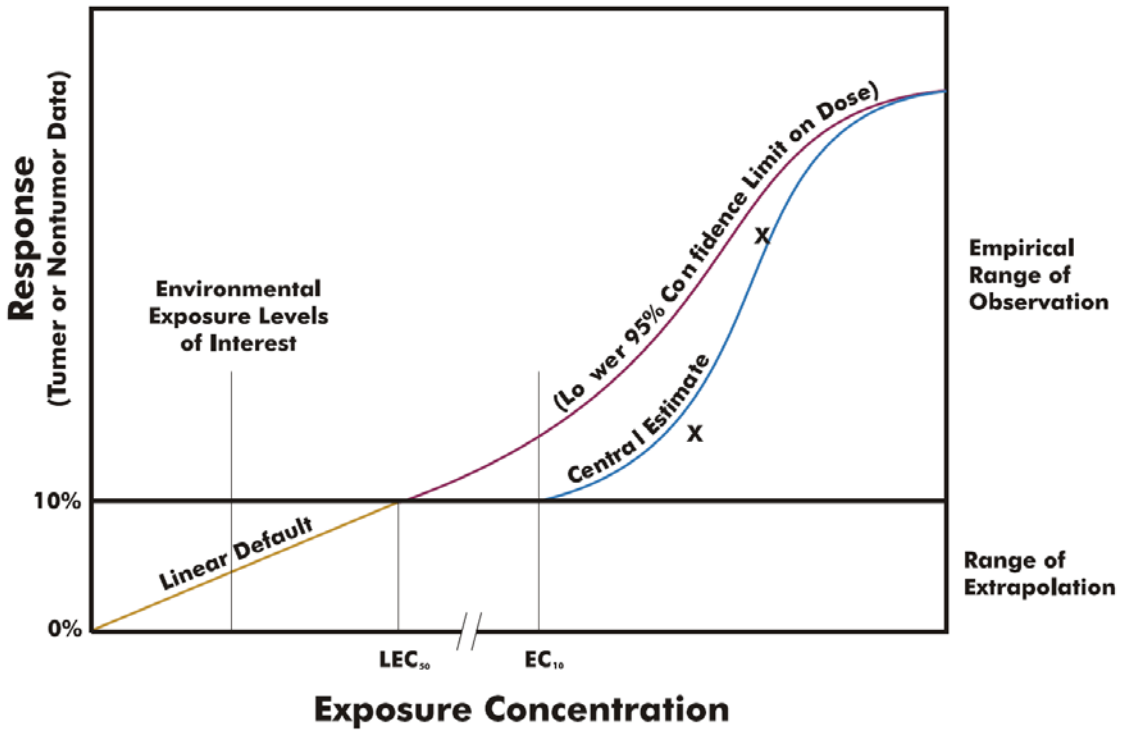


**Figure 7-1 Example of a linear approach to extrapolate to lower exposures**

The terms "EC and LEC" refer to concentration but are analogous to the terms "ED and LED", respectively, which refer to dose (Exhibit 12-3A of USEPA 2004a).

The effective concentration (EC) is defined as the best estimate of the exposure concentration in the inference population corresponding to a specified excess risk of the specified response (either cancer mortality or cancer incidence). The exposure concentration is generally thought of as being at a constant level for a lifetime. In the excess risk calculation, the exposures in the inference situation (public environmental exposure in this case) are transformed to be equivalent to the exposures in the exposure-response modeling (e.g., transforming from an environmental scenario to an occupational scenario). An $EC_{001}$, for example, is the concentration in a specified inference population corresponding to an excess risk of 0.001 (1 in one-thousand).

Two definitions of excess risk are commonly used. One definition of excess risk is added risk where (Equation 7-11):

**Equation 7-11 Added Risk**

$$\text{Added Risk} = P(C) - P(0)$$

Where:

P(C) = the probability of the specified response when the exposure concentration is C units greater than the background concentration level
P(0) = the probability of the specified response when the exposure concentration is at the background concentration level

A second definition of excess risk is extra risk where (Equation 7-12):

**Equation 7-12 Extra Risk**

$$\text{Extra Risk} = \frac{\text{P(C)} - \text{P(0)}}{1 - \text{P(0)}} = \frac{\text{Added Risk}}{1 - \text{P(0)}}$$

Added risk is the absolute increase in the probability of the specified response. For example, an added risk of 0.10 means that in an inference population of 100,000 individuals, it is expected that there will be 0.10 × 100,000 = 10,000 more individuals with the specified response if the exposure concentration is C units greater than the background concentration level compared to the expected number of individuals with the specified response if exposure concentration is the background concentration level. That is, an increase of 10,000 individuals with the specified response. On the other hand, the meaning of extra risk (which is always greater than or equal to the added risk) depends on P(0), the probability of the specified response when the exposure concentration is at the background concentration level. For example, if 25% of the inference population is expected to have the specified response when the exposure concentration is at the background concentration level (i.e., P(0)=0.25), then an extra risk of 0.10 implies that, of the 75% (i.e., 100% - 25%) of the inference population that is not expected to have the specified response when the exposure concentration is at the background concentration level, 10% are expected to have the specified response when the exposure concentration is C units greater than the background concentration level. That is, an increase of 0.10 × 0.75 × 100,000 = 7,500 individuals with the specified response. Although the USEPA generally defines their excess risk as extra risks, when they communicate excess risk to the public it is generally interpreted by the public as if it were added risk. This potential for misinterpretation would be avoided if excess risk were defined as added risk. For rare responses, added and extra risks are very similar. Currently, the TCEQ generally uses estimates of extra risk when deriving carcinogenic toxicity factors (e.g., URF, SFo).

In the definitions of excess risk, “0” refers to the background concentration level which may or may not be zero. Similarly “C” refers to the concentration above and beyond the background concentration level and not the total concentration of exposure.

Returning to the concept of an EC, the 95% lower confidence limit (lower bound) on the EC is denoted by LEC. The numerical value of the LEC depends on the method of calculating the lower bound. Different computer software programs use different methods, and no one method is universally acknowledged as best. The LEC reflects only part of the uncertainty regarding the inference population’s exposure-response relationship. In some circumstances (e.g., when the observed dose-response data is nonlinear with no increase in the number of observed responses at the lower doses), the LEC is much less responsive to the observed epidemiology data than the EC. (For

example, Chapter 3 in Holland and Sielken (1993) shows six study outcomes with very different dose-response relationships yet the largest of the six corresponding bounds (like LECs) differs from the smallest by less than one order of magnitude.) Furthermore, the LEC is determined more by study designs (e.g., number of observations per dose level and the number and spacing of dose levels) and statistical assumptions than by the observed data. Consequently, for the purposes of comparing the potency of two toxicants or substances, the EC or the corresponding URF (MLE) (rather than the LEC or the corresponding URF (95% UCL)) is the best basis for comparison (USEPA 1995, 2000a, f). The TCEQ reports EC values as well as LEC and 95% upper confidence limit (upper bound or UEC) values in the DSDs, as recommended by USEPA (2005a).

The specified excess risk level (BMR) in the definition of an EC (or LEC) can be any value between zero and one, although in practice it is generally the lowest BMR supported by the data. The BMR is a probability for a dichotomous endpoint like cancer mortality or incidence (the BMR for a continuous endpoint such as a measurement may be defined differently). For example, $EC_{10}$, $EC_{01}$, $EC_{001,}$ etc., correspond to excess risks of 0.10, 0.01, 0.001, etc. When the EC (LEC) is used as a POD for extrapolation to low-exposure levels, then the BMR should be chosen so that the exposure corresponding to the EC (LEC) is within the observed data and should not be so small that it is unnecessarily dependent upon the assumed shape of the exposure-response model.

If the probability of the specified response in the exposure-response model includes time (age), then the excess risk and the definition of the EC also includes a specified time (age). For example, most exposure-response models used for epidemiology data incorporate the time at which a response is observed. In these models, the excess risk and the definition of the EC also include a specified time (age). In the calculation of excess risk, it is assumed that the exposure scenario remains unchanged up to that time (age) (i.e., a constant exposure concentration up to that age is presupposed). Furthermore, it is assumed that the estimated exposure-response model is appropriate up to that time (age). For example, if an exposure-response model is estimated using occupational epidemiology data that only includes workers up to age 65 years, then calculating an excess risk up to age 70 years or higher involves an extrapolation over age that may or may not be warranted. Also, because the excess risks and ECs are often heavily dependent upon the specified time (age), it is important to consider what the specified time (age) is when interpreting the results. For example, time might be age and the specified time be set to 70 years. In which case, the excess risk refers to the excess risk by age 70 years. As is common in regulatory risk assessment, the TCEQ uses a default exposure duration of 70 years as discussed in Chapter 1. Another reason to use an exposure duration of 70 years for calculation of excess risk using epidemiology data is that the background rates of the disease and survival rates for a population used in the life-table analysis (BIER IV approach) discussed in the following section are more uncertain after 70 years.

Some exposure-response models (e.g., the multistage model commonly used with bioassay data) do not explicitly include time or age but rather consider the presence or absence of the specified response during the lifetime of the individual. For these models, extra risks and ECs refer to lifetimes rather than a specified time (age).

Returning to definitions, the BMD (BMC) in the context of a dichotomous response (e.g., the presence or absence of a specified tumor) is analogous to the EC. The 95% lower confidence limit (lower bound) on the BMD (BMC) is denoted by BMDL (BMCL). The meaning of the BMR is the same for BMD (BMC) as it is for EC.

## 7.9 Excess Risk Calculations for the General Population

Some definitions of quantitative dose-response characterizations in the context of the presence or absence of a response like cancer (either cancer mortality or cancer incidence) are given in Section 7.8. The calculation of excess risk for the inference population (i.e., the Texas general population) is the focus of the current section. The TCEQ uses these calculations to derive toxicity factors (e.g., URF, SFo).

Dose-response models that are multiplicative background response models (or additive background response models) characterize the effect of exposure as a multiplier of (or in addition to) the background hazard rate. When the dose-response model is being estimated (and the estimate of the slope, β, multiplying dose in the linear portion of the model is being determined), the background hazard rate should correspond to the epidemiology study cohort. Because quantitative risk characterizations are for a specific inference population, when the hazard is being characterized for a specific inference population (e.g., the Texas general population), the background hazard rate should correspond to that specific inference population (e.g., the general public in Texas). An inference population can be relatively general group (the entire US) or more specific group (e.g., Texans). The general population of Texas is the inference population generally evaluated by the TCEQ.

Quantitative risk characterizations for different inference populations are usually different, although the differences in the derived URF values are often slight. For example, the URF for 1,3-butadiene based on Texas background rates was $1.097\times10^{-6}$ per ppb whereas the URF based on US background rates was $1.062\times10^{-6}$ per ppb (Grant et al. 2009). Similar small differences in the URFs based on US background rates as opposed to Texas background rates were obtained for nickel (TCEQ 2011, Haney et al. 2012), silica (TCEQ 2009b), and arsenic (TCEQ 2012, Erraguntla et al. 2012).

### *7.9.1 Life-Table Calculations for Excess Risks*

In preparation for the calculation of excess risks, epidemiology data are modeled (Section 7.7) and the corresponding dose-dependent adjustment to the background hazard rate is identified (Section 7.7.4). Then, the maximum likelihood estimate (MLE) of the slope, β, multiplying dose in the linear portion of the model is obtained as well as the SE of the estimate of β. Using a standard normal distribution, the 95% LCL and 95% UCL on the slope β are calculated as follows (Equation 7-13 and Equation 7-14):

**Equation 7-13 95% LCL on the Slope β for a Standard Normal Distribution**

$$\beta(95\%\ \text{LCL}) = \beta - (1.645 \times \text{SE})$$

**Equation 7-14 95% UCL on the Slope β for a Standard Normal Distribution**

$$\beta(95\%\ \text{UCL}) = \beta + (1.645 \times \text{SE})$$

These characterizations (MLE, 95% LCL, and 95% UCL) of the slope estimate β are used to calculate an air concentration (or oral dose) corresponding to a known risk level using a life-table calculation for excess risk. From this air concentration (or oral dose), the URF or SFo value (i.e., increase in risk for the general population per ppb or μg/m$^3$ or per mg/kg-day) can then be determined. For example, if the $LEC_{10}$ is used as the POD, then the slope of the line from the $LEC_{10}$ to the origin yields the inhalation URF (95% UCL), that is, the upper-bound excess lifetime cancer risk estimated to result from continuous lifetime exposure to an agent at a concentration of 1 μg/m$^3$ in air (Equation 7-15):

**Equation 7-15 Inhalation URF (95% UCL) using the $LEC_{10}$**

$$\text{URF}\ (95\%\ \text{UCL}) = \frac{0.10}{\text{LEC}_{10}}$$

Thus, the risk slope (e.g., URF) is not the same as β although its determination depends on β because the POD depends on β.

Life-table calculations are sequential calculations that follow an individual from birth to a specified age. The life-table method is sometimes called the actuarial method. In the life-table method, for each year of an individual's lifetime (year 1 from birth to the age 1 birthday, year 2 from the age 1 birthday to the age 2 birthday, etc.) the life-table calculation incorporates the age-specific values of the individual's exposure (the exposure metric in the exposure-response model), the background (all-cause) survival probability, the background probability of the specified response, the effect of the exposure on the probability of the specified response, and any ADAFs. The life-table method of calculating excess risks is described in the BEIR IV report (NRC 1988). Computational details of the BEIR IV methodology are also described in Sielken and Valdez-Flores (2009b). Sielken & Associates have prepared an EXCEL implementation of the BEIR IV methodology for both incidence and mortality responses for the TCEQ (Valdez-Flores and Sielken 2010). Because life-table calculations used to be computationally intensive, there have been simpler alternatives to the BEIR IV methodology proposed in the early literature (e.g., USEPA 1986d, Gail 1975). However, high speed computers have eliminated the need for such approximations.

When calculating excess risk for the inference population (e.g., the Texas general public), the portion of the dose-response model fit to epidemiology data corresponding to the estimate of the background hazard rate is replaced by the inference population background hazards rates. That is, inference population background hazards rates are combined with the dose-response model fit to the epidemiology data (excluding the estimated background hazard rate estimated for the epidemiology data) in the characterization of risks. Population-specific background hazard rates and all-cause mortality rates depend on age, sex, race and other factors that need to be incorporated into the characterization of risks. The TCEQ uses appropriate methodology (e.g., life-table calculations) to take into account all these factors when characterizing lifetime risks to the extent possible and necessary, which is usually accomplished by incorporating rates for the general population of Texas that inherently reflect these factors.

### 7.9.2 Characterizing Risks for Older Ages and Different Health Endpoints

There are several alternatives in the calculation of excess risks that would increase the uncertainty associated with the corresponding calculated excess risks. Methods to account for this uncertainty are discussed in Section 7.10. Characterizing risks at low environmental doses usually well below the range of doses in the epidemiology study used to fit the model increases the uncertainty of the estimates.

Similarly, using dose-response models to characterize risks at ages other than those observed in the epidemiology data adds uncertainty to the risk estimates. Because many cancer responses have a background hazard rate that increases greatly at older ages, the choice of the terminal age in a life-table calculation from birth to a specified (terminal) age can have a substantial impact on calculated excess risks. Any comparisons of excess risk across chemicals should reflect any differences in the specified terminal age. The choice of the terminal age for a specific case should reflect the reasonableness of the assumption that individuals in the inference population would be exposed at the older ages. In addition, the choice should reflect the reasonableness of extrapolating from the exposure ages in the epidemiology study to the exposure ages being assumed for the inference population. As mentioned previously, consistent with standard risk assessment practice, the TCEQ uses 70 years as the default exposure duration to calculate URF and SFo values.

Uncertainty is also increased if the endpoint used in calculating excess risks is different than the endpoint used in the dose-response modeling. For example, in USEPA (2006d) one health endpoint was used in the dose-response model fitting and a different health endpoint was used to calculate excess risks. There the dose-response model and the estimated $\beta$ slope used mortality as the health endpoint (i.e., death with the specified cancer), but the health endpoint used to calculate excess risks was incidence (presence of the cancer but not necessarily death with the cancer). It is most appropriate, when excess risks for the inference population are being calculated, for the health endpoint to be the same health endpoint as was used in the dose-response modeling. Here, mortality refers to death from or with the disease whereas incidence is the onset or diagnosis of the disease that may or may not result in death. Similarly, an exposure-response model that has estimated a $\beta$ slope using an incidence response is appropriate when excess risks using a life-table analysis are being calculated for that same response (i.e., incidence of the specified response as opposed to the mortality with/from the specified response). The TCEQ does not generally use a mortality-based exposure-response model as the basis for the calculation of excess risks for an incidence response, or vice versa. The computational details of the BEIR IV methodology are different for incidence and mortality as shown in Sielken and Valdez-Flores (2009b).

As a general rule, the health endpoint used for dose-response modeling and excess risk calculation should match. However, there are instances (i.e., exceptions) in which a model based on mortality can be used to approximate (represent) the risk for incidence (e.g., TCEQ 2009b). For example, in the silica DSD, TCEQ (2009b) justified using the mortality-based lung cancer model to characterize risk of lung cancer incidence because "mortality rates for lung cancer are high and correlate well with incidence." Another

example of using a model for one health endpoint to characterize risks for a different health endpoint is given in the Arsenic DSD (TCEQ 2012, Erraguntla et al. 2012). There, the TCEQ used models fit to respiratory cancer mortality to characterize the risk of lung cancer incidence. TCEQ (2012) stated that "respiratory cancer mortality data …. are a reasonable surrogate for lung cancer as most (96 %) of the observed deaths …. were due to lung cancer," adding "lung cancer mortality, and consequently respiratory cancer mortality, are reasonably predictive of lung cancer incidence." Consequently, for arsenic, where respiratory cancer mortality was used to "represent" lung cancer mortality, lung cancer background mortality rates were used in the life-table calculation of excess risks in lieu of respiratory cancer mortality rates.

### *7.9.3 Dosimetric Adjustments*

As indicated in Sections 7.6 and 7.8, the exposure or dose metric used in the dose-response model and the excess risk calculation using the life-table analyses should be the same. For example, if the dose metric is cumulative exposure, then the method of calculating cumulative exposure should be exactly the same in both the dose-response model and the excess risk calculation. This includes any weightings, lags, windows of exposure, etc.

The dose-response model used in the BEIR IV life-table analysis should be the same as that used to fit the epidemiology data. For example, if the dose-response model were the multiplicative background linear model given by

$$\lambda = \lambda_0 \times \text{Covariate Effects} \times (1 + \beta \times d),$$

then the slope β estimated by fitting the epidemiology data should be used in the life-table analysis to calculate excess risks using the same dose-response model.

In order to calculate excess risks for environmental exposures, the units of exposure in the inference situation (e.g., environmental exposures to the Texas general public) need to be converted to the units of exposure in the estimation situation (e.g., the occupational exposures in the dose-response model estimated using the epidemiology data). Environmental concentrations for the general population ($\text{Concentration}_{HEC}$) are converted to Occupational concentrations ($\text{Concentration}_{OC}$) using the following equation (Equation 7-16):

**Equation 7-16 Conversion of Environmental Concentrations to Occupational Concentrations**

$$\text{Concentration}_{OC} = \text{Concentration}_{HEC} \times \frac{VE_h}{VE_{ho}} \times \frac{\text{days per week}_{res}}{\text{days per week}_{oc}}$$

Where:

$VE_h$ = non-occupational ventilation rate for a 24-h day (20 $m^3$/day)
$VE_{ho}$ = occupational ventilation rate for an 8-h day (10 $m^3$/day)
$\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per week)

days per week$_{oc}$ = occupational weekly exposure frequency (default of 5 days per week)

### 7.9.4 Adjustments for Early-Age Exposures

USEPA's Supplemental Guidance (USEPA 2005b, Sections 5 and 6) documented their procedure for incorporating ADAFs into lifetime excess risk calculations if the chemical acts through a mutagenic MOA. As detailed in Sielken and Valdez-Flores (2009a), USEPA's first attempt to implement an ADAF when the dose–response model had a cumulative dose metric failed to successfully follow USEPA's own mathematical procedural guidelines (USEPA 2005b). The failure overstated the impact of ADAFs by approximately 8,000 fold. Because cumulative exposure is a common dose metric in dose-response models of epidemiology data, if it is decided to incorporate ADAFs based on a mutagenic MOA for carcinogenicity and the incorporation of ADAFs is to follow USEPA guidelines, then the TCEQ will incorporate ADAFs into the life-table analyses using the BEIR IV approach using procedures outlined in Sielken and Valdez-Flores (2009a).

## 7.10 Determination of URFs and SFo Values from Dose-Response Modeling

As indicated in Section 7.9, the risk of an adverse health endpoint for a specific population exposed to a specified dose can be calculated using life-table calculations once a dose-response model has been fit to the epidemiology data. Dose-response models are fit to epidemiology data with individuals usually exposed to high doses. Several different shapes of dose-response models can fit the same epidemiology data equally well in the observed range of the data but may have very different behavior at doses below the range of the observed data. That is, for example, the risks predicted by different models at doses in the observed range can be similar but risks predicted at doses much lower than the observed doses may be very different.

The observed doses in epidemiology studies are usually much greater than the doses of interest in risk characterization (i.e., typical environmental doses). Risk estimates at doses much lower than the doses in epidemiology studies are subject to potentially substantial uncertainty. In the interest of accounting for the effect of uncertainty on risk estimates below the dose range in epidemiology studies, the TCEQ uses default, health-protective methods to calculate low-dose risks. The TCEQ uses procedures consistent with those discussed below when deriving carcinogenic toxicity factors (e.g., URF, SFo).

### 7.10.1 Linear Model

If the MOA is mutagenic or the MOA is unknown, then the default is to determine a POD based on the observed data and perform a linear extrapolation from the POD to determine the URF or SFo (Chapter 3 and Chapter 5).

The 2005 USEPA Guidelines for Carcinogen Risk Assessment defines a POD as marking

> *... the beginning of extrapolation to lower doses. The POD is an estimated dose (usually expressed in human-equivalent terms) near the lower end of the observed range, without significant extrapolation to lower doses.*

This particular definition of the POD is trying to ensure that the POD reflects the observed exposure-response information without extrapolating beyond the observed data and without having to unduly depend on the assumptions or choices underlying the estimated dose-response model. Depending on the characteristics of the epidemiology study, the selected endpoint, and the underlying exposure-response relationship, the POD of an epidemiology study can be the dose corresponding to an excess risk of 1/100 or 1/1,000 or in some cases as low as 1/100,000 or 1/1,000,000 (e.g., ethylene oxide (Valdez-Flores and Sielken 2010) and butadiene (Sielken and Valdez-Flores 2011)). In contrast, the POD from an animal study is typically the dose associated with an excess risk of 1/10. The important point is that the POD should be in the range of the observed data -- "near the lower end of the observed range, without significant extrapolation to lower doses" (USEPA 2005a, page 1-13).

Given the intent of the POD to reflect the observed data without over-dependence on the exposure-response modeling, the time/age in the definition of the EC, BMD, etc. should be within the range of the observed data. Most epidemiology studies follow-up with workers even after retirement age and several individuals live past the age for which the POD is to be estimated. However, if workers in an epidemiology study are observed only until a limited age (e.g., prior to retirement at age 65 years), then for the purpose of establishing a POD, the corresponding exposure-response model should not be extrapolated substantially beyond the age of 65 years. Extrapolations beyond the range of observation (i.e., below the observed exposure levels, above the observed exposure levels, or beyond the ages observed in the study) should be discussed in an uncertainty analysis.

Again, if the MOA is mutagenic or the MOA is unknown, then the default approach would be to determine a POD and perform a linear extrapolation from the POD (Chapter 3 and Chapter 5). If the excess risk is to be linearly extrapolated below the POD, then the URF is defined as (Equation 7-17):

**Equation 7-17 URF if Excess Risk is Linearly Extrapolated Below the POD**

$$\text{URF} = \frac{\text{excess risk at POD}}{\text{POD}}$$

For example, if the POD is the concentration corresponding to an excess risk of 1 in 1,000 (i.e., $EC_{0.001}$), then:

$$\text{URF (MLE)} = \frac{0.001}{\text{EC}_{0.001}}$$

which is an assumed rate of increase (slope per unit concentration) between zero excess risk at concentration zero and an excess risk of 1/1,000 at concentration $EC_{0.001}$.

The URF can be denoted on whether it is a best estimate or a bound. For example, URF (MLE) is based on the maximum likelihood estimate of the concentration (e.g., EC or BMD) with the specified excess risk. On the other hand, URF (95% UCL) is based on the lowest concentration that has a 95% upper confidence limit on the excess risk equal to the specified excess risk. The LEC is the lowest concentration that has a 95% upper confidence limit on the excess risk equal to the specified excess risk. Thus, for example,

$$\text{LEC}_{0.001} < \text{EC}_{0.001}, \text{and}$$

$$\text{URF}(95\%\ \text{UCL}) = \frac{0.001}{\text{LEC}_{001}}$$

is an upper bound on the URF, and URF(95% UCL) is greater than

$$\text{URF}(\text{MLE}) = \frac{0.001}{\text{EC}_{0.001}}$$

The lower bounds (LEC or BMDL) on the concentration with a specified excess risk are not very responsive to the observed dose-response data. That is, very different observed dose-response data (for the same study design) may result in very similar LEC and BMDL values. Given the non-responsiveness of the LEC and BMDL and the overestimation of the likely true low-dose risk when the POD is a lower bound instead of a best estimate, URF (95% UCL) values are a poorer basis for comparing the potency of different chemicals than URF (MLE) values.

URF (95% UCL) values reflect the uncertainty present in the dose-response data. However, because they are statistical bounds heavily impacted by that uncertainty and not maximum likelihood estimates primarily impacted by the observed data rather than the uncertainty, URF (95% UCL) values derived from epidemiology data may not be the best estimates for risk management decisions based on the above discussion (see also Section 7.8 and USEPA 2000a, f).

The TCEQ will provide the URF (MLE), as well as the URF (95% LCL) and the URF (95% UCL). The URF (MLE) is preferred because it is, by definition, the estimate that maximizes the likelihood of the observed data, and therefore, the best estimate to be used. This is especially true in situations where URFs from different studies are combined. However, ultimately, scientific judgment is used to decide what estimate of the URF is most applicable based on these considerations, MOA information, and other chemical-specific information.

The basic procedures used to derive URFs are also used to derive SFo values. Both are the slopes in an assumed linear extrapolation between the excess risk at a POD and zero excess risk at zero concentration. As discussed previously, URFs generally refer to studies involving inhalation exposure where the POD is a concentration. SFo values

generally refer to studies involving oral exposure where the POD is a dose. For example, a SFo has a POD in units of mg/kg-day and is the rate of increase (slope per unit dose) between zero excess risk at zero dose (mg/kg-day) and a specified risk at the ED, BMD, LED or BMDL (assuming a linear extrapolation below the POD).

### *7.10.2 Nonlinear Models*

If there is sufficient MOA information indicating a nonlinear dose-response relationship at low doses, then a nonlinear approach can be used to extrapolate risks to doses below the POD. USEPA (2005a) Carcinogen Risk Assessment Guidelines state that "the linear approach is used when: (1) there is an absence of sufficient information on modes of action or (2) the mode of action information indicates that the dose-response curve at low dose is or is expected to be linear. Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration."

Nonlinear low-dose extrapolation can refer to different types of low-dose extrapolations (See Pottenger et al. 2011 for a general discussion.). For instance, nonlinear often refers to dose-response relationships that have a threshold, in which case a reference dose or a reference value can be developed based on procedures in Chapter 3 and Chapter 5. In other circumstances, nonlinear refers to dose-response relationships which are not linear throughout the range of doses, although risk may be linear at lower doses. For example, Kirman et al. (2004) estimated the dose-response relationship for ethylene oxide using a quadratic relationship between concentration and cancer risk and used this fitted model to determine a POD. Then, Kirman et al. compared low-dose quadratic and low-dose linear extrapolations below the POD. This comparison followed the general guidance assumptions that linear extrapolations of risks for doses below the POD should be presented alongside nonlinear extrapolations even if there is sufficient biological information justifying the low-dose nonlinear extrapolation relationship.

## 7.11 Meta-Analyses

Meta-analysis is a technique used to combine and summarize results from several different independent analyses. It is frequently difficult to complete a meta-analysis adequately. The TCEQ may use meta-analyses as appropriate when several epidemiology studies are being used to derive a carcinogenic toxicity factor, depending on time and resource constraints. There are two types of meta-analyses; qualitative and quantitative. Qualitative meta-analyses include little to no quantitative manipulation of the results from individual analyses. Qualitative meta-analyses are for the purpose of summarizing, comparing and contrasting results from different sources. Quantitative meta-analyses, on the other hand, are statistical methods used to combine individual results into a summary value. The focus of these guidelines is on evaluating and conducting quantitative meta-analyses of epidemiology studies published in the scientific literature for the purpose of risk estimation. In 1995, the ILSI Risk Science Institute and the Office of Research and

Development, Office of Health and Environmental Assessment, and USEPA funded a group of scientists to develop guidelines for the application of meta-analysis in epidemiological assessments (Blair et al. 1995). The application of meta-analyses to epidemiology studies has evolved and their application has been expanded since that time. The guidelines presented here summarize and supplement the guidelines published by Blair et al. (1995). The TCEQ may perform meta-analysis of risk measures (e.g., URFs) (Section 7.11.3) or meta-analysis of slope estimates (e.g., β values) (7.11.4) depending on the availability of data and resources.

The traditional notion of quantitative meta-analysis is that of calculating a single risk measure from a set of risk measures from different independent individual studies. Epidemiology studies with agents and health endpoints thoroughly researched offer more data than simple estimates of risk. Meta-analyses based on these data-rich studies can be performed at a higher level by modeling combined summary exposure-response data (rather than combining summary results as is done in the traditional meta-analyses) to estimate a risk that is based on the combined dose-response data rather than the combined individual measures of risk.

There are several necessary steps in the performance of a quantitative meta-analysis of epidemiology studies. First, the epidemiology studies relevant to the agent of concern and the specific health endpoint have to be identified. Then, the studies that meet qualitative inclusion criteria set *a priori* need to be identified and selected to be part of the quantitative meta-analysis. Depending on the information available for each of the selected studies, the results are either used as reported or re-calculated/verified. Then, the selected epidemiology studies can be combined in several different ways using meta-analysis techniques. The next sections will discuss in detail guidelines to follow in the performance of meta-analyses given different alternative levels of information available. The arsenic DSD provides a case study in the context of arsenic (Section 4.2.4.6 Sensitivity Analysis with Various Meta-Analysis Procedures (TCEQ 2012) and Erraguntla et al. 2012).

### *7.11.1 Identification of Individual Studies*

In this step, all the literature corresponding to the chemical of concern should be identified. The most reliable and updated results should be preferred over outdated and less relevant analyses. The studies should include published and unpublished results and data. The studies identified can be used for a WOE narrative in a risk assessment document even if they do not meet the selection criteria to be included in the meta-analysis.

### *7.11.2 Selection of Individual Studies for Quantitative Meta-Analysis*

Once all studies relevant to the agent of concern have been identified and a WOE assessment has been performed, studies for inclusion in the meta-analysis should be

selected. The studies selected for meta-analysis are a subset of the studies identified for WOE. In the process of evaluating the WOE, it should become clear what health endpoint(s) is the main concern. The studies selected should meet specified criteria to be included in the meta-analysis. These selection criteria should include, but are not limited to: risk measure, endpoint consistency, dose or exposure metric consistency, exposure- or dose-response modeling, quality of data, quality of analyses, and data availability.

Although different criteria for selection of individual studies should be tailored to the problem at hand, the criteria should follow some pre-established guidelines to be valid. The criteria should be developed *a priori*, before a meta-analysis is started, to avoid selection bias. Different aspects to consider in study selection for quantitative meta-analysis are as follows:

1) Health endpoint. The studies selected for a meta-analysis should, ideally, be based on the same health endpoint. For example, if the health endpoint is lung cancer mortality, then all the studies selected for meta-analysis should be based on lung cancer mortality. There are instances in which epidemiology studies with different endpoints can be combined in a meta-analysis. For example, if necessary, a meta-analysis can combine results from epidemiology studies that report lung cancer mortality and lung cancer incidence because lung cancer incidence is reasonably predictive of lung cancer mortality. Lung cancer and respiratory cancer are another example of different endpoints that could be combined in a meta-analysis if most of the respiratory cancers are lung cancers and the mortality/incidence of both endpoints are similar.
2) Study design. The design of the study should be such that the health endpoint investigated was selected *a priori* and not an endpoint that came out as a result of exploratory analyses.
3) Study quality. The epidemiology studies selected for the meta-analysis should have comparable and reliable exposure estimates. Preferably, the exposure estimates will include quantitative rather than qualitative estimates. In addition, exposure estimates of selected epidemiology studies should meet quality criteria that make them credible. Epidemiology studies selected for meta-analyses should also be studies with a high degree of health endpoint ascertainment. In other words, there should be a high percentage of workers with the health endpoint of interest ascertained. The magnitude of the risk or statistical the significance of the findings is not an indicator of the quality of the study.
4) Data reliability. The source of the data should be reliable. Epidemiology data that have not been peer-reviewed and gone through some scientific scrutiny should be considered with caution or excluded from the meta-analysis.
5) Data availability. Depending on the reliability of the results and the extent of information reported in the open literature for the epidemiology studies selected, there may be a need for more data to estimate model parameters. The more accessible the individual data, the more valuable the study is because a meta-analysis using individual epidemiology data has much more modeling

flexibility and potential control of study heterogeneity and other statistical issues.

6) Dose measure. The dose metric should, preferably, be the same for all the epidemiology studies selected for a meta-analysis. For example, if cumulative exposure is used as the dose metric, then all the studies included in the meta-analysis have to use cumulative exposure as their dose metric. If one epidemiology study uses lagged cumulative exposure, for example, then that study cannot be combined in a quantitative meta-analysis with studies that used un-lagged cumulative exposures as the dose metric. Meta-analyses of risk measures where the dose metrics of the individual studies are different can be performed but with careful consideration to the potential heterogeneity of the individual risk estimates.

7) Risk measure. Risk in epidemiology studies is reported several different ways. The studies selected for a meta-analysis should all report the same measure of risk that the meta-analysis is intended to report. For example, if a meta-analysis to estimate the odds ratio is to be performed, then all the selected epidemiology studies should report the odds ratio for the health endpoint of interest or provide enough information to calculate the odds ratio. Epidemiology studies that qualify for inclusion in a meta-analysis are to be included whether their findings are positive or negative and regardless of the magnitude of the risk estimates.

8) Reproducibility of results. Epidemiology studies selected for inclusion in a meta-analysis should include enough information to corroborate or reproduce the results (calculations) used for the meta-analysis. Studies that only include summary data without enough data to support the reported results should be seriously considered for exclusion from the meta-analysis.

9) Methodology. Studies selected for a meta-analysis should use the same, or at least similar, methodology to derive the individual risk estimates. There are several modeling issues that can affect the potential summarization of different results into one meta-analysis. The studies could adjust for different covariates using different types of adjustment (e.g., parametric or nonparametric). The individual risk estimates may have been derived using different statistical techniques (e.g., Poisson regression modeling, Cox proportional hazards modeling). The models fit to the epidemiology data of the individual studies may incorporate different assumptions (e.g., multiplicative background rates, additive background rates). Results derived from different epidemiology studies with different methodologies can be combined in a meta-analysis as long as the combination takes into account those differences. For example, the URF derived from an epidemiology study where the model was a polynomial in dose can be combined with a URF derived from an epidemiology study where the model was linear in dose. This can be done because the URFs already incorporate all the assumptions made in the derivation of these values. In contrast, for example, the URF derived using the U.S. population background hazard rates should not be combined with a URF derived using China

population background hazard rates (unless the U.S. and China population background rates prove to be sufficiently similar).

The epidemiology study selection criteria for inclusion in a meta-analysis listed above is for guidance purposes. TCEQ staff may supplement or adjust these selection criteria guidelines according to their needs. There are circumstances in which a particular study report does not satisfy the selection criteria, but the authors can be contacted and are willing to share information that is not necessarily available in the open literature, making the study usable for the meta-analysis.

### 7.11.3 Meta-Analyses of Risk Measures

If estimates of risk (e.g., URFs) are the only available data, then a meta-analysis that combines risk estimates into a single risk estimate is the only possible option of estimating a single summary risk estimate. Such meta-analyses estimate the summary risk as a weighted average of the individual risk estimates. The weights of the individual study estimates are usually the inverse of the variance of the risk estimates (e.g., the inverse of the variance of the URF). The standard errors of the risk estimates are frequently reported in published studies or they can be back-calculated from reported confidence intervals, upper bounds or lower bounds.

Meta-analyses of estimates of risk have the advantage that they can accommodate results from individual epidemiology studies with differences in several characteristics of the risk characterization process. Risks based on different dose metrics, different dose-response models, etc. can be combined provided that the final risk estimates are based on the same risk metric (e.g., URFs in the same units), same health endpoint, same risk estimation methodology (e.g., the method of incorporating ADAFs, using life-table analyses, and using the same method of low-dose extrapolation), etc. The flexibility offered by meta-analyses based on individual study risk estimates is also a potential weakness in that different studies infrequently present estimates of risk using the same methodology, the same target population at risk and the same risk metric.

The standard error of the meta-analysis summary risk estimate can be similarly calculated from the standard errors of the risk estimates from the individual studies.

Other weighting factors that reflect the precision of the estimates can also be considered as alternatives to, or to supplement, the standard errors of the estimates of the individual studies. For example, if the standard errors are not available, the numbers of person-years at risk or the numbers of workers in the study are some alternative weighting factors to consider.

### 7.11.4 Meta-Analyses of Slope Estimates

A meta-analysis that combines slope ($\beta$) estimates, as opposed to final risk estimates (e.g., URFs), of individual epidemiology studies is more reliable than a meta-analysis that combines final risk estimates. A meta-analysis combining slope ($\beta$) estimates requires that the slopes of the individual studies be available and that the units of the slope be

identical. That is, for example, if the slope (β) is in terms of risk increase per unit cumulative exposure, then all the slopes (β values) have to be in terms of risk increase per unit cumulative exposure and the cumulative exposure has to have been calculated in a similar way. Cumulative exposures could have been calculated un-weighted, weighted, lagged, etc., but must be calculated the same way in all studies. Such a meta-analysis estimates the summary slope (β) as a weighted average of the individual slope estimates. The weights of the individual study slope estimates are usually the inverse of the variance of the estimates. The standard errors of the slope (β) estimates are frequently reported in published studies or they can be back-calculated from reported confidence intervals, upper bounds or lower bounds.

Meta-analyses based on slopes (β values) of individual studies have the advantage that the estimates of risk can be calculated from the slope (β) determined from the meta-analysis, thereby avoiding any potential heterogeneity in the methods used to calculate excess risks from estimated slopes. There is, however, the disadvantage that individual studies based on different dose metrics or different models cannot be combined to calculate a single slope. There is always the possibility, if the slopes are available, of estimating risks for each individual study using a standard methodology and then using a meta-analysis to combine individual risks as described above.

The standard error of the meta-analysis summary slope estimate can be similarly calculated from the standard errors of the slope (β) estimates from the individual studies.

Other weighting factors that reflect the precision of the estimates can also be considered as alternatives to, or to supplement, the standard errors of the estimates of the individual studies. For example, if the standard errors are not available, the numbers of person-years at risk or the numbers of workers in the study are some alternative weighting factors to consider.

### *7.11.5 Meta-Analyses of Individual Data*

A meta-analysis based on all the individual data from the individual epidemiology studies is most desirable. This meta-analysis can control for all possible covariates and sources of heterogeneity. Alternatively, a meta-analysis that is based on summary (e.g., grouped) characterizations of exposures, observed number of events, expected number of events, standardized mortality or incidence ratios, etc., from individual studies can be used to perform a meta-analyses that can control for some sources of heterogeneity.

A meta-analysis based on the combined individual data or summary characterizations of the individual study data can be modeled. That is, a dose-response model can be fit to all the individual data combined (or all of the summary characterizations combined). This modeling can be done using a consistent methodology and adjusting for potential covariate effects like study, plant, co-exposures, sub-cohorts, etc. In such cases, the results of the meta-analysis include estimates of the standard errors of the model parameters and the risk estimates, and the individual studies are intrinsically weighted by the number of person-years, number of cases, etc. (see e.g., Valdez-Flores et al. 2010).

### 7.11.6 Heterogeneity and Uncertainty Analyses

The presentation of a meta-analysis should include the presentation and discussion of the individual study estimates. In addition, an uncertainty analysis for the sensitivity of the summary estimate to including and excluding each individual study result should be performed.

Implicit in a meta-analysis is the assumption that the individual study results are homogeneous with respect to the effect being estimated. Significant departures of individual study results from the expected results should be noted and, when possible, accounted for by discussing differences in study designs, methods of analysis, etc. The meta-analysis should include a detailed evaluation of the homogeneity of the individual study results, and if there is any heterogeneity detected, a discussion of the reasons for such heterogeneity and a justification for inclusion of the individual study in the meta-analysis.

## 7.12 Reality Checks

A special type of "reality check" is the evaluation of the consistency between epidemiological findings and toxicological results in animals (e.g., Teta et al. 1999, Kirman et al. 2005, Schwarze et al. 2006, Boyes et al. 2007, Adami et al. 2011, and Simpkins et al. 2011).

Reality checks on the predictions of risk based on the estimated toxicity factors (e.g., URF) are frequently worthwhile and are best made on a case-by-case basis. Reality checks can be used to at least partially evaluate the reasonableness of dose-response modeling assumptions and resulting estimates and bounds. Upper bounds can substantially overestimate their targets, and lower bounds can substantially underestimate their targets. Calculating both upper and lower bounds on the same target provides some measure of the uncertainty involved in the bounding methods.

Reality checks on bounds are also useful. For example, if the number of specified responses expected in a study cohort using a particular URF value is statistically significantly greater than the actual observed number of specified responses in that cohort, then the URF value is unrealistically high (i.e., results in unrealistically high risk estimates). In addition to making reality checks in terms of the study population, reality checks can be based on another population (e.g., another study or data source other than the epidemiology study used for dose-response modeling). For example, the estimated toxicity factor from the epidemiology study used for dose-response modeling can be used to predict the number of responses in the other population and the reasonableness of this prediction evaluated.

Another possible reality check applies for rare (or relatively rare) tumors. One can calculate the expected response in the reference population based on the estimated URF and estimated exposure. This estimated incidence for a population can then be compared with the reported incidence in a registry such as SEER. If the estimated incidence of the

cancer from the one chemical source is substantially higher than all reported cancers of that type, this suggests that the risk has been overestimated.

The utility of the toxicity factor in setting reasonable and/or meaningful risk management goals may also be evaluated using reality checks of the feasibility of attaining health-protective environmental (and other media) levels which would result from the toxicity factor. (Unattainability does not necessarily imply that the dose-response modeling is incorrect.) The corresponding toxicity factors may represent an unrealistic characterization of environmental risk (at least from a regulatory compliance perspective). The possibilities of such unreasonableness should be evaluated based on all relevant information (e.g., MOA, background exposure and rates of response, reliable typical human breath concentrations due to endogenous production, and data related to possible thresholds).

Another form of a reality check is to estimate the number of response mortalities in the entire U.S. (or other specified population) in a year (e.g., 2010) that would be eliminated if the chemical's exposure via ambient air were reduced from a specified value to zero. If that number is less than 1 or an extremely small fraction of the background response rate, then any such reduction in the chemical's exposure may not be a meaningful risk management goal in terms of significantly reducing risk relative to total risk. This can happen simply because the chemical may not be associated with a significant environmental risk due to the presence of other substantial risk factors for the response in the population (e.g., other exposures, lifestyle choice factors).

## 7.13 Uncertainty Analysis

Risk characterizations based on epidemiology data contain an inherent degree of uncertainty and variability. The susceptibility to a specific agent of different persons, differences in lifestyle habits (e.g., smoking, drinking), and the differences in dose received by different individuals are examples of variability. Although all relevant variability may not be able to be controlled, it should be characterized. Uncertainty, on the other hand, refers to gaps in knowledge. The form of the dose-response model, the dose metric, the estimates of dose, job exposure histories, job classifications, and identification of causes of death are examples of uncertainty. Although uncertainties can be reduced with more research, a risk characterization based on the available epidemiology data should recognize and characterize the uncertainties.

USEPA (2005a) and the National Research Council (NRC 1990 and NRC 1999) emphasize that uncertainty analysis is an essential part of a risk characterization based on epidemiology data. The exclusion of an uncertainty analysis from a risk assessment prevents decision makers from taking well-informed actions in setting health-protective standards for chemicals that cause adverse health effects.

Uncertainty analyses are done on a case-by-case basis, and their components may be numerous and variable. For example, the uncertainty may refer to the model, the model parameters, the endpoint selected, the modeling methodology, the exposure estimation, etc. TCEQ (2008, Grant et al. 2009) includes an extensive uncertainty analysis

characterizing the impact of several alternative risk assessments. In their analysis, TCEQ (2008, Grant et al. 2009), considered the uncertainty of their risk characterization with respect to:

1) Population at risk: the effect of having only adult males in the epidemiology cohort and characterizing risk for the general population that includes females and young individuals.
2) Exposure estimation: The effect of occupational exposure estimation error when compared with actual measurements obtained for validation of the exposure estimates.
3) Statistical Methodology: the effect of using Cox proportional hazards modeling as opposed to Poisson regression modeling.
4) Dose-response modeling: The effects of including/excluding exposure peaks from the model.
5) Dose-response modeling: The effect of using individual exposure estimates instead of mean-scored deciles.
6) Dose-response modeling: The effect of including all the person-years or workers in the cohort as opposed to excluding the person-years or individuals with the highest doses.
7) Endpoint selection: The effect of the endpoint being mortality as opposed to incidence of the health effect.

In addition, TCEQ (2008, Grant et al. 2009), presented the uncertainty in the model's parameter estimates by presenting 95% confidence intervals in their risk characterization of 1,3-butadiene exposures.

The extent of the uncertainty analysis depends on and should be tailored to, the particular data and model(s) available for use. For example, if the risk characterization is based on a group of different epidemiology studies, the uncertainty about the inclusion/exclusion of some of the data from the risk characterization should be discussed and evaluated. The results of the individual epidemiology studies in addition to the results of a meta-analysis can be used to characterize the distribution of the uncertainty related to the selection of epidemiology studies.

# References

Adami, H. O., Berry, S. C., Breckenridge, C. B., Smith, L. L., Swenberg, J. A., Trichopoulos, D., . . . Pastoor, T. P. (2011). Toxicology and epidemiology: improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference. Toxicol Sci, 122(2), 223-234. doi: 10.1093/toxsci/kfr113

Agalliu, I., Kriebel, D., Quinn, M. M., Wegman, D. H., & Eisen, E. A. (2005). Prostate cancer incidence in relation to time windows of exposure to metalworking fluids in the auto industry. Epidemiology, 16(5), 664-671.

Agency for Toxic Substances and Disease Registry (ATSDR). (2004). Toxicological profile for Ammonia. Retrieved from www.atsdr.cdc.gov/ToxProfiles/tp126.pdf.

Agency for Toxic Substances and Disease Registry (ATSDR). (2007). Guidance for the Preparation of a Twenty First Set Toxicological Profile. Retrieved from www.atsdr.cdc.gov/toxprofiles/guidance/set_21_guidance.pdf.

Alexeeff, G. V., Broadwin, R., Liaw, J., & Dawson, S. V. (2002). Characterization of the LOAEL-to-NOAEL uncertainty factor for mild adverse effects from acute inhalation exposures. [Evaluation Studies]. Regul Toxicol Pharmacol, 36(1), 96-105.

Allen, B., Zeiger, E., Lawrence, G., Friedman, M., & Shipp, A. (2005). Dose-response modeling of in vivo genotoxicity data for use in risk assessment: some approaches illustrated by an analysis of acrylamide. Regul Toxicol Pharmacol, 41(1), 6-27. doi: 10.1016/j.yrtph.2004.09.006

Allison, P. D. (2010). Survival analysis using SAS : a practical guide. Cary, NC: SAS Institute.

Altman, D. G., Lausen, B., Sauerbrei, W., & Schumacher, M. (1994). Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. J Natl Cancer Inst, 86(11), 829-835.

American Conference of Industial Hygienists (ACGIH). (2011). 2011 TLVs and BEIs. American Conference of Governmental Industrial Hygiensts Publication #0111.

American Thoracic Society (ATS). (2000). What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. Am J Respir Crit Care Med, 161(2 Pt 1), 665-673. Available for download here: ajrccm.atsjournals.org/cgi/content/full/161/2/665#B6.

Andersen, M. E., Dennison, J. E., Thomas, R. S., & Conolly, R. B. (2005). New directions in incidence-dose modeling. [Review]. Trends Biotechnol, 23(3), 122-127. doi: 10.1016/j.tibtech.2005.01.007

Anderson, G. D. (2002). Children versus adults: pharmacokinetic and adverse-effect differences. [Review]. Epilepsia, 43 Suppl 3, 53-59.

Anjilvel, S., & Asgharian, B. (1995). A multiple-path model of particle deposition in the rat lung. Fundam Appl Toxicol, 28(1), 41-50.

Applied Research Associates, Inc (ARA). (2009). Multiple Path Particle Dosimetry Model (MPPD v 2.1): A Model for Human and Rat Airway Particle Dosimetry. Available for download here: www.ara.com/products/mppd.htm.

Aylward, L.L., Goodman, J.E., Charnley, G., and Rhomberg, L.R. (2008). A Margin-of-Exposure Approach to Assessment of Noncancer Risks of Dioxins Based on Human Exposure and Response Data; Environ Health Perspect 116:1344–1351.

Bailey, G. S., Reddy, A. P., Pereira, C. B., Harttig, U., Baird, W., Spitsbergen, J. M., . . . Swenberg, J. A. (2009). Nonlinear cancer response at ultralow dose: a 40800-animal ED(001) tumor and biomarker study. Chem Res Toxicol, 22(7), 1264-1276. doi: 10.1021/tx9000754

Barnes, D. G., Daston, G. P., Evans, J. S., Jarabek, A. M., Kavlock, R. J., Kimmel, C. A., . . . Spitzer, H. L. (1995). Benchmark Dose Workshop: criteria for use of a benchmark dose to estimate a reference dose. Regul Toxicol Pharmacol, 21(2), 296-306. doi: 10.1006/rtph.1995.1043

Beck, B. D., Conolly, R. B., Dourson, M. L., Guth, D., Hattis, D., Kimmel, C., & Lewis, S. C. (1993). Improvements in quantitative noncancer risk assessment. Sponsored by the Risk Assessment Specialty Section of the Society of Toxicology Fundam Appl Toxicol (Vol. 20, pp. 1-14). United States.

Bell, J. N. B., & Treshow, M. (2002). Air pollution and plant life. Chichester: John Wiley & Sons Ltd.

Benson, W. H., Gallagher, K., & McClintock, J. T. (2007). U.S. Environmental Protection Agency's activities to prepare for regulatory and risk assessment applications of genomics information. Environ Mol Mutagen, 48(5), 359-362. doi: 10.1002/em.20302

Blair, A., Burg, J., Foran, J., Gibb, H., Greenland, S., Morris, R., . . . et al. (1995). Guidelines for application of meta-analysis in environmental epidemiology. ISLI Risk Science Institute. [Guideline]. Regul Toxicol Pharmacol, 22(2), 189-197.

Boekelheide, K., Andersen, M.E. (2010). A mechanistic redefinition of adverse effects - a key step in the toxicity testing paradigm shift. ALTEX 27, 243-252. Available for

download here:
www.altex.ch/resources/ALTEX_4_10_Boekelheide_Andersen.pdf.

Bogdanffy, M. S., & Jarabek, A. M. (1995). Understanding mechanisms of inhaled toxicants: implications for replacing default factors with chemical-specific data. [Review]. Toxicol Lett, 82-83, 919-932.

Bolt, H. M. (2003). Genotoxicity--threshold or not? Introduction of cases of industrial chemicals. [Review]. Toxicol Lett, 140-141, 43-51.

Bonita, R., Beaglehole, R., & Kjellström, T. (2006). Basic epidemiology (2nd ed.). Geneva, Switzerland: World Health Organization.

Boobis, A. R., Cohen, S. M., Dellarco, V., McGregor, D., Meek, M. E., Vickers, C., . . . Farland, W. (2006). IPCS framework for analyzing the relevance of a cancer mode of action for humans. Crit Rev Toxicol, 36(10), 781-792. doi: 10.1080/10408440600977677

Boobis, A. R., Doe, J. E., Heinrich-Hirsch, B., Meek, M. E., Munn, S., Ruchirawat, M., . . . Vickers, C. (2008). IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit Rev Toxicol, 38(2), 87-96. doi: 10.1080/10408440701749421

Boyes, W. K., Evans, M. V., Eklund, C., Janssen, P., & Simmons, J. E. (2005). Duration adjustment of acute exposure guideline level values for trichloroethylene using a physiologically-based pharmacokinetic model. [Comparative Study]. Risk Anal, 25(3), 677-686. doi: 10.1111/j.1539-6924.2005.00622.x

Boyes, W. K., Moser, V. C., Geller, A. M., Benignus, V. A., Bushnell, P. J., & Kamel, F. (2007). Integrating epidemiology and toxicology in neurotoxicity risk assessment. [Meta-Analysis; Review]. Hum Exp Toxicol, 26(4), 283-293. doi: 10.1177/0960327106070481

Brachman, P. S. (1996). Chapter 9 - Epidemiology. In S. Baron (Ed.), Medical Microbiology (4th ed.): University of Texas Medical Branch at Galveston, TX.

Breslow, N. E., & Day, N. E. (1980). Statistical Methods in Cancer Research: Volume I – The Analysis of Case-Control Studies. International Agency for Research on Cancer. Lyon, France.

Breslow, N. E., & Day, N. E. (1987). Statistical Methods in Cancer Research: Volume II – The Design and Analysis of Cohort Studies. International Agency for Research on Cancer. Lyon, France.

Bruckner, J. V. (2000). Differences in sensitivity of children and adults to chemical toxicity: the NAS panel report. [Comparative Study]. Regul Toxicol Pharmacol, 31(3), 280-285. doi: 10.1006/rtph.2000.1393

Buchanan, D., Miller, B. G., & Soutar, C. A. (2003). Quantitative relations between exposure to respirable quartz and risk of silicosis. Occup Environ Med, 60(3), 159-164.

Cain, W. S., Murphy, C. L. (1980). Interaction between chemoreceptive modalities of odour and irritation. Nature, 284(5753), 255-257.

Chaisson, C. F., Sielken, R. L., Jr., & Waylett, D. K. (1999). Overestimation bias and other pitfalls associated with the estimated 99.9th percentile in acute dietary exposure assessments. Regul Toxicol Pharmacol, 29(2 Pt 1), 102-127. doi: 10.1006/rtph.1998.1225

Checkoway, H., Pearce, N. E., & Crawford-Brown, D. J. (1989). Research Methods in Occupational Epidemiology. New York, NY: Oxford University Press, Inc.

Checkoway, H., & Rice, C. H. (1992). Time-weighted averages, peaks, and other indices of exposure in occupational epidemiology. Am J Ind Med, 21(1), 25-33.

Chemical Industry Institute of Toxicology (CIIT). (2004). Multiple path particle dosimetry model MPPD, V. 2.0 (CIIT transitioned to The Hamner Institutes for Health Sciences in 2007).

Chen, C., & Farland, W. (1991). Incorporating Cell Proliferation in Quantitative Cancer Risk Assessment: Approaches, Issues, and Uncertainties. In B. Butterworth, T. Slaga, W. Farland & M. McClain (Eds.), Chemical Induced Cell Proliferation: Implications for Risk Assessment (pp. 481-499). New York: Wiley-Liss.

Cheng, H., Sathiakumar, N., Graff, J., Matthews, R., & Delzell, E. (2007). 1,3-Butadiene and leukemia among synthetic rubber industry workers: exposure-response relationships. Chem Biol Interact, 166(1-3), 15-24. doi: 10.1016/j.cbi.2006.10.004

Chou, C.-H. S. J., Holler, J. S., & De Rosa, C. T. (1998). Minimal risk levels (MRLs) for hazardous substances. J Clean Technol Environ Toxicol & Occup Med, 7(1), 1-24.

Cimino, M. C. (2006). Comparative overview of current international strategies and guidelines for genetic toxicology testing for regulatory purposes. [Comparative Study; Review]. Environ Mol Mutagen, 47(5), 362-390. doi: 10.1002/em.20216

Clewell, H. J., Gentry, P. R., Covington, T. R., Sarangapani, R., & Teeguarden, J. G. (2004). Evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. [Comparative Study]. Toxicol Sci, 79(2), 381-393. doi: 10.1093/toxsci/kfh109

Collins, J. F., Brown, J. P., Alexeeff, G. V., & Salmon, A. G. (1998). Potency equivalency factors for some polycyclic aromatic hydrocarbons and polycyclic aromatic hydrocarbon derivatives. Regul Toxicol Pharmacol, 28(1), 45-54. doi: 10.1006/rtph.1998.1235

Collins, J. J., Ireland, B., Buckley, C. F., & Shepperly, D. (2003). Lymphohaematopoeitic cancer mortality among workers with benzene exposure. Occup Environ Med, 60(9), 676-679.

Cone, J. E., & Shusterman, D. (1991). Health effects of indoor odorants. Environ Health Perspect, 95, 53-59.

Copes, R., Thomas, D., & Becklake, M. R. (1985). Temporal patterns of exposure and nonmalignant pulmonary abnormality in Quebec chrysotile workers. Arch Environ Health, 40(2), 80-87.

Cox, D. R. (1972). Regression Models and Life-Tables. Journal of the Royal Statistical Society, B34(2), 187-220.

Cox, L. A., Jr., Bird, M. G., & Griffis, L. (1996). Isoprene cancer risk and the time pattern of dose administration. Toxicology, 113(1-3), 263-272.

Cronin, M. T., Dearden, J. C., Walker, J. D., & Worth, A. P. (2003). Quantitative structure-activity relationships for human health effects: commonalities with other endpoints. [Review]. Environ Toxicol Chem, 22(8), 1829-1843.

Crump, C., Crump, K., Hack, E., Luippold, R., Mundt, K., Liebig, E., . . . Proctor, D. (2003). Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal, 23(6), 1147-1163.

Crump, K. S. (1994). Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health, 42(2), 219-242. doi: 10.1080/15287399409531875

Crump, K. S. (2005). The effect of random error in exposure measurement upon the shape of the exposure response. Dose Response, 3(4), 456-464. doi: 10.2203/dose-response.003.04.002

Crump, K. S., & Allen, B. C. (1985). Methods for Quantitative Risk Assessment Using Occupational Studies. The American Statistician, 39(4), 442-450.

Crump, K. S., Hoel, D. G., Langley, C. H., & Peto, R. (1976). Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Res, 36(9 pt.1), 2973-2979.

Daston, G., Faustman, E., Ginsberg, G., Fenner-Crisp, P., Olin, S., Sonawane, B., . . . McLaughlin, T. J. (2004). A framework for assessing risks to children from exposure to environmental agents. [Review]. Environ Health Perspect, 112(2), 238-256.

Davidson, I. W., Parker, J. C., & Beliles, R. P. (1986). Biological basis for extrapolation across mammalian species. [Comparative Study]. Regul Toxicol Pharmacol, 6(3), 211-237.

Davis, A., Gift, J. S., Woodall, G. M., Narotsky, M. G., & Foureman, G. L. (2009). The role of developmental toxicity studies in acute exposure assessments: analysis of single-day vs. multiple-day exposure regimens. Regul Toxicol Pharmacol, 54(2), 134-142. doi: 10.1016/j.yrtph.2009.03.006

de Winter-Sorkina, R., & Cassee, F. R. (2002). From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats (pp. 1-36). RIVM report 650010031/2002:1 - 36.

Dearfield, K. L., Auletta, A. E., Cimino, M. C., & Moore, M. M. (1991). Considerations in the U.S. Environmental Protection Agency's testing approach for mutagenicity. [Guideline; Review]. Mutat Res, 258(3), 259-283.

Dearfield, K. L., & Moore, M. M. (2005). Use of genetic toxicology information for risk assessment. Environ Mol Mutagen, 46(4), 236-245. doi: 10.1002/em.20176

Dearfield, K. L., Thybaud, V., Cimino, M. C., Custer, L., Czich, A., Harvey, J. S., . . . Witt, K. L. (2011). Follow-up actions from positive results of in vitro genetic toxicity testing. [Review]. Environ Mol Mutagen, 52(3), 177-204. doi: 10.1002/em.20617

Dearman, R. J., Warbrick, E. V., Humphreys, I. R., & Kimber, I. (2000). Characterization in mice of the immunological properties of five allergenic acid anhydrides. J Appl Toxicol, 20(3), 221-230.

Dekkers, S., de Heer, C., & Rennen, M. A. (2001). Critical effect sizes in toxicological risk assessment: a comprehensive and critical evaluation. Environ Toxicol Pharmacol, 10(1-2), 33-52.

Department of Pesticide Regulation (DPR). (2004a). Guidance for Benchmark Dose (BMD) Approach – Quantal Data. (DPR MT-1). Health Assessment Section, Medical Toxicology Branch. Cal/EPA.

Department of Pesticide Regulation (DPR). (2004b). Guidance for Benchmark Dose (BMD) Approach – Continuous Data. (DPR MT-2). Health Assessment Section, Medical Toxicology Branch. Cal/EPA.

Dix, D. J., Gallagher, K., Benson, W. H., Groskinsky, B. L., McClintock, J. T., Dearfield, K. L., & Farland, W. H. (2006). A framework for the use of genomics data at the EPA. Nat Biotechnol, 24(9), 1108-1111. doi: 10.1038/nbt0906-1108

Dorato, M. A., & Engelhardt, J. A. (2005). The no-observed-adverse-effect-level in drug safety evaluations: use, issues, and definition(s). [Review]. Regul Toxicol Pharmacol, 42(3), 265-274. doi: 10.1016/j.yrtph.2005.05.004

Dorne, J. L. (2010). Metabolism, variability and risk assessment. [Review]. Toxicology, 268(3), 156-164. doi: 10.1016/j.tox.2009.11.004

Dorne, J. L., Walton, K., & Renwick, A. G. (2005). Human variability in xenobiotic metabolism and pathway-related uncertainty factors for chemical risk assessment: a review. [Review]. Food Chem Toxicol, 43(2), 203-216. doi: 10.1016/j.fct.2004.05.011

Dourson, M. (1996). Uncertainty factors in noncancer risk assessment. [Comment; Editorial]. Regul Toxicol Pharmacol, 24(2 Pt 1), 107. doi: 10.1006/rtph.1996.0115

Dourson, M., Charnley, G., & Scheuplein, R. (2002). Differential sensitivity of children and adults to chemical toxicity. II. Risk and regulation. [Comparative Study; Review]. Regul Toxicol Pharmacol, 35(3), 448-467.

Dourson, M. L., Felter, S. P., & Robinson, D. (1996). Evolution of science-based uncertainty factors in noncancer risk assessment. [Review]. Regul Toxicol Pharmacol, 24(2 Pt 1), 108-120. doi: 10.1006/rtph.1996.0116

Dourson, M. L., Knauf, L. A., & Swartout, J. C. (1992). On reference dose (RfD) and its underlying toxicity data base. Toxicol Ind Health, 8(3), 171-189.

Dugger, W. M. (1974). Air pollution effects on plant growth: a symposium sponsored by the Division of Agricultural and Food Chemistry at the 167th meeting of the American Chemical Society, Los Angeles, Calif., April 1, 1974, Washington, D.C.

Eastmond, D. A., Hartwig, A., Anderson, D., Anwar, W. A., Cimino, M. C., Dobrev, I., . . . Vickers, C. (2009). Mutagenicity testing for chemical risk assessment: update of the WHO/IPCS Harmonized Scheme. Mutagenesis, 24(4), 341-349. doi: 10.1093/mutage/gep014

Elespuru, R. K., Agarwal, R., Atrakchi, A. H., Bigger, C. A., Heflich, R. H., Jagannath, D. R., . . . Dearfield, K. L. (2009). Current and future application of genetic toxicity assays: the role and value of in vitro mammalian assays. Toxicol Sci, 109(2), 172-179. doi: 10.1093/toxsci/kfp067

Elhajouji, A., Lukamowicz, M., Cammerer, Z., & Kirsch-Volders, M. (2011). Potential thresholds for genotoxic effects by micronucleus scoring. [Review]. Mutagenesis, 26(1), 199-204. doi: 10.1093/mutage/geq089

Enterline, P. E., Day, R., & Marsh, G. M. (1995). Cancers related to exposure to arsenic at a copper smelter. Occup Environ Med, 52(1), 28-32.

Erraguntla, N. K., Sielken, R. L., Valdez-Flores, C., & Grant, R. L. (2012). An updated unit risk factor for arsenic and inorganic arsenic compounds based on a combined analysis of epidemiology studies. Regul Toxicol and Pharmacol, in press.

European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC). (2002). Adverse and nonadverse effects in toxicity studies. (ECETOC Technical Report 85). Brussels, Belgium.

European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC). (2003). Derivation of Assessment Factors for Human Health Risk Assessment. (ECETOC TR No. 86). Brussels, Belgium: Retrieved from members.ecetoc.org/Documents/Document/TR%20086.pdf.

European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC). (2010). Guidance on Assessment Factors to Derive a DNEL. (ECETOC Technical Report 110). Brussels, Belgium.

Evans, M. V., Boyes, W. K., Simmons, J. E., Litton, D. K., & Easterling, M. R. (2002). A comparison of Haber's rule at different ages using a physiologically based pharmacokinetic (PBPK) model for chloroform in rats. Toxicology, 176(1-2), 11-23.

Farland, W. F., & Dourson, M. L. (1992). Noncancer Health Endpoints: Approaches to Quantitative Risk Assessment. In C. R. Cothern (Ed.), Risk Assessment (pp. 87-106). Boca Raton: Lewis Publ.

Faustman, E. M. (1996). Review of Noncancer Risk Assessment: Application of Benchmark Dose Methods. Prepared for the Presidential/Congressional Commission on Risk Assessment and Risk Management (PCCRARM 1997). Retrieved from www.epa.gov/ncea/pdfs/riskcom/faustman.pdf.

Federal Focus. (1995). Principles for Evaluating Epidemiologic Data in Regulatory Risk Assessment. Paper presented at the Developed by an Expert Panel at a Conference in London, England, October 1995.

Fedorov, V., Mannino, F., & Zhang, R. (2009). Consequences of dichotomization. Pharm Stat, 8(1), 50-61. doi: 10.1002/pst.331

Figueiras, A., & Cadarso-Suarez, C. (2001). Application of nonparametric models for calculating odds ratios and their confidence intervals for continuous exposures. Am J Epidemiol, 154(3), 264-275.

Filipsson, A. F., Sand, S., Nilsson, J., & Victorin, K. (2003). The benchmark dose method--review of available models, and recommendations for application in health risk assessment. [Review]. Crit Rev Toxicol, 33(5), 505-542.

Flagler, R. B. (1998). Recognition of Air Pollution Injury to Vegetation: A Pictorial Atlas (Second Edition ed.). Pittsburgh, Pennsylvania: Air & Waste Management Association.

Food and Drug Administration (FDA). (1995). Food Additives; Threshold of Regulation for Substances Used In Food-Contact Articles. Federal Register 60 (136): 36582-96.

Food and Drug Administration (FDA). (2002). Immunotoxicology Evaluation of Investigational New Drugs. Silver Spring, MD: Retrieved from www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079239.pdf.

Foos, B., Marty, M., Schwartz, J., Bennett, W., Moya, J., Jarabek, A. M., & Salmon, A. G. (2008). Focusing on children's inhalation dosimetry and health effects for risk assessment: an introduction. [Review]. J Toxicol Environ Health A, 71(3), 149-165. doi: 10.1080/15287390701597871

Fowles, J. R., Alexeeff, G. V., & Dodge, D. (1999). The use of benchmark dose methodology with acute inhalation lethality data. Regul Toxicol Pharmacol, 29(3), 262-278. doi: 10.1006/rtph.1999.1295

Gail, M. (1975). Measuring the benefit of reduced exposure to environmental carcinogens. J Chronic Dis, 28(3), 135-147.

Garcia, G. J., Schroeter, J. D., Segal, R. A., Stanek, J., Foureman, G. L., & Kimbell, J. S. (2009). Dosimetry of nasal uptake of water-soluble and reactive gases: a first study of interhuman variability. Inhal Toxicol, 21(7), 607-618. doi: 10.1080/08958370802320186

Gaylor, D. W. (1992). Incidence of developmental defects at the no observed adverse effect level (NOAEL). Regul Toxicol Pharmacol, 15(2 Pt 1), 151-160.

Gerrity, T. R., & Henry, C. J. (1990). Summary Report of The Workshops on Principles of Route-To-Route Extrapolation for Risk Assessment Principles of Route-to-Route Extrapolation for Risk Assessment, Proceedings Of The Workshops; March and July; Hilton Head, S.C. and Durham, N.C. (pp. 1-12). New York, N.Y.: Elsevier Science Publishing Co., Inc.

Ginevan, M. E., & Watkins, D. K. (2010). Logarithmic dose transformation in epidemiologic dose-response analysis: use with caution. Regul Toxicol Pharmacol, 58(2), 336-340. doi: 10.1016/j.yrtph.2010.07.007

Ginsberg, G., Hattis, D., Sonawane, B., Russ, A., Banati, P., Kozlak, M., . . . Goble, R. (2002). Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. [Comparative Study]. Toxicol Sci, 66(2), 185-200.

Ginsberg, G. L. (2003). Assessing cancer risks from short-term exposures in children. [Review]. Risk Anal, 23(1), 19-34.

Ginsberg, G. L., Asgharian, B., Kimbell, J. S., Ultman, J. S., & Jarabek, A. M. (2008). Modeling approaches for estimating the dosimetry of inhaled toxicants in children. [Review]. J Toxicol Environ Health A, 71(3), 166-195. doi: 10.1080/15287390701597889

Glass, L. R., Easterly, C. E., Jones, T. D., & Walsh, P. J. (1991). Ranking of carcinogenic potency using a relative potency approach. Arch Environ Contam Toxicol, 21(2), 169-176.

Globally Harmonized System of Classification and Labelling of Chemicals (GHS). (2009). Chapter 3.4 Respiratory or Skin Sensitization. United Nations Retrieved from www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev03/English/00e_intro.pdf.

Goddard, M. J., Murdoch, D. J., & Krewski, D. (1995). Temporal Aspects of Risk Characterization. Inhalation Toxicology, 7(6), 1005-1018. doi: 10.3109/08958379509012806

Goldbohm, R. A., Tielemans, E. L., Heederik, D., Rubingh, C. M., Dekkers, S., Willems, M. I., & Dinant Kroese, E. (2006). Risk estimation for carcinogens based on epidemiological data: a structured approach, illustrated by an example on chromium. Regul Toxicol Pharmacol, 44(3), 294-310. doi: 10.1016/j.yrtph.2006.01.007

Graham, J. P. (1994). The Role of Epidemiology in Regulatory Risk Assessment. Paper presented at the Conference on the Proper Role of Epidemiology in Risk Analysis, Boston, MA.

Granett, A. L., & Taylor, O. C. (1977). The Effect of Designated Pollutants on Plants, Second Annual Report: University of California, Irvine.

Grant, R. L., Haney, J., Curry, A. L., & Honeycutt, M. (2009). Development of a unit risk factor for 1,3-butadiene based on an updated carcinogenic toxicity assessment. Risk Anal, 29(12), 1726-1742. doi: 10.1111/j.1539-6924.2009.01302.x

Grant, R. L., Kadlubar, B. J., Erraguntla, N. K., & Honeycutt, M. (2007). Evaluation of acute inhalation toxicity for chemicals with limited toxicity information. Regul Toxicol Pharmacol, 47(3), 261-273. doi: 10.1016/j.yrtph.2006.11.003

Guzelian, P. S., & Henry, C. J. (1992). Conference Summary. In Similarities and Differences between Children and Adults: Implications for Risk Assessment.

Haber, F. (1924). Zur Geschichte des Gaskrieges Fünf Vorträge aus den Jahren 1920-1923 (pp. 76-92). Berlin: Springer-Verlag.

Haber, L., Krishnana, K., Hack, C. E., Gentry, R., & Zhao, J. (2009). Child-Adult Differences in Inhalation Dosimetry of Gases: Application to Selected Systemically-Acting Volatile Organic Chemicals.

Haney, J. T., Jr., McCant, D. D., Sielken, R. L., Jr., Valdez-Flores, C., & Grant, R. L. (2012). Development of a unit risk factor for nickel and inorganic nickel compounds based on an updated carcinogenic toxicity assessment. Regul Toxicol Pharmacol, 62(1), 191-201. doi: 10.1016/j.yrtph.2011.10.005

Hanna, L. M., Lou, S. R., Su, S., & Jarabek, A. M. (2001). Mass transport analysis: inhalation rfc methods framework for interspecies dosimetric adjustment. Inhal Toxicol, 13(5), 437-463. doi: 10.1080/08958370119198

Harris, J. E. (1983). Diesel Emissions and Lung Cancer Revisited. Risk Analysis, 3(2), 139-146. doi: 10.1111/j.1539-6924.1983.tb00115.x

Hattis, D., Ginsberg, G., Sonawane, B., Smolenski, S., Russ, A., Kozlak, M., & Goble, R. (2003). Differences in pharmacokinetics between children and adults--II. Children's variability in drug elimination half-lives and in some parameters needed for physiologically-based pharmacokinetic modeling. Risk Anal, 23(1), 117-142.

Hays, S. M., Aylward, L. L., & Lakind, J. S. (2008). Introduction to the Biomonitoring Equivalents Pilot Project: development of guidelines for the derivation and communication of Biomonitoring Equivalents. [Introductory]. Regul Toxicol Pharmacol, 51(3 Suppl), S1-2. doi: 10.1016/j.yrtph.2008.02.007

Hays, S. M., Becker, R. A., Leung, H. W., Aylward, L. L., & Pyatt, D. W. (2007). Biomonitoring equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective. [Review]. Regul Toxicol Pharmacol, 47(1), 96-109. doi: 10.1016/j.yrtph.2006.08.004

Health Canada. (2008). Science Policy Note: The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides. Retrieved from www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/spn2008-01/index-eng.php.

Heck, W. W., & Brandt, C. S. (1977). Effects on Vegetation: Native, Crops, Forests. In A. C. Stern (Ed.), Air Pollution (Third Edition ed., Vol. II). New York: Academic Press.

Hertz-Picciotto, I. (1995). Epidemiology and quantitative risk assessment: a bridge from science to policy. Am J Public Health, 85(4), 484-491.

Hewett, P. (2001). Misinterpretation and misuse of exposure limits. Appl Occup Environ Hyg, 16(2), 251-256. doi: 10.1080/10473220118280

Hill, A. B. (1965). The Environment and Disease: Association or Causation? Proc R Soc Med, 58, 295-300.

Hines, R. N., Sargent, D., Autrup, H., Birnbaum, L. S., Brent, R. L., Doerrer, N. G., . . . Slikker, W. (2010). Approaches for assessing risks to sensitive populations: lessons learned from evaluating risks in the pediatric population. [Review]. Toxicol Sci, 113(1), 4-26. doi: 10.1093/toxsci/kfp217

Höfler, M. (2005). The Bradford Hill considerations on causality: a counterfactual perspective. Emerg Themes Epidemiol, 2, 11. doi: 10.1186/1742-7622-2-11

Holland, C. D., & Sielken, R. L. (1993). Quantitative Cancer Modeling and Risk Assessment. Englewood Cliffs, NJ: P T R Prentice Hall.

Hollander, N., Sauerbrei, W., & Schumacher, M. (2004). Confidence intervals for the effect of a prognostic factor after selection of an 'optimal' cutpoint. Stat Med, 23(11), 1701-1713. doi: 10.1002/sim.1611

Honma, T., & Suda, M. (1998). Correlation of lethal doses of industrial chemicals between oral or intraperitoneal administration and inhalation exposure. Ind Health, 36(3), 273-281.

Howick, J., Glasziou, P., & Aronson, J. K. (2009). The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute? J R Soc Med, 102(5), 186-194. doi: 10.1258/jrsm.2009.090020

International Commission on Radiological Protection (ICRP). (1994). Human Respiratory Tract Model for Radiological Protection. (ICRP Publication 66). Tarrytown, NY: Elsevier Science Inc.

International Conference on Harmonization (ICH). (2008). Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use S2(R1). Retrieved from www.ich.org/LOB/media/MEDIA4474.pdf.

International Programme on Chemical Safety (IPCS). (1999). Principles for the Assessment of Risks to Human Health from Exposure to Chemicals. Geneva: World Health Organization Retrieved from www.pic.int/secEdoc/Environmental%20Health%20Criteria%20210.pdf.

International Programme on Chemical Safety (IPCS). (2001). Guidance Document for the Use of Data in Development of Chemical-Specific Adjustment Factors (CSAFs) for Interspecies Differences and Human Variability in Dose/Concentration-Response Assessment. (WHO/PCS/01.4). Geneva: World Health Organization Retrieved from www.who.int/ipcs/publications/methods/harmonization/en/csafs_guidance_doc.pdf.

International Programme on Chemical Safety (IPCS). (2005). Chemical-specific adjustment factors for interspecies differences and human variability : guidance document for use of data in dose/concentration-response assessment. (Harmonization Project Document No. 2). Geneva: World Health Organization Retrieved from whqlibdoc.who.int/publications/2005/9241546786_eng.pdf.

International Programme on Chemical Safety (IPCS). (2006). IPCS framework for analysing the relevance of a cancer mode of action for humans and case studies. Retrieved from www.who.int/ipcs/methods/harmonization/areas/cancer_mode.pdf.

Jacobson, J. S., & Hill, A. C. (1970). Recognition of air pollution injury to vegetation: a pictorial atlas: Air Pollution Control Association.

Jarabek, A. M. (1995a). Consideration of Temporal Toxicity Challenges Current Default Assumptions. Inhal Toxicol, 7(6), 927-946. doi: 10.3109/08958379509012801

Jarabek, A. M. (1995b). The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches. [Review]. Toxicol Lett, 79(1-3), 171-184.

Jarabek, A. M., Asgharian, B., & Miller, F. J. (2005). Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles (PSP). Inhal Toxicol, 17(7-8), 317-334. doi: 10.1080/08958370590929394

Jenkins, G. J., Zair, Z., Johnson, G. E., & Doak, S. H. (2010). Genotoxic thresholds, DNA repair, and susceptibility in human populations. [Review]. Toxicology, 278(3), 305-310. doi: 10.1016/j.tox.2009.11.016

Julien, E., Boobis, A. R., & Olin, S. S. (2009). The Key Events Dose-Response Framework: a cross-disciplinary mode-of-action based approach to examining dose-response and thresholds. Crit Rev Food Sci Nutr, 49(8), 682-689. doi: 10.1080/10408390903110692

Kim, E., Little, J. C., & Chiu, N. (2004). Estimating exposure to chemical contaminants in drinking water. Environ Sci Technol, 38(6), 1799-1806.

Kimber, I., & Basketter, D. A. (1992). The murine local lymph node assay: a commentary on collaborative studies and new directions. [Review]. Food Chem Toxicol, 30(2), 165-169.

Kimmel, C. A. (1990). Quantitative approaches to human risk assessment for noncancer health effects. [Review]. Neurotoxicology, 11(2), 189-198.

Kirkland, D. J., Aardema, M., Banduhn, N., Carmichael, P., Fautz, R., Meunier, J. R., & Pfuhler, S. (2007). In vitro approaches to develop weight of evidence (WoE) and mode of action (MoA) discussions with positive in vitro genotoxicity results. [Review]. Mutagenesis, 22(3), 161-175. doi: 10.1093/mutage/gem006

Kirman, C. R., Sweeney, L. M., Teta, M. J., Sielken, R. L., Valdez-Flores, C., Albertini, R. J., & Gargas, M. L. (2004). Addressing nonlinearity in the exposure-response relationship for a genotoxic carcinogen: cancer potency estimates for ethylene oxide. Risk Anal, 24(5), 1165-1183. doi: 10.1111/j.0272-4332.2004.00517.x

Kirsch-Volders, M., Sofuni, T., Aardema, M., Albertini, S., Eastmond, D., Fenech, M., . . . Wakata, A. (2003). Report from the in vitro micronucleus assay working group. Mutat Res, 540(2), 153-163.

Klein, C. B., Leszczynska, J., Hickey, C., & Rossman, T. G. (2007). Further evidence against a direct genotoxic mode of action for arsenic-induced cancer. Toxicol Appl Pharmacol, 222(3), 289-297. doi: 10.1016/j.taap.2006.12.033

Komori, M., Nishio, K., Kitada, M., Shiramatsu, K., Muroya, K., Soma, M., . . . Kamataki, T. (1990). Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry, 29(18), 4430-4433.

Layton, D. W., Mallon, B. J., Rosenblatt, D. H., & Small, M. J. (1987). Deriving allowable daily intakes for systemic toxicants lacking chronic toxicity data. Regul Toxicol Pharmacol, 7(1), 96-112.

Leeder, J. S., & Kearns, G. L. (1997). Pharmacogenetics in pediatrics. Implications for practice. Pediatr Clin North Am, 44(1), 55-77.

Lemeshow, S., & Hosmer Jr., D. W. (1982). A Review of Goodness of Fit Statistics for use in the Development of Logistic Regression Models. American Journal of Epidemiology, 115(1), 92-106.

Leonardos, G. (1996). Review of Odor Control Regulations in the USA. Proceedings of a Specialty Conference, Air & Waste Management Associate. Odors, Indoor and Environmental Air, 73-54.

Lewis, R. W., Billington, R., Debryune, E., Gamer, A., Lang, B., & Carpanini, F. (2002). Recognition of adverse and nonadverse effects in toxicity studies. [Review]. Toxicol Pathol, 30(1), 66-74. Available from: tpx.sagepub.com/content/30/1/66.

Little, J. C., & Chiu, N. (1998). Exposure to Contaminant in Drinking Water: Estimating Uptake Through the Skin and by Inhalation (R. S. I. W. G. ILSI, Trans.). In Olin (Ed.), (pp. 93).

Lynch, A. M., Sasaki, J. C., Elespuru, R., Jacobson-Kram, D., Thybaud, V., De Boeck, M., . . . Kim, J. H. (2011). New and emerging technologies for genetic toxicity testing. [Review]. Environ Mol Mutagen, 52(3), 205-223. doi: 10.1002/em.20614

Lyman, W.J., Rosenblatt, D.H., and Reehl, W.J. (1990). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds. American Chemical Society.

Manos, M. M., Leyden, W. A., Murphy, R. C., Terrault, N. A., & Bell, B. P. (2008). Limitations of conventionally derived chronic liver disease mortality rates: Results of a comprehensive assessment. Hepatology, 47(4), 1150-1157. doi: 10.1002/hep.22181

McCarroll, N., Keshava, N., Chen, J., Akerman, G., Kligerman, A., & Rinde, E. (2010). An evaluation of the mode of action framework for mutagenic carcinogens case study II: chromium (VI). [Review]. Environ Mol Mutagen, 51(2), 89-111. doi: 10.1002/em.20525

McKone, T. E. (1987). Human exposure to volatile organic compounds in household tap water: the indoor inhalation pathway. Environ Sci Technol, 21(12), 1194-1201. doi: 10.1021/es00165a006

Meek, M. E. (2008). Recent developments in frameworks to consider human relevance of hypothesized modes of action for tumours in animals. [Review]. Environ Mol Mutagen, 49(2), 110-116. doi: 10.1002/em.20369

Meek, M. E., Bucher, J. R., Cohen, S. M., Dellarco, V., Hill, R. N., Lehman-McKeeman, L. D., . . . Patton, D. E. (2003). A framework for human relevance analysis of information on carcinogenic modes of action. [Review]. Crit Rev Toxicol, 33(6), 591-653. doi: 10.1080/713608373

Ménache, M. G., Miller, F. J., and Raabe, O. G. (1995). Particle inhalability curves for humans and small laboratory animals. Ann Occup Hyg, 39, 317–328.

Merrill, & Timmreck. (2006). Introduction to epidemiology (4th edition ed.). Ontario: Jones and Bartlett Publishers, Inc.

Miller, F. J., Schlosser, P. M., & Janszen, D. B. (2000). Haber's rule: a special case in a family of curves relating concentration and duration of exposure to a fixed level of response for a given endpoint. [Review]. Toxicology, 149(1), 21-34.

Moolgavkar, S. H., & Knudson, A. G., Jr. (1981). Mutation and cancer: a model for human carcinogenesis. J Natl Cancer Inst, 66(6), 1037-1052.

Moolgavkar, S. H., & Knudson, A. G., Jr. (1981). Mutation and cancer: a model for human carcinogenesis. J Natl Cancer Inst, 66(6), 1037-1052.

Moore, M. M., Heflich, R. H., Haber, L. T., Allen, B. C., Shipp, A. M., & Kodell, R. L. (2008). Analysis of in vivo mutation data can inform cancer risk assessment. Regul Toxicol Pharmacol, 51(2), 151-161. doi: 10.1016/j.yrtph.2008.01.015

Moseman, R. F., & Oswald, E. O. (1980). Ch. 13 - Development of Analytical Methodology for Assessment of Human Exposure to Pesticides Pesticide Analytical Methodology: American Chemical Society.

Murdoch, D. J., Krewski, D., & Wargo, J. (1992). Cancer risk assessment with intermittent exposure. Risk Anal, 12(4), 569-577.

National Center for Environmental Assessment (NCEA). (2009). Policy and Procedures for Conducting IRIS Peer Reviews (PDF). Retrieved from www.epa.gov/iris/pdfs/Policy_IRIS_Peer_Reviews.pdf.

National Institute for Public Health and the Environment (RIVM). (2002). Multiple Path Particle Dosimetry Model (MPPD v 1.0): A Model for Human and Rat Airway Particle Dosimetry. (RIVA Report 650010030). Bilthoven, The Netherlands: National Institute for Public Health and the Environment (RIVM).

National Research Council (NRC). (1983). Risk Assessment in the Federal Government. Washington, D.C.: National Academy Press.

National Research Council (NRC). (1988). Health risks of radon and other internally deposited alpha-emitters. Committee on the Biological Effects of Ionizing Radiation: IV (BEIR IV). Washington, D.C.: National Academy Press.

National Research Council (NRC). (1990). Health effects of exposure to low levels of ionizing radiation: BEIR V. Washington, D.C.: National Academy Press.

National Research Council (NRC). (1993). Pesticides in the Diets of Infants and Children. Washington, D.C.: National Academy Press.

National Research Council (NRC). (1994). Science and Judgment in Risk Assessment. Washington, D.C.: National Academy Press.

National Research Council (NRC). (1999). Health effects of exposure to radon. Committee on the Biological Effects of Ionizing Radiation: VI (BEIR VI). Washington, D.C.: National Academy Press.

National Research Council (NRC). (2001). Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, D.C.: National Academy Press.

National Research Council (NRC). (2003). Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 3. Washington, D.C.: National Academy Press.

National Research Council (NRC). (2007a). Scientific Review of the Proposed Risk Assessment Bulletin from the Office of Management and Budget. Retrieved from www.nap.edu/catalog/11811.html.

National Research Council (NRC). (2007b). Toxicity Testing in the 21st Century: A Vision and A Strategy. ISBN: 0-309-10993-0.

National Research Council (NRC). (2009). Science and Decisions Advancing Risk Assessment. Washington, D.C.

Nicell, J. A. (2009). Assessment and regulation of odour impacts. Atmospheric Environment, 43(1), 196-206. doi: dx.doi.org/10.1016/j.atmosenv.2008.09.033

Nielsen, E., Ostergaard, G., & Larsen, J. C. (2010). Toxicological Risk Assessment of Chemicals: A Practical Guide. New York: Informa Healthcare.

Office of Environmental Health Hazard Assessment (OEHHA). (1999). Acute Toxicity Summary, Mercury (Inorganic). California Environmental Protection Agency.

Office of Environmental Health Hazard Assessment (OEHHA). (2008). Technical support document for the derivation of noncancer reference exposure levels. Oakland, California: California Environmental Protection Agency Retrieved from oehha.ca.gov/air/hot_spots/2008/NoncancerTSD_final.pdf.

Organisation for Economic Co-operation and Development (OECD). (2010). Draft OECD Guidance document for the derivation of an acute reference concentration (ARfC). Paris, France: Retrieved from www.oecd.org/dataoecd/13/49/45799595.pdf.

Ott, W. R., Steinemann, A. C., & Wallace, L. A. (2007). Exposure Analysis: CRC Press.

Overton, J., & Jarabek, A. (1989a). Estimating Human Equivalent No Observed Effect Levels for VOCs Based on Minimal Knowledge of Physiological Parameters. (USEPA, EPA/600/D-89/097 (NTIS PB89224588)). Washington, D.C.

Overton, J. H., & Jarabek, A. M. (1989b). Estimating equivalent human concentrations of no observed adverse effect levels: a comparison of several methods. Exp Pathol, 37(1-4), 89-94.

Overton, J. H. (1990). Respiratory Tract Physiological Processes and the Uptake of Gases. In: Principles of Route-to-route Extrapolation for Risk Assessment. New York, NY: Elsevier Science Publishing Co., Inc.

Ozkaynak, H., Whyatt, R. M., Needham, L. L., Akland, G., & Quackenboss, J. (2005). Exposure assessment implications for the design and implementation of the National Children's Study. Environ Health Perspect, 113(8), 1108-1115.

Paustenbach, D., & Galbraith, D. (2006). Biomonitoring and biomarkers: exposure assessment will never be the same. Environ Health Perspect, 114(8), 1143-1149.

Paustenbach, D. J. (1989). The Risk Assessment of Environmental Hazards: A Textbook of Case Studies. New York: John Wiley & Sons.

Pearce, N. (2000). The ecological fallacy strikes back. J Epidemiol Community Health, 54(5), 326-327.

Phillips, C. V., & Goodman, K. J. (2006). Causal criteria and counterfactuals; nothing more (or less) than scientific common sense. Emerging Themes in Epidemiology, 3, 5.

Phillips, T. D., Ethridge, S. E., & Grant, R. L. (2011). Practical implementation of the threshold of concern and NOAEL-to-LC50 ratio factor approach to determine acute effects screening levels. The Toxicologist, Suppl 2 to Tox Sci 120, Abstract No. #1523.

Pieters, M. N., Kramer, H. J., & Slob, W. (1998). Evaluation of the uncertainty factor for subchronic-to-chronic extrapolation: statistical analysis of toxicity data. Regul Toxicol Pharmacol, 27(2), 108-111. doi: 10.1006/rtph.1997.1196

Pohl, H. R., & Abadin, H. G. (1995). Utilizing uncertainty factors in minimal risk levels derivation. [Review]. Regul Toxicol Pharmacol, 22(2), 180-188. doi: 10.1006/rtph.1995.1083

Portier, C. J. (1987). Statistical properties of a two-stage model of carcinogenesis. Environ Health Perspect, 76, 125-131.

Pottenger, L. H., Becker, R. A., Moran, E. J., & Swenberg, J. A. (2011). Workshop report: identifying key issues underpinning the selection of linear or non-linear dose-response extrapolation for human health risk assessment of systemic toxicants. Regul Toxicol Pharmacol, 59(3), 503-510. doi: 10.1016/j.yrtph.2011.01.005

Pratt, I. S., & Barron, T. (2003). Regulatory recognition of indirect genotoxicity mechanisms in the European Union. [Review]. Toxicol Lett, 140-141, 53-62.

Preston, R. J., & Williams, G. M. (2005). DNA-reactive carcinogens: mode of action and human cancer hazard. [Review]. Crit Rev Toxicol, 35(8-9), 673-683.

Renwick, A. G. (1993). Data-derived safety factors for the evaluation of food additives and environmental contaminants. Food Additives and Contaminants, 10, 275-305.

Renwick, A. G., & Lazarus, N. R. (1998). Human variability and noncancer risk assessment--an analysis of the default uncertainty factor. Regul Toxicol Pharmacol, 27(1 Pt 1), 3-20.

Richardson, D. B., & Loomis, D. (2004). The impact of exposure categorisation for grouped analyses of cohort data. Occup Environ Med, 61(11), 930-935. doi: 10.1136/oem.2004.014159

Rinehart, W. E., & Hatch, T. (1964). Concentration-Time Product (CT) as an Expression of Dose in Sublethal Exposures to Phosgene. Am Ind Hyg Assoc J, 25, 545-553. doi: 10.1080/00028896409342641

Rothman, K. J. (1986). Modern Epidemiology. Boston, MA: Little, Brown and Company.

Royston, P., Altman, D. G., & Sauerbrei, W. (2006). Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med, 25(1), 127-141. doi: 10.1002/sim.2331

Rozman, K. K. (2000). The role of time in toxicology or Haber's c x t product. [Review]. Toxicology, 149(1), 35-42.

Rozman, K. K., & Doull, J. (2000). Dose and time as variables of toxicity. Toxicol, 144, 169-178.

Rozman, K. K., & Doull, J. (2001). The role of time as a quantifiable variable of toxicity and the experimental conditions when Haber's c x t product can be observed: implications for therapeutics. J Pharmacol Exp Ther, 296(3), 663-668.

Sakula, A. (1984). Sir John Floyer's A Treatise of the Asthma (1698). Thorax, 39(4), 248-254.

Sarangapani, R., Gentry, P. R., Covington, T. R., Teeguarden, J. G., & Clewell, H. J., 3rd. (2003). Evaluation of the potential impact of age- and gender-specific lung morphology and ventilation rate on the dosimetry of vapors. Inhal Toxicol, 15(10), 987-1016. doi: 10.1080/08958370390226350

Schiffman, S. S., & Williams, C. M. (2005). Science of odor as a potential health issue. J Environ Qual, 34(1), 129-138.

Schneider, K., Oltmanns, J., & Hassauer, M. (2004). Allometric principles for interspecies extrapolation in toxicological risk assessment--empirical investigations. Regul Toxicol Pharmacol, 39(3), 334-347. doi: 10.1016/j.yrtph.2004.03.001

Schulgen, G., Lausen, B., Olsen, J. H., & Schumacher, M. (1994). Outcome-oriented cutpoints in analysis of quantitative exposures. Am J Epidemiol, 140(2), 172-184.

Schwarze, P. E., Øvrevik, J., Låg, M., Refsnes, M., Nafstad, P., Hetland, R. B., & Dybing, E. (2006). Particulate matter properties and health effects: consistency of epidemiological and toxicological studies. [Review]. Hum Exp Toxicol, 25(10), 559-579.

Seiler, F. A., & Alvarez, J. L. (1994). Definition of a minimum significant risk. Technology: J Franklin Institute, 331A, 83-95.

Shaw, D. G., Huffman, M. D., & Haviland, M. G. (1987). Grouping Continuous Data in Discrete Intervals: Information Loss and Recovery. Journal of Educational Measurement, 24(2), 167-173.

Sherwin, R. P. (1983). What is an adverse health effect? Environ Health Perspect, 52, 177-182.

Shim, C., Williams, M. H., Jr. (1986). Effect of odors in asthma. Am J Med, 80(1), 18-22.

Shore, R. E., Iyer, V., Altshuler, B., & Pasternack, B. S. (1992). Use of human data in quantitative risk assessment of carcinogens: impact on epidemiologic practice and the regulatory process. Regul Toxicol Pharmacol, 15(2 Pt 1), 180-221.

Shusterman, D. (1992). Critical review: the health significance of environmental odor pollution. Arch Environ Health, 47(1), 76-87.

Shusterman, D. (1999). The health significance of environmental odour pollution: revisited. Journal of Environmental Medicine, 1(4), 249-258.

Shusterman, D. (2001). Odor-associated Health Complaints: Competing Explanatory Models. Chemical Senses, 26(3), 339-343.

Shusterman, D., Matovinovic, E., & Salmon, A. (2006). Does Haber's law apply to human sensory irritation? Inhal Toxicol, 18(7), 457-471. doi: 10.1080/08958370600602322

Sielken, R. L., & Flores, C. V. (2009a). Calculating excess risk with age-dependent adjustment factors and cumulative doses: ethylene oxide case study. Regul Toxicol Pharmacol, 55(1), 76-81. doi: 10.1016/j.yrtph.2009.06.004

Sielken, R. L., Jr., & Valdez-Flores, C. (2009b). Life-table calculations of excess risk for incidence versus mortality: ethylene oxide case study. Regul Toxicol Pharmacol, 55(1), 82-89. doi: 10.1016/j.yrtph.2009.06.003

Sielken, R. L., Jr., & Valdez-Flores, C. (2011). Butadiene cancer exposure-response modeling: based on workers in the styrene-butadiene-rubber industry: total leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia. Regul Toxicol Pharmacol, 60(3), 332-341. doi: 10.1016/j.yrtph.2011.05.001

Sielken, R. L., Jr., Valdez-Flores, C., Gargas, M. L., Kirman, C. R., Teta, M. J., & Delzell, E. (2007). Cancer risk assessment for 1,3-butadiene: dose-response modeling from an epidemiological perspective. Chem Biol Interact, 166(1-3), 140-149. doi: 10.1016/j.cbi.2006.06.004

Simpkins, J. W., Swenberg, J. A., Weiss, N., Brusick, D., Eldridge, J. C., Stevens, J. T., . . . Breckenridge, C. B. (2011). Atrazine and breast cancer: a framework assessment of the toxicological and epidemiological evidence. Toxicol Sci, 123(2), 441-459. doi: 10.1093/toxsci/kfr176

Snipes, M. B., James, A. C., & Jarabek, A. M. (1997). The 1994 ICRP66 Human Respiratory Tract Dosimetry Model as a Tool for Predicting Lung Burdens from Exposures to Environmental Aerosols. Appl Occup Environ Hyg, 12(8), 547-554. doi: dx.doi.org/10.1080/1047322X.1997.10390045.

Snodgrass, W. R. (1992). Physiological and biochemical differences between children and adults as determinants of toxic response to environmental pollutants. In P. S. Guzelian, C. J. Henry & S. S. Olin (Eds.), Similarities and Differences between Children and Adults: Implications for Risk Assessment. Washington, D.C.: International Life Sciences Institute (ILSI).

Spielberg, S. P. (1992). Anticonvulsant adverse drug reactions: age depenent and age independent. In P. S. Guzelian, C. J. Henry & S. S. Olin (Eds.), Similarities and Differences between Children and Adults: Implications for Risk Assessment. Washington, D.C.: International Life Sciences Institute (ILSI).

Stayner, L., Smith, R., Bailer, A. J., Luebeck, E. G., & Moolgavkar, S. H. (1995). Modeling epidemiologic studies of occupational cohorts for the quantitative assessment of carcinogenic hazards. [Review]. Am J Ind Med, 27(2), 155-170.

Steenland, K., Deddens, J., & Piacitelli, L. (2001). Risk assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) based on an epidemiologic study. Am J Epidemiol, 154(5), 451-458.

Steenland, K., Deddens, J., & Stayner, L. (1998). Diesel exhaust and lung cancer in the trucking industry: exposure-response analyses and risk assessment. Am J Ind Med, 34(3), 220-228.

Steenland, K., & Deddens, J. A. (2004). A practical guide to dose-response analyses and risk assessment in occupational epidemiology. [Review]. Epidemiology, 15(1), 63-70. doi: 10.1097/01.ede.0000100287.45004.e7

Steenland, K., Stayner, L., & Deddens, J. (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med, 61(1), 2-7.

Steenland, K., Whelan, E., Deddens, J., Stayner, L., & Ward, E. (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control, 14(6), 531-539.

Stein, M., Ottenberg, P. (1958). Role of odors in asthma. Psychosom Med, 20(1), 60-65.

Stewart, P. (1999). Challenges to retrospective exposure assessment. [Review]. Scand J Work Environ Health, 25(6), 505-510.

Suzuki, M. (2009). Children's toxicology from bench to bed--Drug-induced renal injury (4): Effects of nephrotoxic compounds on fetal and developing kidney. J Toxicol Sci, 34 Suppl 2, SP267-271.

Swartout, J. C., Price, P. S., Dourson, M. L., Carlson-Lynch, H. L., & Keenan, R. E. (1998). A probabilistic framework for the reference dose (probabilistic RfD). Risk Anal, 18(3), 271-282.

Swenberg, J. A., Fryar-Tita, E., Jeong, Y. C., Boysen, G., Starr, T., Walker, V. E., & Albertini, R. J. (2008). Biomarkers in toxicology and risk assessment: informing critical dose-response relationships. [Review]. Chem Res Toxicol, 21(1), 253-265. doi: 10.1021/tx700408t

ten Berge, W. F., Zwart, A., & Appelman, L. M. (1986). Concentration—timemortalityresponserelationship of irritant and systemicallyactingvapours and gases. Journal of Hazardous Materials, 13(3), 301-309.

Teta, M. J., Sielken, R. L., Jr., & Valdez-Flores, C. (1999). Ethylene oxide cancer risk assessment based on epidemiological data: application of revised regulatory guidelines. [Meta-Analysis]. Risk Anal, 19(6), 1135-1155.

Texas Clean Air Act. Chapter 382 of the Texas Health and Safety Code (THSC). Retrieved from www.statutes.legis.state.tx.us/Docs/HS/htm/HS.382.htm.

Texas Commission on Environmental Quality (TCEQ). (1999). Air Quality Modeling Guidelines. (RG-25 revised). Austin, TX.

Texas Commission on Environmental Quality (TCEQ). (2006). Guidelines to develop effects screening levels, reference values, and unit risk factors. (RG-442). Retrieved from www.tceq.state.tx.us/files/rg-442.pdf_4452928.pdf.

Texas Commission on Environmental Quality (TCEQ). (2007a). Development Support Document for n-Hexane, CAS Registry Numbers: 100-54-3. Retrieved from www.tceq.texas.gov/toxicology/dsd/final.html.

Texas Commission on Environmental Quality (TCEQ). (2007b). Odor Complaint Investigation Procedures. Retrieved from www.tceq.texas.gov/complaints/protocols/odor_protopdf.html/at_download/file.

Texas Commission on Environmental Quality (TCEQ). (2007c). Development Support Document for Benzene, CAS Registry Number 71-43-2. Retrieved from www.tceq.texas.gov/toxicology/dsd/final.html.

Texas Commission on Environmental Quality (TCEQ). (2008). Development Support Document for 1-3 Butadiene, CAS Registry Number: 106-99-0. Retrieved from www.tceq.texas.gov/toxicology/dsd/final.html.

Texas Commission on Environmental Quality (TCEQ). (2009a). Modeling and Effects Review Applicability: How to Determine the Scope of Modeling and Effects Review for Air Permits. (APDG-5874). Austin, TX.

Texas Commission on Environmental Quality (TCEQ). (2009b). Development Support Document for Silica, Crystalline Forms, CAS Registry Numbers: 14808-60-7 (quartz), 14464-46-1 (cristobalite), 1317-95-9 (tripoli), 15468-32-3 (tridymite). Retrieved from www.tceq.texas.gov/toxicology/dsd/final.html.

Texas Commission on Environmental Quality (TCEQ). (2011). Development Support Document for Nickel and Inorganic Nickel Compounds, CAS Registry Numbers: nickel: 7440-02-0, nickel sulfate: 7786-81-4, nickel subsulfide: 12035-72-2, nickel oxide: 1313-99-1, nickel chloride: 7718-54-9. Retrieved from www.tceq.texas.gov/toxicology/dsd/final.html.

Texas Commission on Environmental Quality (TCEQ). (2012). Development Support Document for Arsenic and Inorganic Arsenic Compounds, CAS Registry Number: 7440-38-2 (Arsenic). Retrieved from www.tceq.texas.gov/toxicology/dsd/final.html.

Texas Commission on Environmental Quality (TCEQ). (2015). TCEQ Position Paper: Approaches to Derive Odor-Based Values [currently proposed and in public comment]. Retrieved from http://www.tceq.state.tx.us/toxicology/dsd/dsds_about.html.

Texas Risk Reduction Program (TRRP). (2006). Rule 30 TAC §350 and Sub chapters A and S of 30 TAC §335. Retrieved from www.tceq.texas.gov/rules/indxpdf.html#350.

Texas Water Code. Chapter 5, Sub chapter D, Section 1.12 (House Bill 2912 (77th Texas Legislature)). Retrieved from www.statutes.legis.state.tx.us/Docs/WA/htm/WA.5.htm.

Thapa, B. R., & Walia, A. (2007). Liver function tests and their interpretation. Indian J Pediatr, 74(7), 663-671.

Thompson, C. M., Haws, L. C., Harris, M. A., Gatto, N. M., & Proctor, D. M. (2011). Application of the U.S. EPA mode of action Framework for purposes of guiding future research: a case study involving the oral carcinogenicity of hexavalent chromium. [Review]. Toxicol Sci, 119(1), 20-40. doi: 10.1093/toxsci/kfq320

Thybaud, V., Macgregor, J. T., Muller, L., Crebelli, R., Dearfield, K., Douglas, G., . . . Van Benthem, J. (2011). Strategies in case of positive in vivo results in genotoxicity testing. Mutat Res, 723(2), 121-128. doi: 10.1016/j.mrgentox.2010.09.002

Törnqvist, M., & Ehrenberg, L. (1992). Risk assessment of urban air pollution. [Review]. Pharmacogenetics, 2(6), 297-303.

Törnqvist, M., & Ehrenberg, L. (1994). On cancer risk estimation of urban air pollution. [Review]. Environ Health Perspect, 102 Suppl 4, 173-182.

Toxicology Excellence for Risk Assessment (TERA). (2005a). Meeting Materials for a Peer Consultation on a Draft Framework to Evaluate whether the Default Uncertainty Factor for Human Kinetic Variability is Adequate for Protecting Children. Retrieved from www.tera.org/peer/.

Toxicology Excellence for Risk Assessment (TERA). (2005b). Interim Final Report: Report of the Peer Consultation Meeting on a Draft Framework to Evaluate whether the Default Uncertainty Factor for human kinetic variability is Adequate for Protecting Children. Retrieved from www.tera.org/peer/.

Toxicology Excellence for Risk Assessment (TERA). (2005c). Final Meeting Report: Report of the Peer Consultation Meeting on the Scientific Rationale for Deriving Database and Toxicodynamic Uncertainty Factors for Reproductive or Developmental Toxicants. Retrieved from www.tera.org/peer/.

Toxicology Excellence for Risk Assessment (TERA). (2007). Meeting Materials for a Peer Consultation on a Draft Framework to evaluate Child-Adult Differences in Inhalation Dosimetry of Gases: Application to Selected Systemically-Acting Volatile Organic Chemicals. Retrieved from www.tera.org/peer/.

Toxicology Excellence for Risk Assessment (TERA). (2008). Report of the Peer Consultation on a Draft Framework to Evaluate Child-Adult Differences in Inhalation Dosimetry of Gases: Application to Selected Systemically-Acting Volatile Organic Chemicals. Retrieved from www.tera.org/peer/.

Toxicology Excellence for Risk Assessment (TERA). 2011. Report of a Letter Peer Review of the Texas Commission on Environmental Quality's (TCEQ) updates to its Guidelines to Develop Inhalation and Oral Cancer and Non-Cancer Toxicity Factors. Final Report. available at www.tera.org/peer/tceqesl/. (accessed August 7, 2012).

Travis, C. C., & White, R. K. (1988). Interspecific scaling of toxicity data. Risk Anal, 8(1), 119-125.

United Nations (UN). (2005). Globally Harmonized System Of Classification And Labeling Of Chemicals (GHS) First revised edition. (ST/SG/AC.10/30/Rev.1 ). New York and Geneva: United Nations.

United States Department of Agriculture. (1974). Air Pollution and Trees: Evaluation of Air Pollution Effects in the South. (Report No. 75-1-4).

United States Department of Energy (USDOE). (2008). DOE Handbook Temporary Emergency Exposure Limits for Chemicals: Methods and Practice. (DOE-HDBK-1046-2008). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1986a). Guidelines for Mutagenicity Risk Assessment. (EPA/630/R-98/003). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1986b). Guidelines for the Health Risk Assessment of Chemical Mixtures. (EPA/630/R-98/002). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1986c). Guidelines for Carcinogen Risk Assessment. (EPA/630/R-00/004). Retrieved from www.epa.gov/cancerguidelines/guidelines-carcinogen-risk-assessment-1986.htm.

United States Environmental Protection Agency (USEPA). (1986d). Health Assessment Document for Nickel and Nickel Compounds. (EPA/600/8-83/012FF). Research Triangle Park, NC.

United States Environmental Protection Agency (USEPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. (EPA/600/6-87/008). Cincinnati, OH.

United States Environmental Protection Agency (USEPA). (1991). Guidelines for Developmental Toxicity Risk Assessment. (EPA/600/FR-91/001). Retrieved from www.epa.gov/raf/publications/guidelines-dev-toxicity-risk-assessment.htm.

United States Environmental Protection Agency (USEPA). (1992a). Draft Report: A Cross-Species Scaling Factor for Carcinogen Risk Assessment Based on Equivalence of mg/kg3/4/Day. (Fed Reg Vol. 57, No. 109).

United States Environmental Protection Agency (USEPA). (1992b). EPA's Approach for Assessing the Risks Associated with Chronic Exposures to Carcinogens. Retrieved from www.epa.gov/iris/carcino.htm.

United States Environmental Protection Agency (USEPA). (1993a). Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons. (EPA/600/R-93/089). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1993b). Reference Dose (RfD): Description and Use in Health Risk Assessments. Retrieved from www.epa.gov/iris/rfd.htm.

United States Environmental Protection Agency (USEPA). (1994a). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. (EPA/600/8-90/066F). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1994b). Interim policy for particle size and limit concentration issues in inhalation toxicity studies: Notice of availability. (Federal Register Notice 59(206): 53799). Retrieved from cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=186068.

United States Environmental Protection Agency (USEPA). (1995). The Use of the Benchmark Dose Approach in Health Risk Assessment. (EPA/630/R-94/007). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1996a). Proposed Guidelines for Carcinogen Risk Assessment (PDF). (EPA/600/P-92/003C). Retrieved from www.epa.gov/raf/publications/pdfs/propcra_1996.pdf.

United States Environmental Protection Agency (USEPA). (1996b). Aroclor 1016 (CAS No. 12674-11-2) Summary Information on the Integrated Risk Information System (IRIS). Washington, D.C. : Retrieved from www.epa.gov/iris/subst/0462.htm.

United States Environmental Protection Agency (USEPA). (1996c). Aroclor 1248 (CAS No. 12672-29-6) Summary Information on the Integrated Risk Information System (IRIS). Washington, D.C. : Retrieved from www.epa.gov/iris/subst/0649.htm.

United States Environmental Protection Agency (USEPA). (1996d). Aroclor 1254 (CAS No. 11097-69-1) Summary Information on the Integrated Risk Information System (IRIS). Washington, D.C. : Retrieved from www.epa.gov/iris/subst/0389.htm.

United States Environmental Protection Agency (USEPA). (1996e). Guidelines for Reproductive Toxicity Risk Assessment. (EPA/630/R-96/009). Retrieved from www.epa.gov/raf/publications/guidelines-reproductive-tox-risk-assessment.htm.

United States Environmental Protection Agency (USEPA). (1997). Health Effects Assessment Summary Tables FY 1997 Update. (EPA-540-R-97/036). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1998a). Guidelines for Neurotoxicity Risk Assessment. (EPA/630/R-95/001F). Retrieved from www.epa.gov/raf/publications/guidelines-neurotoxicity-risk-assessment.htm.

United States Environmental Protection Agency (USEPA). (1998b). Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals. Development of the Acute Reference Exposure. External Review Draft. . (EPA/600/R-98/051). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1998c). Summary of the U.S. Workshop on the Relationship between Exposure Duration and Toxicity. (EPA/600/R-99/081). Washington DC.

United States Environmental Protection Agency (USEPA). (1999a). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. Washington, D.C.

United States Environmental Protection Agency (USEPA). (1999b). Development of Chemical Categories in the High Production Volume Chemicals Challenge Program. Washington, D. C.

United States Environmental Protection Agency (USEPA). (1999c). Guidelines for Carcinogen Risk Assessment Review draft. (NCEA-F-0644). Retrieved from www.epa.gov/cancerguidelines/draft-guidelines-carcinogen-ra-1999.htm.

United States Environmental Protection Agency (USEPA). (2000a). Benchmark Dose Technical Guidance Document. (EPA/630/R-00/001). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2000b). Toxicological Review of Vinyl Chloride (CAS No. 75-01-4) In Support of Summary Information on the Integrated Risk Information System (IRIS). (EPA/635R-00/004). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2000c). Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. (EPA/630/R-00/002). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2000d). Science Policy Council Handbook: Risk Characterization. (EPA 100-B-00-002). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2000e). Science Policy Council Handbook: Peer Review (PDF) Second edition. (EPA 100-B-00-001). Washington, D.C.: Retrieved from www.epa.gov/iris/pdfs/Policy_IRIS_Peer_Reviews.pdf.

United States Environmental Protection Agency (USEPA). (2000f). Summary Report of the Workshop to Peer Review the Benchmark Dose Technical Guidance Document. Washington, D.C.

United States Environmental Protection Agency (USEPA). (2001a). Toxicological Review of Chloroform (CAS No. 67-66-3) In Support of Summary Information on the Integrated Risk Information System (IRIS). (EPA/635/R-01/001). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2001b). Health Assessment of 1,3-Butadiene. (EPA/600/P-98/001B). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2002a). A Review of the Reference Dose and Reference Concentration Processes. (EPA/630/P-02/002F). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2002b). Guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity. Washington, D. C.

United States Environmental Protection Agency (USEPA). (2002c). Determination of the Appropriate FQPA Safety Factor(s)in Tolerance Assessment. Washington, D.C.

United States Environmental Protection Agency (USEPA). (2002d). Toxicological review of benzene (noncancer effects). (EPA/635/R-02/001F). Washington, D.C. .

United States Environmental Protection Agency (USEPA). (2003a). Framework for Cumulative Risk Assessment. (EPA/630/P-02/001F). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2003b). Human Health Toxicity Values in Superfund Risk Assessments. (OSWER Directive 9285.7-53). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2003c). Health Effects Test Guidelines: OPPTS 870.2600 Skin Sensitization. (EPA 712-C-03-197). Arlington, VA.

United States Environmental Protection Agency (USEPA). (2004a). Air Toxics Risk Assessment Reference Library. (EPA-453-K-04-001A). Research Triangle Park, NC.

United States Environmental Protection Agency (USEPA). (2004b). Air Quality Criteria for Particulate Matter. (EPA 600/P-99/002aF-bF). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2004c). Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-P-Dioxin (TCDD) and Related Compounds National Academy Sciences (External Review Draft). U.S. Environmental Protection Agency, Washington, D.C., EPA/600/P-00/001Cb.

United States Environmental Protection Agency (USEPA). (2005a). Guidelines for Carcinogen Risk Assessment. (EPA/630/P-03/001B). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2005b). Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. (EPA/630/R-03/003F). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2005c). Pollution Prevention (P2) Framework. (EPA-748-B-04-001). Retrieved from www.epa.gov/oppt/sf/pubs/p2frame-june05a2.pdf.

United States Environmental Protection Agency (USEPA). (2005d). Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. (EPA/630/P-03/003F). Retrieved from www.epa.gov/raf/publications/pdfs/AGEGROUPS.PDF.

United States Environmental Protection Agency (USEPA). (2006a). Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. (EPA/600/R-05/043). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2006b). A Framework for Assessing Health Risks of Environmental Exposures to Children. (EPA/600/R-05/093F). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2006c). Science Policy Council Handbook: Peer Review, Third edition. (EPA/100/B-06/002). Washington, D.C.: Retrieved from www.epa.gov/spc/2peerrev.htm.

United States Environmental Protection Agency (USEPA). (2006d). Evaluation of the Carcinogenicity of Ethylene Oxide, External Review Draft. (EPA/635/R-06/003). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2007). Draft Framework for Determining a Mutagenic Mode of Action for Carcinogenicity: Using EPA's 2005 Cancer Guidelines and Supplemental Guidance for Assessing Susceptibility From Early-Life Exposure to Carcinogens. (EPA 120/R-07/002-A). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2009a). Graphical Arrays of Chemical-Specific Health Effect Reference Values for Inhalation Exposures. (EPA/600/R-09/061). Research Triangle Park, NC: Office of Research and Development. Retrieved from oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=495646.

United States Environmental Protection Agency (USEPA). (2009b). Status Report: Advances in Inhalation Dosimetry of Gases and Vapors with Portal of Entry Effects in the Upper Respiratory Tract. (EPA/600/R-09/072). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2010a). Draft Toxicological Review of Hexavalent Chromium. (EPA/635/R-10/004A). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2010b). Draft Toxicological Review of Hexachloroethane. (EPA/635/R-09/007A). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2011a). Recommended Use of BW3/4 as the Default Method in Derivation of the Oral Reference Dose. (EPA/100/R11/001). Washington, D.C.: Retrieved from www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf.

United States Environmental Protection Agency (USEPA). (2011b). Integrated Science Assessment for Ozone and Related Photochemical Oxidants. (EPA/600/R-10/076B). Washington, D.C. : Retrieved from cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=226363#Download.

United States Environmental Protection Agency (USEPA). (2011c). Status Report: Advances in Inhalation Dosimetry for Gases with Lower Respiratory Tract and Systemic Effects. (EPA/600/R-11/067). Washington, D.C.

Uinted States Environmental Protection Agency (USEPA). (2012a). Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment. (EPA/600/R-12/044). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2012b). Benchmark Dose Technical Guidance Document. (EPA/100/R-12/001). Washington, D.C.

United States Environmental Protection Agency (USEPA). (2014). Guidance for Applying Quantitative Data to Develop Data-derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. (EPA/100/R-14/002F ). Retrieved from www2.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf.

Valdez-Flores, C., & Sielken, R. L. (2010). Actuarial Computation of Excess Risks and Point of Departures for Rate Ratio and Hazard Rate Models Using Population-Based Age-Specific Background Rates and Competing Risks: Sielken & Associates Technical Report.

Valdez-Flores, C., Sielken, R. L., Jr., & Teta, M. J. (2010). Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regul Toxicol Pharmacol, 56(3), 312-320. doi: 10.1016/j.yrtph.2009.10.001

Van den Berg, M., Birnbaum, L. S., Denison, M., De Vito, M., Farland, W., Feeley, M., . . . Peterson, R. E. (2006). The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. [Review]. Toxicol Sci, 93(2), 223-241. doi: 10.1093/toxsci/kfl055

Van Raaij, M. T. M., Janssen, P. H., & Piersma, A. H. (2003). The relevance of developmental toxicity endpoints for acute limit setting. (RIVM Report 301900004/2003). National Institute for Public Health and the Environment (RIVM).

Venman, B. C., & Flaga, C. (1985). Development of an acceptable factor to estimate chronic end points from acute toxicity data. Toxicol Ind Health, 1(4), 261-269.

Vieira, I., Sonnier, M., & Cresteil, T. (1996). Developmental expression of CYP2E1 in the human liver. Hypermethylation control of gene expression during the neonatal period. Eur J Biochem, 238(2), 476-483.

Wainer, H. (2006). Finding What is not there Through the Unfortunate Binning of Results: The Mendel Effect. Chance, 19, 49-56.

Ward, A. C. (2009). The role of causal criteria in causal inferences: Bradford Hill's "aspects of association". Epidemiol Perspect Innov, 6, 2. doi: 10.1186/1742-5573-6-2

Weller, E., Long, N., Smith, A., Williams, P., Ravi, S., Gill, J., . . . Ryan, L. (1999). Dose-rate effects of ethylene oxide exposure on developmental toxicity. Toxicol Sci, 50(2), 259-270.

Willhite, M. T., & Dydek, S. T. (1989). Use of Odor Thresholds for Predicting Off-Property Odor Impacts. In D. R. Derenzo & A. Gnyp (Eds.), Recent

Developments and Current Practices in Odor Regulations, Controls and Technology (pp. 235-245). Pittsburgh, Pennsylvania: Air & Waste Management Association.

Willhite, M. T., & Dydek, S. T. (1991). Use of Odor Thresholds for Predicting Off-Property Odor Impacts in Recent Developments and Current Practices, in Odor Regulations, Controls and Technology Transactions of the Air & Waste Management Association.

Witschi, H. (1999). Some notes on the history of Haber's law. Toxicol Sci, 50, 164-168.

Woodall, G. M. (2005). Acute health reference values: overview, perspective, and current forecast of needs. J Toxicol Environ Health A, 68(11-12), 901-926. doi: 10.1080/15287390590912199

Woodall, G. M., Gift, J. S., & Foureman, G. L. (2009). Empirical Methods and Default Approaches in Consideration of Exposure Duration in Dose-Response Relationships. In B. Ballantyne, T. C. Marrs & T. Syversen (Eds.), General and Applied Toxicology (3rd edition ed., Vol. 5, pp. 2743-2757). Barcelona, Spain: John Wiley & Sons, Ltd.

World Health Organization (WHO). (2000a). Air Quality Guidelines for Europe, Second Edition. (European Series, No. 91). Copenhagen: WHO Regional Publications Retrieved from www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf.

World Health Organization Working Group (WHO). (2000b). Evaluation and Use of Epidemiological Evidence for Environmental Health Risk Assessment: WHO Guidance Document. Environmental Health Perspectives, 108(10), 997- 1002.

World Health Organization (WHO). (2006). Environmental Health Criteria 237: Principles for Evaluation Health Risks in Children Associated with Exposure to Chemicals. Retrieved from whqlibdoc.who.int/publications/2006/924157237X_eng.pdf.

World Health Organization (WHO). (2010). Guidance for Immunotoxicity Risk Assessment for Chemicals, Draft. Retrieved from www.who.int/ipcs/methods/harmonization/areas/immunotoxicity.pdf.

# Appendix A: Glossary

***NOTE**: The following terms are used in this document. To the extent possible, definitions were taken from the IRIS Glossary 2003.*

**Acute Exposure**: Exposure by the oral, dermal, or inhalation route for 24 hours or less.

**Acute Toxicity**: Any poisonous effect produced within a short period of time following an exposure, usually 24 to 96 hours.

**Adverse Effect**: 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.

**Aggregate:** The combined exposure of an individual (or defined population) to a specific agent or stressor via relevant routes, pathways, and sources.

**Air Monitoring Comparison Value (AMCVs):** AMCVs are chemical-specific air concentrations set to protect human health and welfare. Exposure to an air concentration at or below the AMCV is not likely to cause an adverse health effect in the general public, including sensitive subgroups such as children, the elderly, pregnant women, and people with preexisting health conditions. However, AMCVs may not protect individuals who exhibit idiosyncratic responses which cannot be predicted based on health effects studies. AMCVs are used in the air monitoring process to evaluate the potential for adverse effects to occur as a result of exposure to predicted concentrations of air contaminants. They are comparison levels, not ambient air standards. If predicted airborne levels of a chemical exceed its AMCV, adverse health or welfare effects would not necessarily be expected to result, but a more in-depth review would be triggered. For chemicals with thresholds, the health-based AMCV is equal to the reference value.

**Benchmark Dose (BMD) or Concentration (BMC)**: A dose or concentration that produces a predetermined change (called the benchmark response or BMR) in a specified response rate of an adverse effect compared to background.

**BMDL or BMCL**: A statistical lower confidence limit on the dose or concentration at the BMD or BMC, respectively.

**Benchmark Response (BMR)**: A predetermined response rate change for an adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. For quantal responses (as opposed to continuous response) the change in response rate over background corresponding to the BMR is usually in the range of 5-10%, which is the limit of responses typically observed in well-conducted animal experiments.

**Bioassay**: An assay for determining the potency (or concentration) of a substance that causes a biological change in experimental animals.

**Cancer**: A disease of heritable, somatic mutations affecting cell growth and differentiation, characterized by an abnormal, uncontrolled growth of cells.

**Carcinogen**: An agent capable of inducing cancer.

**Categorical variable:** A variable that is restricted to a finite number of possible values. Categorical variables are usually names or labels such as gender, health status, and type of job. Categorical variables may also be labels for groups of discrete or continuous

variable values. For example, body weight under 100 pounds might be labeled 1; body weight between 100 and 200 pounds might be labeled 2; and body weight over 200 lbs might be labeled 3; in which case this label would be a categorical variable.

**Children:** Individuals from conception to 18 years of age

**Chronic Exposure**: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans. This time period corresponds to 90 days to 2 years in commonly used mammalian laboratory species.

**Chronic Toxicity**: The capacity of a substance to cause adverse human health effects as a result of chronic exposure.

**Continuous variable:** A variable that can take on any value between its minimum value and its maximum value. Continuous variables typically correspond to measurements. For example, body weight is a continuous variable if the weight can be measured to as many decimal points as desired and is not restricted to be a whole number of units.

**Critical Effect**: The first adverse effect, or its known precursor, that occurs in the most sensitive relevant species as the dose rate of an agent increases.

**Cumulative:** The combined risks from aggregate exposures to multiple agents or stressors.

**Developmental Toxicity**: Adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally until the time of sexual maturation. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth, and functional deficiency.

**Discrete variable:** A variable that is restricted to a countable number of possible values. For example, if body weight is restricted to a whole number of pounds (or kilograms), then body weight is discrete.

**Dose**: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The POTENTIAL DOSE (or administered dose) is the amount ingested, inhaled, or applied to the skin. The APPLIED DOSE is the amount presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). The ABSORBED DOSE is the amount crossing a specific absorption barrier (e.g. the exchange boundaries of the skin, lung, and digestive tract) through uptake processes. INTERNAL DOSE is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries. The amount of the chemical available for interaction with any particular organ or cell is termed the DELIVERED or BIOLOGICALLY EFFECTIVE DOSE for that organ or cell.

**Dose-Response Assessment**: A determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response. Response can be expressed as measured or observed incidence or change in level of response, percent response in groups of subjects (or populations), or the probability of occurrence or change in level of response within a population.

**Dose-Response Relationship**: The relationship between a quantified exposure (dose) and the proportion of subjects demonstrating specific biologically significant changes in incidence and/or in degree of change (response).

**Dosimetric Adjustment Factor (DAF):** A multiplicative factor used to adjust observed experimental or epidemiological data to human equivalent concentration for assumed ambient scenario.

**Effective Dose ($ED_{10}$) or Effective Concentration ($EC_{10}$)**: The dose or concentration corresponding to a 10% increase in an adverse effect, relative to the control response.

**Effects Screening Level (ESL):** ESLs are chemical-specific air concentrations set to protect human health and welfare. Exposure to an air concentration at or below the ESL is not likely to cause an adverse health effect in the general public, including sensitive subgroups such as children, the elderly, pregnant women, and people with preexisting health conditions. However, ESLs may not protect individuals who exhibit idiosyncratic responses which cannot be predicted based on health effects studies. ESLs are used in the air permitting process to evaluate the potential for adverse effects to occur as a result of exposure to predicted concentrations of air contaminants. They are comparison levels, not ambient air standards. If predicted airborne levels of a chemical exceed its ESL, adverse health or welfare effects would not necessarily be expected to result, but a more in-depth review would be triggered. For chemicals with thresholds, the health-based ESL is 70% lower than the reference value.

**Endpoint**: An observable or measurable biological event or chemical concentration (e.g., metabolite concentration in a target tissue) used as an index of an effect of a chemical exposure.

**Epidemiology**: The study of the distribution and determinants of health-related states or events in specified populations.

**Exposure**: Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent (i.e., potential or administered dose) available at the exchange boundaries of the organism (e.g., skin, lungs, gut).

**Exposure-Response Assessment**: A determination of the relationship between exposure, which has elements of both magnitude and temporality, and a specific biological response. Response can be expressed as measured or observed incidence or change in level of response, percent response in groups of subjects (or populations), or the probability of occurrence or change in level of response within a population.

**Exposure-Response Relationship**: The relationship between a quantified exposure and the proportion of subjects demonstrating specific biologically significant changes in incidence and/or in degree of change (response).

**Free-Standing NOAEL:** The highest dose that was administered in a toxicity study at which no adverse effects were observed

**Globally Harmonized System of Classification and Labeling of Chemicals (GHS)**: GHS is a system that addresses classification of chemicals by types of hazard and

proposes harmonized hazard communication elements, including labels and safety data sheets. It aims at ensuring that information on physical hazards and toxicity from chemicals is available in order to enhance the protection of human health and the environment during the handling, transport and use of these chemicals. The GHS also provides a basis for harmonization of rules and regulations on chemicals at national, regional and worldwide level, an important factor also for trade facilitation.

**Hazard**: A potential source of harm.

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

**Hazard Characterization**: A description of the potential adverse health effects attributable to a specific environmental agent, the mechanisms by which agents exert their toxic effects, and the associated dose, route, duration, and timing of exposure.

**Hazard Quotient (HQ):** The ratio of the potential chemical exposure level and the level at which no adverse effects are expected. This represents an estimate of hazard for a single chemical.

**Human Equivalent Concentration (HEC) or Dose (HED)**: The human concentration (for inhalation exposure) or dose (for other routes of exposure) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration or dose. This adjustment may incorporate toxicokinetic information on the particular agent, if available, or use a default procedure, such as assuming that daily oral doses experienced for a lifetime are proportional to body weight raised to the 0.75 power.

**Immediately Dangerous to Life and Health (IDLH):** IDLH is a limit for personal exposure to a substance defined by the United States National Institute for Occupational Safety and Health (NIOSH), normally expressed in parts per million (ppm). This concentration is considered to be the limit beyond which an individual will not be capable of escaping death or permanent injury without help in less than thirty minutes.

**Incidence**: The number of new cases of a specified response (e.g., disease) that develop within a specified population over a specified period of time.

**Key Study**: The study that contributes most significantly to the qualitative and quantitative assessment of risk. Also called Principal or Critical Study; also called Principal or Critical Study.

**Lethal Concentration ($LC_{50}$):** A concentration of a pollutant or effluent at which 50% of the test organisms die; a common measure of acute toxicity.

**Linear Dose Response**: A pattern of frequency or severity of biological response that varies directly with the amount of dose of an agent. This linear relationship holds only at low doses in the range of extrapolation.

**Linear Exposure-Response**: A pattern of frequency or severity of biological response that varies directly with the amount of exposure of an agent. This linear relationship may hold (or be assumed to hold) only at low exposures in the range of extrapolation.

**Linearized Multistage Procedure**: A modification of the multistage model, used for estimating carcinogenic risk that incorporates a linear upper bound on extra risk for exposures below the experimental range.

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

**Margin of Exposure (MOE)**: The POD divided by the actual or projected environmental exposure of interest.

**Minimal Risk Level (MRL)**: An estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure.

**Mode of Action (MOA):** The key and obligatory steps that describe the alterations in cellular or organ function leading to toxicity.

**Model**: A mathematical function with parameters that can be adjusted so the function closely describes a set of empirical data. A mechanistic model usually reflects observed or hypothesized biological or physical mechanisms, and has model parameters with real world interpretation. In contrast, statistical or empirical models selected for particular numerical properties are fitted to data, and model parameters may or may not have real world interpretation. When data quality is otherwise equivalent, extrapolation using mechanistic models (e.g., biologically based dose-response or exposure-response models) often carries higher confidence than extrapolation using empirical models (e.g., logistic model).

**Modifying Factor (MF)**: A factor used in the derivation of a reference dose or reference concentration. The magnitude of the MF reflects the scientific uncertainties of the study and database not explicitly treated with standard uncertainty factors (e.g., the completeness of the overall database). An MF is greater than zero and less than or equal to 10, and the default value for the MF is 1. The TCEQ does not utilize an MF.

**Multistage Model**: A mathematical function used to extrapolate the probability of cancer from animal bioassay data, using the form:

$$P(d) = 1 - e^{-(q_0+q_1 d+q_2 d^2+\cdots+q_k d^k)}$$

Where:

P(d) = the probability of a tumor (or other specified response) from lifetime continuous exposure at level d;
$q_i$ = fitted model parameters, i=0, 1, ..., k;
k = usually restricted to be no greater than the number of dose (or exposure) levels -1.

**Multistage-Weibull Model**: A mathematical function used to extrapolate the probability of cancer from animal bioassay data, using the form:

$$P(d,t) = 1 - e^{-(q_0+q_1 d+q_2 d^2+\cdots+q_k d^k)(t-t_0)^z}$$

Where:

P(d,t) = the probability of a tumor (or other response) from lifetime, continuous exposure at dose d until age t (when tumor is fatal)
$q_i$ = fitted dose parameters, i=0, 1, …, k
k = no greater than the number of dose groups – 1
t0 = the time between when a potentially fatal tumor becomes observable and when it causes death
z = fitted time parameter (also called "Weibull" parameter)

**Neoplasm**: An abnormal growth of tissue which may be benign or malignant.

**No-Observed-Adverse-Effect Level (NOAEL)**: The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.

**No-Observed-Effect Level (NOEL)**: An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.

**Nonlinear Dose Response**: A pattern of frequency or severity of biological response that does not vary directly with the amount of dose of an agent. When MOA information indicates that responses may not follow a linear pattern below the dose range of the observed data, nonlinear methods for determining risk at low dose may be justified.

**Nonlinear Exposure-Response**: A pattern of frequency or severity of biological response that does not vary directly with the amount of dose (exposure) of an agent. When MOA information indicates that responses may not follow a linear pattern below the dose (exposure) range of the observed data, nonlinear methods for determining risk at low dose (exposure) may be justified.

**Occupational Exposure Limits (OELs)**: Values set by government agencies or other relevant organizations as limits for concentrations of hazardous compounds in workplace air. An OEL is the maximum average air concentration that most workers can be exposed to for an 8 hour work day, 40 hour work week for a working lifetime (40 years) without experiencing significant adverse health effects. A very small percentage of individuals experience some discomfort or adverse health effects at or below the exposure limit because of a wide variation in individual sensitivities or pre-existing conditions.

**Odds:** If the probability of a specified event is p, then the odds in favor of that specified event is:

$$\frac{p}{(1-p)}$$

**Odds Ratio (OR):** The odds of disease among exposed individuals divided by the odds of disease among unexposed.

**Permissible Exposure Limit (PEL):** The maximum permitted 8-hour time-weighted average concentration of an airborne contaminant; an Occupational Safety and Health Administration exposure value.

**Person-Years at Risk**: The number of years that an individual is at risk of responding to exposure. In a cohort, usually the person-years at risk include the time since start of follow-up or start of employment in the plants being studied and the time that the individual was observed.

**Physiologically Based Pharmacokinetic (PBPK) Model**: 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.

**Point of Departure (POD)**: The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response.

**Portal of Entry (POE)**: The tissue or organ of first contact between the biological system and the toxicant.

**ppb**: A unit of measure expressed as parts per billion. Equivalent to $1 \times 10^{-9}$.

**ppm**: A unit of measure expressed as parts per million. Equivalent to $1 \times 10^{-6}$.

**PPM-Years**: Units of exposure (ppm) in the epidemiology study corresponding to inhaling 10 $m^3$ per day for 5 days a week. PPM-years of exposure in the inference situation might correspond to environmental exposure of 20 $m^3$ per day for 7 days per week. The conversion from an environmental concentration relevant to the general population of 1 ppm to an occupational exposure concentration used in the estimated dose-response would be:

$$(1 \text{ ppm}) \times \left(\frac{20 \text{ m}^3}{10 \text{ m}^3}\right) \times \left(\frac{7 \text{ days}}{5 \text{ days}}\right)$$

Similarly, if the "slope" in an estimated occupational dose-response model is β per ppm-day, then that slope can be converted to units of ppm-years as follows:

$$\beta \times 356 \text{ per ppm-year}$$

**Quantitative Structure Activity Relationship (QSAR):** Quantitative structure activity relationships (QSARs) use a mathematical relationship to link chemical structure and pharmacological activity in a quantitative manner for a series of compounds.

**Random Variable:** A function that associates a unique numerical value with every outcome of an experiment.

**Reactivity**: The propensity of a chemical for dissociation as well as the ability to serve as a substrate for metabolism in the respiratory tract.

**Reference Concentration (RfC)**: 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. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments.

**Reference Dose (RfD)**: An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments.

**Reference Exposure Level (REL)**: The concentration level at or below which no adverse health effects are anticipated for a specified exposure duration.

**Reference Value (ReV)**: An estimation of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another suitable POD, with uncertainty/variability factors applied to reflect limitations of the data used.

**Regional Deposited Dose (RDD)**: The deposited dose of particles calculated for a respiratory tract region of interest as related to an observed toxicity. For respiratory effects of particles, the deposited dose is adjusted for ventilatory volumes and the surface area of the respiratory region effected (mg/min-sq. cm). For extra respiratory effects of particles, the deposited dose in the total respiratory system is adjusted for ventilatory volumes and body weight (mg/min-kg).

**Regional Deposited Dose Ratio (RDDR)**: The ratio of the regional deposited dose calculated for a given exposure in the animal species of interest to the regional deposited dose of the same exposure in a human. This ratio is used to adjust the exposure effect level for interspecies dosimetric differences to derive a human equivalent concentration for particles.

**Regional Gas Dose (RGD)**: The gas dose calculated for the region of interest as related to the observed effect for respiratory effects. The deposited dose is adjusted for ventilatory volumes and the surface area of the respiratory region affected (mg/min-sq.cm).

**Regional Gas Dose Ratio (RGDR)**: The ratio of the regional gas dose calculated for a given exposure in the animal species of interest to the regional gas dose of the same exposure in humans. This ratio is used to adjust the exposure effect level for interspecies dosimetric differences to derive a human equivalent concentration for gases with respiratory effects.

**Relative Potency/Relative Toxicity**: The dose of a reference compound required to cause a particular incidence of a specific toxic response divided by the dose of a test compound needed to cause an equal incidence of that same effect.

**Relative Risk (RR):** The relative risk ratio, or more simply the relative risk, is the probability of a specified event occurring in the exposed group divided by the probability of a specified event occurring in the non-exposed group.

**Risk** (in the context of human health): The probability of adverse effects resulting from exposure to an environmental agent or mixture of agents.

**Risk Assessment** (in the context of human health): The evaluation of scientific information on the hazardous properties of environmental agents (hazard characterization), the dose-response relationship (dose-response assessment), and the extent of human exposure to those agents (exposure assessment). The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree (risk characterization).

**Risk Characterization** (in the context of human health): The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.

**Risk Management** (in the context of human health): A decision making process that accounts for risk-related information together with political, social, economic and engineering implications in order to develop, analyze, and compare management options and select the appropriate managerial response to a potential chronic health hazard.

**Sensitivity**: The capacity for higher risk due to the combined effect of susceptibility (biological factors) and differences in exposure.

**Short Term Exposure Limit (STEL):** A 15-minute time-weighted average exposure which is not to be exceeded at any time during a workday even if the 8-hour time-weighted average is below the PEL; an occupational exposure value.

**Standardized Mortality Ratio (SMR):** The ratio of observed deaths in a study population to the expected number of deaths calculated for a specified standard population usually comparable to the population being observed.

**Structure Activity Relationship (SAR):** Structural activity relationships (SARs) can be described as the relationship of the molecular structure of a chemical with a physicochemical property, environmental fate attribute, and/or specific effect on human health or an environmental species.

**Subchronic Exposure**: Exposure to a substance spanning approximately 10% of the lifetime of an organism.

**Subacute Exposure**: Repeated or continuous exposure to a chemical for 1 month or less.

**Sufficient Evidence**: A term used in evaluating study data for the classification of a carcinogen under the 1986 U.S. EPA guidelines for carcinogen risk assessment. This classification indicates that there is a causal relationship between the agent or agents and human cancer.

**Superfund**: Federal authority, established by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) in 1980, to respond directly to

releases or threatened releases of hazardous substances that may endanger health or welfare.

**Supporting Studies**: Studies that contain information useful for providing insight and support for conclusions.

**Susceptibility**: 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).

**Susceptible Subgroups**: May refer to life stages, for example, children or the elderly, or to other segments of the population, for example, asthmatics or the immune-compromised, but are likely to be somewhat chemical-specific and may not be consistently defined in all cases.

**Systemic Effects or Systemic Toxicity**: Toxic effects as a result of absorption and distribution of a toxicant to a site distant from its entry point.

**Target Organ**: The biological organ(s) most adversely affected by exposure to a chemical, physical, or biological agent.

**Threshold**: The dose or exposure below which no deleterious effect is expected to occur.

**Threshold of Concern (TOC):** TOC can be defined as a conservative screening approach that is used to identify exposure levels that are unlikely to produce adverse health effects under specific exposure conditions.

**Threshold Limit Value (TLV)**: Recommended guidelines for occupational exposure to airborne contaminants published by the ACGIH. TLVs represent the average concentration in mg/m3 for an 8-hour workday and a 40-hour work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

**Toxic Equivalency Factor (TEF):** Factors that compare the relative toxicity of each dioxin and dioxin-like compound to the toxicity of the most highly studied dibenzo-p-dioxin, 2,3,7,8-TCDD. These factors or TEFs are used to calculate the toxicity equivalence or TEQ of a mixture of “dioxins,” which is the amount of 2,3,7,8-TCDD it would take to equal the combined toxic effect of all the “dioxins” and “dioxin-like” compounds found in the mixture.

**Toxicity**: Deleterious or adverse biological effects elicited by a chemical, physical, or biological agent.

**Toxicodynamics**: The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (sometimes referred to as pharmacodynamics).

**Toxicokinetics**: The determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of chemicals (sometimes referred to as pharmacokinetics).

**Toxicology**: The study of harmful interactions between chemical, physical, or biological agents and biological systems.

**Toxic Substance**: A chemical, physical, or biological agent that may cause an adverse effect or effects to biological systems.

**Tumor**: An abnormal, uncontrolled growth of cells. Synonym: neoplasm

**Uncertainty**: Uncertainty occurs because of a lack of knowledge. It is not the same as variability. For example, a risk assessor may be very certain that different people drink different amounts of water but may be uncertain about how much variability there is in water intakes within the population. Uncertainty can often be reduced by collecting more and better data, whereas variability is an inherent property of the population being evaluated. Variability can be better characterized with more data but it cannot be reduced or eliminated. Efforts to clearly distinguish between variability and uncertainty are important for both risk assessment and risk characterization.

**Uncertainty Factor** (UF): One of several, generally 10-fold, default factors used in operationally deriving the RfD and RfC from experimental data. The factors are intended to account for: (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) uncertainty associated with an incomplete database.

**Unit Risk**: The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/L in water, or 1 $\mu g/m^3$ in air. The interpretation of unit risk would be as follows: if unit risk = $1.5 \times 10^{-6}$ μg/L, 1.5 excess tumors are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 μg of the chemical in 1 liter of drinking water.

**Upper bound**: A statistical estimate of the upper limit for the value of a quantity.

**Variability**: Variability refers to true heterogeneity or diversity. For example, among a population that drinks water from the same source and with the same contaminant concentration, the risks from consuming the water may vary. This may be due to differences in exposure (i.e., different people drinking different amounts of water and having different body weights, different exposure frequencies, and different exposure durations) as well as differences in response (e.g., genetic differences in resistance to a chemical dose). Those inherent differences are referred to as variability. Differences among individuals in a population are referred to as inter-individual variability, differences for one individual over time is referred to as intra-individual variability.

**Weight of Evidence (WOE) for Carcinogenicity**: A system used by the USEPA for characterizing the extent to which the available data support the hypothesis that an agent causes cancer in humans. Under USEPA's 1986 risk assessment guidelines, the WOE was described by categories "A through E", Group A for known human carcinogens through Group E for agents with evidence of noncarcinogenicity. The approach outlined in USEPA's Guidelines for Carcinogen Risk Assessment (2005a) considers all scientific information in determining whether and under what conditions an agent may cause

cancer in humans, and provides a narrative approach to characterize carcinogenicity rather than categories.

# Appendix B: OEHHA's (1999) Classification of Severity Levels

**Table B- 1 USEPA Effect Severity Levels (USEPA 1994) and Corresponding OEHHA Levels (OEHHA 2008)**

| USEPA Severity Level | Effect Category | Effect | OEHHA Effect Severity Level |
|---|---|---|---|
| 0 | NOEL | No observed effects. | < Mild |
| 1 | NOAEL | Enzyme induction or other biochemical change, consistent with possible mechanism of action, with no pathologic changes and no change in organ weights. | < Mild |
| 2 | NOAEL | Enzyme induction and subcellular proliferation or other changes in organelles, consistent with possible mechanism of action, but no other apparent effect. | < Mild |
| 3 | NOAEL | Hyperplasia, hypertrophy, or atrophy, but without changes in organ weight. | ≤ Mild |
| 4 | NOAEL/LOAEL | Hyperplasia, hypertrophy, or atrophy, with changes in organ weight. | Mild |
| 5 | LOAEL | Reversible cellular changes including cloudy swelling, hydropic change, or fatty changes. | Mild / Severe |
| 6 | (LO)AEL | Degenerative or necrotic tissue changes with no apparent decrement in organ function. | Severe |
| 7 | (LO)AEL/FEL | Reversible slight changes in organ function. | Severe |
| 8 | FEL | Pathological changes with definite organ dysfunction that are unlikely to be fully reversible. | Severe |
| 9 | FEL | Pronounced pathological change with severe organ dysfunction and long-term sequelae. | Severe |
| 10 | FEL | Life-shortening or death. | Life-threatening |

*NOEL* – no observed effect level; *NOAEL* – no observed adverse effect level; *LOAEL* – lowest observed adverse effect level; *AEL* – adverse effect level; *FEL* – frank effect level

**Table B- 2 OEHHA (2008) Categorization of Adverse Health Effects into Severity Levels [1]**

| Acute Exposure Level | Symptoms | Signs/Laboratory Findings |
|---|---|---|
| Mild Adverse | Mild subjective complaints with few to no objective findings:<br>Mild mucous membrane (eye, nose, throat) irritation<br>Mild skin irritation<br>Mild headache, dizziness, nausea | Statistically significant findings of preclinical significance:<br>Mild conjunctivitis<br>Mild lung function changes [2]<br>Abnormal immunotoxicity test results<br>Mild decreases in hemoglobin concentration |
| Severe Adverse | Potentially disabling effects that affect one's judgment and ability to take protective actions; prolonged exposure may result in irreversible effects:<br>Severe mucous membrane irritation<br>Blurry vision<br>Shortness of breath, wheezing<br>Severe nausea<br>Severe headache<br>In coordination<br>Drowsiness<br>Panic, confusion | Clinically significant findings:<br>Findings consistent with central or peripheral nervous system toxicity<br>Loss of consciousness<br>Hemolysis<br>Asthma exacerbation<br>"Mild" pulmonary edema<br>Clinically significant lung function changes [2]<br>Cardiac ischemia<br>Some cardiac arrhythmias (e.g., atrial fibrillation)<br>Renal insufficiency<br>Hepatitis<br>Reproductive/developmental Endpoints (e.g., infertility, spontaneous abortion, congenital anomalies) |
| Life-threatening | | Potentially lethal effects:<br>Severe pulmonary edema<br>Respiratory arrest<br>Ventricular arrhythmias<br>Cardiac arrest |

[1] This table is intended to provide examples of health effects commonly considered for each level. It is not meant to be a comprehensive list of all possible health effects. Please refer to OEHHA (1999).
[2] Refer to Table E-3 for detailed categorization of lung function tests.

**Table B- 3 System for Categorization of Pulmonary Function into Effect Severity Levels (OEHHA 2008)**

| Endpoint [1] | Mild | Severe | Life-Threatening |
|---|---|---|---|
| Spirometry Test Result (compared to baseline) | Statistically significant but <20% decrement in $FEV_1$ [2] | > 20% decrement in $FEV_1$ | Not applicable |
| Methacholine Challenge Test Result | ≥ 100% increase in specific airway resistance ($SR_{aw}$) or<br><br>≥ 50% decrease in airway conductance ($SG_{aw}$)<br><br>No symptoms of bronchoconstriction<br><br>< 20% decrement in $FEV_1$ | 100% increase in specific airway resistence ($SR_{aw}$) or<br><br>50% decrease in airway conductance ($SG_{aw}$)<br><br>Accompanied by: (1) symptoms of bronchoconstriction or (2) > 20% decrement in $FEV_1$ | Not applicable |
| Clinical Findings | None anticipated | Chest tightness, shortness of breath, wheezing<br><br>Wheeze detected by examination<br><br>Hypoxia or decreased oxygen saturation | Status asthmaticus<br><br>Respiratory arrest |

[1] A finding under one endpoint category is sufficient to categorize a response into a particular severity level.
[2] Forced expiratory volume in one second

# Appendix C: White Paper on Child-Adult Differences in Inhalation Dosimetry of Gases

# White Paper on

# Child-Adult Differences in Inhalation Dosimetry of Gases:

# Application to Selected Systemically-Acting Volatile Organic Chemicals

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## 1.0 BACKGROUND

A number of scientific and policy initiatives beginning in the mid to late 1990s have resulted in increased attention to considerations of the risk to fetuses, infants, and children and consideration of how such risks should be evaluated. The U.S. EPA is explicitly mandated to consider fetuses, infants and children as potentially sensitive subpopulations. In 1995, EPA established an agency-wide policy that calls for consistent and explicit consideration of the risk to infants and children in all risk assessments and characterizations, as well as in environmental and public health standards (Memorandum from the Office of the Administrator, October 20, 1995). The Food Quality Protection Act (FQPA) of 1996 mandated that, in setting pesticide tolerances, an additional ten-fold margin of safety be applied to infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children, but noted that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." The Safe Drinking Water Act amendments of 1996 also stipulated that in establishing Maximum Contaminant Levels (MCLs) the Agency shall consider "the effect of such contaminants upon subgroups that comprise a meaningful portion of the general population (such as infants, children, pregnant women, the elderly, individuals with a history of serious illness or other subpopulations) that are identifiable as being at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." On April 21, 1997, President Clinton signed an Executive Order (13045) that federal health and safety standards must include an evaluation of the potential risks to children in planned regulations.

Similar policies have been initiated in Europe and Canada to evaluate more fully the potential differences in risk from chemical exposure to children. For example, a recent report by the European Environment Agency (EEA) and the World Health Organization (WHO) identified policy priorities for protecting children's health from environmental hazards (EEA and WHO 2002). The European Union also recently announced a new initiative, **S**cience, **C**hildren, **A**wareness, EU **L**egislation and Continuous **E**valuation (SCALE), focusing on children. In addition, Canada's Pesticide Management Regulatory Agency has developed a policy notice regarding children (Health Canada 2002), and the National Institute of Public Health and the Environment (RIVM) in the Netherlands has conducted research on pharmacokinetics of xenobiotics in children (de Zwart et al. 2002).[1]

1 The risk to adults and children could differ due to differences in exposure, toxicodynamics, or toxicokinetics. (Unless otherwise specified, the term child is used in this report to refer to the entire period between birth and attainment of physical and sexual maturity.) For example, differences in intake parameters or activity patterns (e.g., hand-to-mouth behavior in infants, children playing in dirt) can affect exposure. Toxicodynamic differences may result from windows of increased susceptibility in developing tissues. In addition, damage to developing tissue may manifest at a later stage in growth (de Zwart et al. 2002). Toxicokinetic differences may result from numerous age-related differences in absorption, distribution, metabolism, and excretion, and their resulting effect on internal dose of the active form of the chemical. These differences have been catalogued in numerous papers. This report focuses on the impact of toxicokinetic differences between adults and children.

These differences have led to research by a number of investigators comparing kinetic parameters in adults and children, and, where possible, comparing internal dose in adults and children. A number of studies have reviewed physiological and metabolic differences between adults and children (e.g., Renwick 1998; Ginsberg et al. 2002; Scheuplein et al. 2002; Wolterink et al. 2002; de Zwart et al. 2004; IPCS 2007). Determining the impact of these differences on internal dose is challenging. However, data on pharmaceuticals have been used to evaluate age-related differences in such parameters as clearance, half-life, area under the blood concentration-time curve (AUC) and blood concentration, and the resulting impact on internal dose (Renwick 1998; Renwick et al. 2000; Ginsberg et al. 2002, 2004; Hattis et al. 2003). These latter studies have concluded that the major differences are in the first six months of life, primarily in the first two months.

Hattis, Ginsberg, and colleagues have developed a substantial database of kinetic parameters for 44 chemicals (primarily pharmaceuticals), available at www2.clarku.edu/faculty/dhattis. This database has been used for a number of analyses describing variability of half-life with age and by metabolic enzyme class (e.g., CYP3A substrates, CYP1A2 substrates, etc.) (Ginsberg et al. 2002, 2004). These studies found that the average ratio of child:adult half-life for all substrates, and for most individual classes, was greater than 3 for premature neonates. The average ratio was also elevated for full-term neonates through about two months, depending on the substrate. The child half-life tended to be less than adult half-life in the six-month to two-year age range, with lower half-lives sometimes extending through 12 years, depending on the substrate.

These analyses, based primarily on pharmaceutical data, provide much useful information regarding the impact of age-related kinetic differences. However, there are a number of issues that need to be considered in extrapolating such data to environmental chemicals. Many of these issues have been described by Clewell et al. (2004). They include: (1) pharmaceuticals are usually water-soluble, while environmental chemicals are often lipophilic; (2) different metabolic systems may apply; (3) the parent is usually (though not always) the active agent for pharmaceuticals, while competing activation and detoxification reactions may be important for environmental chemicals; (4) pharmaceutical data are primarily for administration via the oral route; and (5) exposure to pharmaceuticals is usually at doses designed to cause an effect, meaning that it is at the upper end of the dose-response curve for therapeutic effectiveness, while exposure to environmental chemicals is typically at the low end of the dose-response curve. An additional factor is that much of the data collected on pharmaceuticals are based on half-life, and differences in half-life do not necessarily translate directly into differences in clearance (which is inversely related to AUC). Half-life needs to be corrected for volume of distribution to be related to clearance. While Ginsberg et al. (2002) concluded that differences in volume of distribution did not affect the elimination half-life for the drugs they studied, differences in volume of distribution may be more important for chemicals that are lipophilic, concentrate in other tissues, or bind significantly to plasma proteins.

To address these considerations, a number of analyses have been conducted with a focus on environmental chemicals. Age-specific metabolic and physiological data have been collected and collated in several studies (Renwick 1998; Hattis et al. 2003). PBPK models and other kinetic analyses (Haddad et al. 1999; Pelekis et al. 2001; Sarangapani et al. 2003; Ginsberg et al. 2004a; Clewell et al. 2004; Ginsberg et al. 2005; Price et al.

2003; Nong et al. 2006) and particle dosimetry models (Martonen et al. 2000; Ginsberg et al. 2005; Jarabek et al. 2005) have been used by several authors to evaluate age-related differences in kinetics. Consistent with results reported for pharmaceuticals (Renwick et al. 2000; Hattis et al. 2003), these authors found that the largest differences were in the first year of life. The largest differences were observed at the earliest time point (1 month of age), and differences were generally in the range of two-fold or less by 1 year. This is consistent with the early immaturity and development of enzyme systems.

As part of a project of the International Life Science Institute (ILSI) on evaluating children's risk from exposure to environmental chemicals, Daston et al. (2004) developed a framework for assessing children's risk, ranging from problem formulation through analysis and risk characterization, and Ginsberg et al. (2004) presented a framework for considering toxicokinetic issues related to children's risk, highlighting a number of questions and issues that need to be considered.

The purpose of this current report is to build on the frameworks developed as part of the ILSI process. The framework presented here (Figure 1) presents an analytical approach for evaluating the relative tissue dosimetry in adults and children for inhaled gases. Case studies were conducted for systemic effects of gases under various metabolic scenarios to provide some perspective on the potential range of internal dose in children and adults for various combinations of physicochemical characteristics and mode of action. Illustrative analyses are also presented on relative dosimetry for chemicals that show significant age-related variability in enzyme capacity. To illustrate the application of the framework and demonstrate consistency with more data-intensive approaches, the results of these analyses were compared with the results obtained using PBPK modeling for chemicals with similar metabolic characteristics.

The framework presented here reflects the input from a peer consultation with an expert panel. The initial peer consultation on an early draft provided substantial input on the structure of the framework. Based on this input, additional analyses were conducted, and a second peer consultation is being held to consider the revised framework, including the bounding analyses and case studies conducted as part of verification of the framework.

The framework focuses on the dosimetric comparison, i.e., a comparison of the mean internal dose in adults and children. This information is useful both for analyses of individual chemicals, and to aid risk assessors in identifying the parameters and chemical characteristics that result in children receiving a higher (or lower) internal dose than adults. Such information can provide useful perspective to individual chemical assessments, and can focus efforts for obtaining additional data and for more refined analyses to those cases and categories of chemicals where there is the greatest potential or likelihood of children being at greater risk. Although the focus is on mean dose, risk assessors and risk managers can use the dosimetry data, combined with information on variability, to evaluate the adequacy of default uncertainty factors for protecting children, or to determine if chemical-specific modifications to uncertainty factors are needed to adequately protect children. While there are a number of areas in which this initial framework can be enhanced and expanded, the intent is to provide a structure that highlights key issues and identifies some standard approaches. It is hoped that this report and framework will serve as a starting point for more in-depth analyses, and to focus

generic and chemical-specific research on the key issues for addressing children's risk due to kinetic differences.

## 2.0 FRAMEWORK

### 2.1 Overview

Figure 1 presents the draft framework for evaluating age-related differences in inhalation dosimetry and the resulting impact on internal dose. This framework, as well as the associated analyses presented below, is designed to help the risk assessor choose the appropriate tools and approaches to be applied for evaluating dosimetry differences between adults and children, as well as to identify chemical characteristics leading to markedly higher or lower internal dose for children compared to adults.

The first step in this process is to consider the duration of exposure, the nature of the critical effect and the mode of action for that effect. The initial decision point in this framework relates to the duration of exposure for which child-adult comparisons of dosimetry are intended. Chronic exposures will generally follow the right-hand side of the framework. The exception is if there is a window of vulnerability (based on toxicodynamic considerations). Such a critical window would mean that the effects and dosimetry associated with a shorter-term exposure would drive the assessment, and therefore the exposure would be considered using the same approach as used for acute exposures. Therefore, the left-side arm of the diagram will be described as "acute" for the rest of this discussion. The next consideration, applicable to both arms of the diagram, is whether the critical effect is systemic (i.e., remote effects) or local (i.e., portal of entry effects)[2] in nature. For gases and vapors that cause local effects (e.g., highly reactive or water soluble gases), the child-adult comparison is based on dose to the specific regions of the respiratory tract (section 2.2). However, for systemically-acting gases and vapors, child-adult comparisons would be based on active form (parent chemical or metabolite), its level (concentration or amount), and intensity (peak, average or integral), calculated using pharmacokinetic models and equations that reflect the attainment or not of steady-state during the specified exposure condition (section 2.3).

### 2.2 Evaluating child-adult differences in dosimetry of gases and vapors causing portal of entry effects (Category 1 and 2 gases under the U.S. EPA RfC scheme):

For chemicals that are highly reactive or highly water soluble, effects are often local in nature and as such estimates of the delivery of chemical to the various regions of the respiratory tract should be obtained. Typically the Category 1 gases and vapors do not accumulate significantly in blood, and as such systemic distribution and the extent of extrapulmonary effects is minimal or negligible (e.g., formaldehyde, hydrogen fluoride, chlorine, volatile organic esters). Category 2 gases (e.g., ozone, sulfur dioxide, xylenes, propanol) are moderately water soluble and rapidly reversibly reactive or slowly irreversibly metabolized in the respiratory tract. This lower reactivity means that they can both cause respiratory tract effects and accumulate in the blood, causing systemic effects.

[2]Respiratory effects occasionally occur as the result of systemic exposure from the endothelial side of the cell layer, or as a combination of both direct contact effect and systemic exposure. Such effects would be addressed using both the methods for systemic and portal of entry dosimetry.

For the respiratory tract effects of Category 1 and 2 gases, the airway regions such as larynx, trachea, bronchi and bronchioles cannot be considered as inert tubes carrying the chemical to the alveolar region. For these chemicals, several modeling approaches are useful, including the more sophisticated CFD (computational fluid dynamics) descriptions, that take into account the regional mass transfer coefficients, as well as surface area and ventilation rates (US EPA 1994; Kimbell et al. 1993; Asgharian et al. 1995; Hanna et al. 2001; Bogdanffy and Sarangapani 2003). Data on ventilation rates and pulmonary surface area for children of various age groups as well as adults are available in the literature (Clewell et al. 2002; Snodgrass 1992; Plunkett et al. 1992; U.S. EPA 1997). Hofmann (1982) published empirical equations to determine the length and diameter of the trachea, bronchial airways, and alveoli diameter in children as a function of age. These data, integrated within full-blown regional dosimetry models or steady-state solutions for these models, as appropriate, can be used to compute the child-adult differences in regional dosimetry (Hoffman 1982; Overton and Graham 1989; Martonen et al. 1989). In these approaches, the mass transported per surface area per unit time is calculated as follows:

$$\text{Flux} = V_E/SA\ (C_i - C_x) \qquad \text{Equation 1}$$

where $V_E$ is the ventilation rate, SA is the surface area of the region of interest, and $C_i$ and $C_x$ are the inlet and outlet concentrations, respectively (Hanna et al. 2001).

Depending upon the mode of action, the flux or another measure of dose metric (e.g., peak tissue concentration (Cmax), area under the tissue concentration vs time curve (AUC)) may be computed for evaluating child-adult differences in regional dosimetry gases and vapors causing direct respiratory tract effects. If the parent chemical is the toxic moiety implicated in the portal of entry effects, then the appropriate dose metric is likely to be Cmax for acute effects and AUC for chronic effects. When additional data on the nature and extent of toxic moiety-tissue interaction exist, they may permit the use of other mechanistically relevant dose metrics (e.g., pH alteration resulting from exposure to vinyl acetate, [Bogdanffy et al. 2001]).

### 2.3 Evaluating child-adult differences in dosimetry of gases and vapors causing systemic effects (Category 2 and 3 gases under the U.S. EPA RfC scheme):

Category 3 gases are relatively water-insoluble, with little reactivity in the respiratory tract and perfusion-limited uptake in the pulmonary region, uptake in the blood, and toxic effects usually occurring remotely. The approaches described in this section also apply to systemic effects of Category 2 gases. However, because Category 2 gases also react in the respiratory tract, the steady state equations described in this section may be less accurate for those gases. Differences between respiratory tract dose in adults and children (and therefore differences in the amount of chemical available for uptake to the blood) are not fully captured by the steady state equations presented here, but both the general approach of the framework and the general trends illustrated in the case studies in Section 3.3 would also apply to Category 2 gases.

For systemically-acting gases and vapors, the inhalation dosimetric adjustment between animals and humans has been conducted on the basis of the ratio of blood:air partition coefficients (U.S. EPA 1994). This approach, applied in the absence of PBPK models, is

most appropriate when (i) the parent chemical is the toxic moiety, (ii) hepatic and extrahepatic metabolism processes are not significant, and (iii) the arterial blood concentration attains steady-state during the relevant duration of exposures. Accordingly, for evaluating the child-adult differences in the dosimetry of Category 3 chemicals, the differences in blood:air partition coefficients may be evaluated. However, due to existing evidence on the child-adult differences in metabolic clearance, the direct application of the RfC default approach to evaluate age-related dosimetry differences for Category 3 gases and vapors may not be adequate. As indicated in Figure 1, the evaluation of child-adult differences in dosimetry for these chemicals may be conducted on the basis of whether the endpoint of interest is caused by the parent or a metabolite. For many chronic toxic effects, the concentration of the toxic form of chemical in target tissue integrated over time has been considered to be a reasonable dose metric (U.S. EPA 2006). Accordingly, the child-adult comparisons of internal dose of Category 3 chemicals may be conducted using the AUC or daily average of the dose metric. When the parent chemical is the toxic form, the average concentration in arterial blood (proportional to the AUC) during chronic exposures can be computed as: dose rate/clearance. Whereas the dose rate is determined by the inhaled concentration and alveolar ventilation rate, the clearance is the net result of the pulmonary, metabolic (hepatic and extrahepatic) as well as renal elimination processes, all of which are to known vary as a function of age (Clewell et al. 2002).

The next consideration is whether the toxic effect is due to the parent, a stable metabolite, or a reactive metabolite. IPCS (2005) discusses considerations and data that can be used to make this determination.

The child-adult differences in dosimetry of Category 3 gases and vapors, for which parent chemical is the toxic moiety, can be evaluated using a steady-state algorithm of the following form:

$$\mathrm{CA_{ss}} = \frac{\mathrm{QP}\times\mathrm{CI}}{\mathrm{QP/PB}+\mathrm{QL}\times\mathrm{E}} \qquad \text{Equation 2}$$

where CAss is the arterial blood concentration; QP is the alveolar ventilation rate, CI is the chemical concentration in inhaled air, QL is liver blood flow, E is hepatic extraction ratio; and PB is the blood:air partition coefficient.

Using the age-specific values for each of the above parameters, CAss can be computed and compared among the different age groups. There is no need to perform calculations of steady-state concentrations of chemicals in target tissues (as opposed to arterial blood concentration) because: (i) target tissue concentrations are proportional to CAss as defined by the partition coefficients (Lam et al. 1982; Krishnan 2007; Pelekis et al. 1997), and (ii) there is no evidence to date that indicates the tissue water and lipid contents would be significantly different, particularly for children aged >3 months in comparison with adults (Price et al. 2003; White et al. 1991; Woodward and White 1986).

For Category 3 gases which exert their toxicity via the formation of reactive metabolites, the child-adult dosimetry comparison can be conducted on the basis of the rate of metabolism in the tissue (i.e., amount per L tissue per unit time). The steady-state rate of

metabolism (i.e., average during chronic exposures) may be calculated on the basis of the steady-state arterial blood concentration (Equation 3). In this case then,

$AMT = (CA_{ss} \times QL \times E)/VL$ Equation 3

where AMT = amount of metabolite formed per unit time per unit volume of tissue, $CA_{ss}$ = arterial blood concentration of the parent chemical, QL = hepatic blood flow rate, E = hepatic extraction ratio and VL = liver volume.

For Category 3 chemicals producing stable or circulating metabolites, the rate of clearance of the metabolite in both adults and children should be additionally taken into account for calculating the dosimetry differences (Figure 1). In the case of metabolites, the clearance via kidney is likely to become more important (compared to parent form of Category 3 gases) such that child-adult differences in glomerular filtration rate (Clewell et al. 2002) might play an important role in determining the magnitude of the dose differences between various age groups. The steady-state equation in such cases would be of the following form:

$$\text{Cmet} = \frac{\text{CA}_{\text{ss}} \times \text{QL} \times \text{E}}{\text{CL}_{\text{metabolite}}}$$ Equation 4

Steady-state is achieved rapidly for gases and vapors that have a low volume of distribution and those that are cleared effectively by the biochemical processes. Category 3 gases generally have low blood:air partition coefficients but variable fat:blood partition coefficients (Table 1). U.S. EPA (1994), based on PBPK modeling in rats, indicated that steady-state is attained during subchronic or chronic inhalation exposures to gases with a blood:air partition coefficient < 100 and fat:blood partition coefficient < 100. In effect, almost all of the known Category 3 gases and vapors are expected to attain steady-state during continuous inhalation exposures in humans, even though only the proof of concept is available (Pelekis et al. 1997). In such cases, the use of a steady-state algorithm is likely to be sufficient for evaluating child-adult differences in dosimetry. The same approach is applicable to “acute” scenario, if the parent compound is the toxic agent and steady state is reached. However if the steady state is not reached in the “acute” scenario, regardless of whether toxic moiety is the parent chemical or metabolite (reactive or stable), the child-adult difference in systemic uptake and internal dose may be computed using full-blown physiologically-based pharmacokinetic (PBPK) models.

It is recognized that for several chemicals, based on the current state of knowledge of the mode of action, greater or less information may be available. For example, information on the extent of receptor occupancy, DNA adducts in target site, depletion of glutathione in target tissues, etc. can be used for estimating the child-adult differences in internal dose; however, such data are often not available. In fact, for many chemicals, the appropriate dose metric is not known. In such cases, it is reasonable to use the AUC of the parent chemical as the dose surrogate (U.S. EPA 2000, 2006; Clewell et al. 2002) and evaluate the child-adult differences in dosimetry. This is consistent with the approach for calculating Human Equivalent Concentrations (HECs) under the U.S. EPA’s RfC guidance (U.S. EPA 1994). However, in such cases, the assessor should note the uncertainty introduced by this assumption, and include appropriate caveats.

For some chemicals, limited information may be available for the estimation of chemical-specific kinetic parameters needed for the application of the proposed framework. In those cases, information from a surrogate compound with similar chemical properties or structure activity relationships may be useful in evaluating potential child-adult differences. For example, Beliveau et al. (2003, 2005) used quantitative structure-property relationships to estimate partition coefficients and hepatic clearance for a number of volatile organic compounds. Again, the risk assessors would need to consider any uncertainty introduced by the reliance upon information for a surrogate.

## 3.0 ANALYSES: APPLICATION OF THE CHILD-ADULT FRAMEWORK TO CHEMICALS WITH SYSTEMIC EFFECTS (CATEGORY 2 AND CATEGORY 3 GASES)

### 3.1 Introduction

The magnitude of child-adult differences in internal dose of Category 3 gases and vapors has been evaluated using age-specific physiological data as well as chemical-specific partitioning and clearance data in PBPK models or steady-state algorithms (Price et al. 2003; Pelekis et al. 2003; Clewell et al. 2004; Ginsberg et al. 2002; Hattis et al. 2003; Sarangapani et al. 2003). As outlined in Section 2, steady-state algorithms are adequate for estimating the magnitude of child-adult difference in the dosimetry of Category 3 gases when the toxic moiety is the parent chemical or a metabolite. The steady-state approach requires the knowledge of certain parameters that are known to vary as a function of age: alveolar ventilation rate, hepatic blood flow, liver volume and clearance (renal, hepatic and/or pulmonary). Most of the previous analyses estimated the child-adult magnitude in internal dose of Category 3 gases and vapors, using physiological parameters for children (particularly neonates) derived from adult values on the basis of an allometric or regression relationships (Clewell et al. 2004; Ginsberg et al. 2002; Sarangapani et al. 2003). In order to facilitate a broader understanding of the extent of child-adult differences in dosimetry for Category 3 gases as well as to identify situations and parameters leading to maximal magnitude of child-adult differences in the dosimetry for these gases, the present study conducted a number of bounding analyses and case studies in various age groups: (neonates (3 months), toddlers (1 year), preschooler (5 years), middle schooler (10 years)). Accordingly, calculations of internal dose (i.e., steady-state concentration of parent chemical in blood, steady-state concentration of reactive metabolite in liver, and steady-state concentration of circulating metabolite in the body) in adults and children of various age groups were performed by setting hepatic clearance in children equal to (1) zero, (2) blood flow rate to the organ, or (3) a fraction of metabolic capacity of adults based on information on delayed enzyme ontogeny.

### 3.2 Approach

#### 3.2.1 Child-adult differences in dosimetry for Category 3 gases for which parent chemical is the toxic moiety

The steady-state blood concentration of Category 3 gases that are metabolized primarily in liver and eliminated by clearance processes in both liver and lung can be calculated with the knowledge of age-specific blood:air partition coefficient (Pb), alveolar ventilation rate (QP), hepatic blood flow rate (QL) and intrinsic clearance (CLint)

(Andersen 1981; Pelekis et al. 1997; Csanady and Filser 2001; Clewell et al. 2004). Available information suggest that neither the blood:air partition coefficient nor the composition of blood (lipid and water content) vary markedly as a function of age (Table 2) (Berenson et al. 1982; Lerman et al. 1984; White et al. 1991; Family Practice Notebook 2005). Therefore, the evaluation of child-adult differences in parent chemical concentrations can be performed with the knowledge of QP, QL and CLint for the various age groups, as well as using the Pb value for one of the age groups (usually adults).

The computation of steady-state blood concentration of Category 3 gases was performed on the basis of Eqn. 2 of the framework:

$$CA_{ss} = \frac{QP \times CI}{CLp + CLh}$$

where CAss = steady-state arterial blood concentration (µg/L), QP = alveolar ventilation rate (L/h), CI = inhaled concentraton (µg/L), CLp = pulmonary clearance (= QP divided by blood:air partition coefficient (PB)) and CLh = hepatic clearance (= CLint x QL/ (CLint + QL) where CLint = intrinsic clearance (= maximal velocity divided by Michaelis constant) and QL = hepatic blood flow rate (L/h).

The upper-bound of the magnitude of child-adult difference in CAss was calculated, initially, by assuming minimal metabolism in children (i.e., CLh = 0) and maximal metabolism in adults (i.e., CLh = hepatic blood flow rate) such that the hepatic extraction ratio equals 1. The calculations conducted under this scenario focused on identifying the maximal child-adult factor that is likely to be associated with Category 3 gases and vapors for which the parent form represents the toxic moiety. A second bounding analysis was conducted using Eqn. 2 for highly metabolized chemicals, for which hepatic clearance is blood-flow limited in both adults and children. The resulting child-adult ratios of CAss from this scenario would essentially reflect the lower-bound of the child-adult differences in internal dose. A third scenario involved the use of age-specific data on metabolizing enzyme capacity in Eqn. 2. Enzyme ontogeny data were used to estimate CLint in children on the basis of adult values as follows (Clewell et al. 2004; Nong et al. 2006):

$$CLint_{Child} = CLint_{Adult} * F * VL_{Child} / VL_{Adult},$$

where VL is the volume of liver and F is the enzyme activity as a fraction of the adult value. This particular approach was applied to hepatic CYP2E1 and alcohol dehydrogenase (ADH) using data summarized by Clewell et al. (2004).

### 3.2.2 Child-adult differences in dosimetry for Category 3 gases for which reactive metabolite is the toxic moiety

For Category 3 gases exerting toxicity via reactive metabolites, the child-adult dosimetry comparisons of internal dose (i.e., amount per L tissue per unit time) was computed on the basis of Eqn. 3 of the framework:

$$AMT_{Reactive\ metabolite} = (CA_{ss} \times CLh)/VL$$

The magnitude of child-adult differences in internal dose was calculated for the three scenarios described in section 3.1. Accordingly, the CLh value was first set to 0 in children and to QL in adults, as a bounding case. Then, the CLh was set equal to hepatic blood flow in both children and adults, to compute an upper bound of the child-adult difference in internal dose of reactive metabolites. Finally, the age-specific CLh was computed according to the information on the relative content of metabolizing enzyme (CYP2E1, ADH) in children relative to adults.

### 3.2.3 Child-adult differences in dosimetry for Category 3 gases for which circulating metabolite is the toxic moiety

As noted above, for calculating the internal dose of stable or circulating metabolites, the clearance of metabolites subsequent to their formation should be taken into account (Krishnan and Andersen 1991; Sarangapani et al. 2003; Gentry et al. 2002). Because kidney clearance is likely to play an important role for such metabolites, child-adult differences in glomerular filtration rate need to be taken into account in determining the magnitude of the dose differences between various age groups. The steady-state equation for computing the internal concentration[3] of circulating metabolites (as shown in section 2.3) is:

$$C_{\text{Stable metabolite}} = \frac{CA_{ss} \times QL \times E}{CL_{\text{metabolite}}}$$

The magnitude of child-adult differences in internal dose was initially calculated for the three scenarios described in section 3.2.1. (i.e., bounding case, flow-limited clearance, delayed ontogeny of metabolizing enzymes). For all three scenarios, $CL_{metabolite}$ was assumed to be adequately represented by renal clearance which was set equal to the age-specific value of glomerular filtration rate (GFR). Additionally, calculation of $C_{Stable\ metabolite}$ was done for a situation in which $CL_{metabolite}$ is determined by both renal and metabolic clearance processes, subsequent to flow-limited metabolism of parent chemical in adults and children. This particular scenario facilitates the evaluation of an extreme case of child-adult difference in internal dose, in which the capacity-limited difference in clearance of metabolite and flow-limited clearance of parent chemicals might both apply and result in higher child-adult dose ratio (Clewell et al. 2004; Sarangapani et al. 2003; Ginsberg et al. 2005).

### 3.2.4 Parameter and data sources

For the analyses presented here, the value of CI for all age groups was set to 1 µg/L in air. The physiological parameters (QP, QL and VL) for the children of various age groups were obtained from Price et al. (2003), whereas those for adults were obtained from Arms and Travis (1988). The delayed development of renal function (GFR) and liver metabolism (CYP2E1, ADH) in children was expressed as a fraction of the adult value based on data summarized by Clewell et al. (2004) and Sarangapani et al. (2003). For the various calculations, CLint was varied from 0.1 L/hr (capacity-limited metabolism) to 1000 L/hr (flow-limited metabolism), and the PB was varied between 0.1 and 50 (which generally reflects the values for commonly known Category 3 gases and vapors (Table

[3] Because the dose metric of interest is the concentration of the chemical, comparison of concentrations can be considered a comparison of internal dose.

1)). The internal dose at steady-state was calculated using Microsoft EXCEL® for each age group using Eqns. 2 – 4, and then the child-adult factors were derived for each of the three scenarios as ratios of internal doses.

## 3.3 Results

### 3.3.1 Child-adult differences in dosimetry for Category 3 gases for which parent chemical is the toxic moiety

Figures 2-3 summarize the results of child/adult steady-state concentration ratios for the first two scenarios of bounding cases, (1) upper bound based on zero metabolism in children of all age groups and maximal metabolism (i.e., equal to hepatic blood flow) in adults (scenario 1), and (2) lower bound based on flow-limited clearance in both adults and children (scenario 2). Figure 2 shows that the child:adult ratio of CAss would increase with increasing PB for scenario 1 when $E_{child} = 0$ and $E_{adult} = 1$. For this worst-case scenario, hepatic clearance was set to zero for all four ages of children, and so only one curve is shown. The increase of the child:adult ratio of CAss is a direct result of the fact the CAss in children in this scenario is determined only by pulmonary clearance, whereas in adults it is determined additionally by CLh. For chemicals with very low CLint values (e.g., 0.01 L/hr), hepatic clearance (CLh) is negligible compared to pulmonary clearance (CLp) such that the child/adult ratio of CAss approximates the ratio of PB in child and adult, which essentially is 1. For increasing CLint values, however, the child/adult ratio exceeds 1, with the actual magnitude being determined by the relative contributions of pulmonary clearance and hepatic clearance to total clearance in adults as well as the extent of the deviation of total clearance in adults from the pulmonary clearance in children. If $CLh_{adults}$ is near full capacity and $CLh_{child}$ is near zero (worst case scenario), then the child/adult ratio of CAss will continue to increase as a function of PB (Figure 2). At any given PB value, the lower bound of child/adult ratio for parent chemical dose can be simulated by assuming blood flow-limited metabolism in both adults and children (scenario 2; Figure 3). In this case, the maximal value of child/adult ratio of CAss (2.1) is associated with the age group of 3 month-old and gases with high PB values (e.g., 50) (Figure 3). When age group-specific metabolic capacity is known, a better estimate of the magnitude of child/adult ratio of CAss can be obtained, which should be between the upper and lower bound estimates presented above, as shown in scenario 3 with ADH and CYP2E1 as examples.

The results of the steady-state analysis for CAss based on age-dependent CYP2E1 and ADH activity are shown in Figures 4a and 4b, respectively (scenario 3)[4]. In both cases, the 3 month old, the youngest group evaluated, has the greatest difference in parent concentration relative to the adults. This is not surprising since the ADH and CYP2E1 are at the lowest levels at birth, and gradually increase to adult levels. Similar to the results obtained for scenarios 1 and 2, the highest child/adult ratio for CAss (approximately 2.3 for ADH) (Figure 4b) was associated with high CLint values (i.e., 1000 L/hr) reflective of flow-limited metabolism in adults but not necessarily in all other age groups. For gases with very low CLint values, however, the metabolism rate is unlikely to be a sensitive parameter in estimating CAss and thus the child/adult ratio is close to unity (not shown).

[4] Note: Ratio 3/A = 3 months:adult; 1/A = 1 year:adult; 5/A = 5 years:adult; 10/A = 10 years:adult

### 3.3.2 Child-adult differences in dosimetry for Category 3 gases for which reactive metabolite is the toxic moiety

Figure 5 depicts the child-to-adult ratio of the internal dose of reactive metabolite resulting from continuous exposure to Category 3 gases with PB values up to 50. Here, the upper bound of the child/adult ratios (shown in Figure 5) results when metabolism is flow-limited in both adults and children whereas the lower bound (i.e., zero) is associated with scenario 1 (i.e., when $CLh_{child}$ is zero and $CLh_{adults}$ is near full capacity). The highest value of the upper-bound of child-to-adult ratios of internal dose of reactive metabolites (1.45) was obtained for 10-year-old children. Under flow-limited conditions, the internal dose of reactive metabolites is determined by QL/VL which is about 33 in younger age groups (3 months to 5 years) and 47 in 10-year-old children, compared to 53 in adults (Price et al. 2003). The relative difference in these determinants between children and adults, coupled with the difference in CAss (section 3.3.1) would explain the magnitude of child-adult ratios in the liver concentration of reactive metabolites computed in this study (Figure 5).

Using information on delayed ontogeny of metabolizing enzymes (ADH and CYP2E1), it would appear that the internal dose of reactive metabolites for poorly metabolized Category 3 gases (assuming an intrinsic clearance of 0.1 L/hour) would be lower in children of all age groups compared to adults (Figures 6 for ADH and Figure 7 for CYP2E1). In case of highly metabolized gases (e.g., CLint = 1000 L/hour), however, the formation of reactive metabolites in older children (5 year old and 10 year old) and in the 3-month-old (but not in the 1-year-old) might slightly exceed the levels formed in adults (Figure 8). The quantitative behavior depicted in Figure 8 applies to both ADH and CYP2E1 (not shown).

### 3.3.3 Child-adult differences in dosimetry for Category 3 gases for which circulating metabolite is the toxic moiety

The child/adult ratios of the steady-state concentration of stable (circulating) metabolite were initially calculated on the basis of the rate of formation (i.e., hepatic metabolism of parent chemical) and rate of elimination (i.e., renal clearance of metabolite) for the three scenarios described in section 3.1. In this case, the upper bound of the child-adult ratios resulting from flow-limited metabolism in both adults and children combined with renal excretion as described by the developmental data, range between 0.9 – 1.3 (Figure 9). The lower bound of the child/adult ratio of the stable metabolite is essentially zero, which is associated with scenario 1 described in section 3.1. (i.e., when $CLh_{child}$ is zero and $CLh_{adults}$ is near full capacity). Calculations based on the delayed ontogeny of ADH and CYP2E1 enzymes involved in the formation of stable metabolites yield child/adult factors that are essentially in this range both for highly metabolized vapors and gases (Figures 10a for ADH and 10b for CYP2E1) and poorly metabolized ones (Figures 11a for ADH and 11b for CYP2E1).

The rate of formation of stable metabolite is determined by QL, E and CAss. Therefore, for flow-limited metabolism in both children and adults (i.e., when E=1), the values of QL and CAss would determine the magnitude of child/adult ratio of the amount of stable metabolites formed at steady-state. Given that child/adult ratio of CAss for Category 3 gases is within a factor of 2, and that the QL is about 14 times lower in neonates

compared to adults, the overall amount formed would be several times (up to 7-fold) lower in young children. However, since the GFR is also lower in neonates compared to adults (by a factor of about 7), the net effect is that the resulting child/adult ratio of steady-state concentration of circulating metabolite is about 1. The relative dose in children could be substantially higher if there is significant child-adult difference in metabolic clearance (e.g., when $CLh_{child}$ is zero and $CLh_{adults}$ is near maximum capacity). Figures 12-13 depict the adult/child factors for highly metabolized (Figure 12) and poorly metabolized (Figure 13) Category 3 gases and vapors, for which the toxic moiety is a stable metabolite cleared efficiently in adults (i.e., flow limited process) but not at all in children (i.e., hepatic extraction ratio = 0). The upper bound value for this child-adult difference would be approximately 17 (Figure 12); however, if the CLh of metabolites in children varies as a function of metabolic capacity of the enzymes involved (e.g., ADH or CYP2E1), then the child/adult factors are likely to be lower than these upper bound values.

## 4.0 DISCUSSION

This document presents a framework for evaluating relative dosimetry in children and adults for inhaled gases. For effects at the portal of entry, a range of potential approaches are noted; however, the focus of this analysis was for those gases or vapors expected to have an impact systemically, with the appropriate choice of approach depending on the chemical's mode of action. The framework presents specific considerations for systemic effects, with certain modes of action and exposure scenarios leading to recommended analytical approaches. Case studies were conducted to demonstrate the potential quantitative differences between children and adults for chemicals for which the parent, reactive metabolite, or stable metabolite is the toxic moiety of concern.

The differences in internal dose to adults and children evaluated by the framework have the largest impact under two scenarios. The first is when there is a window of increased susceptibility. If the window of susceptibility falls during childhood, the internal dose during that period of time is a key determinant of response, and it is important to consider the relative internal dose to children and adults for a given air concentration, regardless of the total exposure duration. The second situation when differences in the child and adult dose would be of particular interest is when the exposure duration is generally comparable to or shorter than the duration of the age range of interest. Although the approach used in the framework can be used to evaluate the relative dose to children and adults in scenarios involving longer durations of exposure, the impact on response would be much smaller when the response is related to lifetime exposure (e.g., when the appropriate metric is Lifetime Average Daily Dose, or LADD). This is because estimates of cumulative dose over a lifetime resulting from exposure to low concentrations of environmental chemicals are fairly insensitive to age-related kinetic differences, because the greatest differences persist for only a short time (Pelekis et al. 1997; Clewell et al. 2004). Thus, if toxicity for the relevant endpoint is related to cumulative dose, these increases in internal dose would not have a significant effect on risk, unless a window of susceptibility coincided with the period of increased dose.

It should also be noted that analyses presented here are a simplified approach and are not intended to be used quantitatively in risk assessment, in the absence of chemical-specific

data. Instead, the intent is to identify situations in which dose metrics in the child may be substantially different from those in the adult. The proposed framework would provide a potential screen to determine if the default toxicokinetic component is adequate when considering exposure to children, noting the additional need to consider variability.

### 4.1 Comparison with results in the literature

The analyses presented along with the framework were conducted to provide some initial direction regarding conditions under which there are significant dosimetric differences between adults and children. The results of these analyses are consistent with individual chemical-specific analyses in the literature. They suggest that the child/adult difference in steady state arterial concentration (CAss) of the parent chemical is likely to be within a factor of 2.1 for highly metabolized Category 3 gases and vapors. This observation is consistent with the conclusions of the detailed inhalation PBPK modeling studies conducted with selected Category 3 chemicals (furan: 1.5 (Price et al. 2003); styrene 1.8 and vinyl chloride 1.13 (Sarangapani et al. 2003). This is also consistent with the results of Ginsberg et al. (2005), who reported that the maximal child/adult factor for steady-state arterial blood concentration of parent chemicals belonging to Category 3 was 1.75, particularly for flow-limited metabolism in both adults and neonates. In the case of poorly metabolized gases and vapors, the child/adult ratio is likely to be about 1, since child-adult differences in metabolic clearance barely have an influence on the kinetics and internal dose, as shown in this study. This observation is consistent with that of Sarangapani et al. (2003) for perchlorethylene (child/adult ratio = 1.02), a poorly metabolized Category 3 vapor. Larger child/adult ratios would result in the hypothetical case where there is no hepatic clearance in the child and high hepatic clearance in the adult, but such extreme cases were not located in the chemical literature.

Regarding Category 3 gases forming reactive metabolites, the analyses conducted here indicate that the child-adult difference would be maximal when metabolism is flow-limited in adults and children. The maximal value of child-to-adult ratios of internal dose of reactive metabolites found in the present study (1.45) is comparable to those reported for vinyl chloride (1.34) and styrene (1.83) by Sarangapani et al. (2003). The small difference between the present study and the previous studies might be due to the derivation of liver blood flow values by the previous studies on the basis of difference in liver volume between children and adults. The present study, however, used liver blood flow values determined in children following radioactive gold administration (Szantay et al. 1974). The child/adult ratio of the internal dose of reactive metabolite approaches zero as the intrinsic clearance (Clint) becomes smaller (Figures 6 and 7). This is also in agreement with the results of the PBPK modeling study by Sarangapani et al. (2003) in which the child/adult ratio for a poorly metabolized Category 3 chemical (perchloroethylene) was reported to be 0.27.

For Category 3 gases forming stable metabolites, the analyses were based on the assumption that renal clearance would be the sole mechanism of elimination, or it considered both the renal and hepatic routes of clearance to be relevant. In the first case, the calculated ratios ranged from 0.9 to 1.3. However, the child/adult ratio increased if there was a significant child-adult difference in metabolic clearance of the metabolite. In the case of Category 3 gases and vapors for which the stable metabolite (toxic moiety) is

cleared efficiently in adults (i.e., flow limited process) but not at all in children (i.e., hepatic extraction ratio = 0), the child/adult ratio can be as high as 18. This is in accord with the observations of a PBPK modeling study of the formation and clearance of a stable metabolite (acetone from isopropanol), which reported a neonate/adult factor ranging from approximately 7 to 9 (Saragapani et al. 2003). Note also that isopropanol is a Category 2 gas, illustrating that the simplified steady state approaches described here give reasonable estimates of the relative systemic dose for children and adults, even for a moderately water soluble chemical. Further studies are required to systematically evaluate the relative contribution of renal, hepatic and pulmonary clearance processes to the total clearance of circulating metabolites formed from similar gases, as well as their overall contribution to the relative dose in children and adults, so as to be able to pinpoint characteristics of gases and vapors that might lead to situations where the dose to children is much higher than that to adults.

Quantitative differences between the examples presented here and previous published analyses were generally due to differences in the age-specific parameters. For example, in addition to the differences noted above regarding age-specific liver blood flow, there were differences in the alveolar ventilation rate (QP). Sarangapani et al. (2003) and Clewell et al. (2004) estimated the age-dependent alveolar ventilation as 66% of the pulmonary ventilation data compiled by U.S. EPA (1997). Because the alveolar dead space may vary with age, the current analysis focused on actual measured values when possible, using the approach of Price et al. (2003). Specifically, the QP for the 3-month old used measured data from Lees et al. (1967), and Price et al. (2003) developed a regression equation to calculate the QP values for ages 1, 5 and 10 years. Inputs to the development of the regression equation were age-specific data on respiratory frequency and tidal volume, and an equation relating physiological dead space to body weight.

The results presented here are also consistent with those of Ginsberg et al. (2005), who identified several conditions under which greater metabolite levels may occur in the infant liver than the adult liver. These conditions include: (1) highly metabolized gases; (2) Category 3 gases at 1 year of age for metabolism pathways that have reached full maturity by this age; and (3) cases where the metabolite formation rate is considerably greater than the metabolite removal rate and the metabolite removal rate involves a cytochrome P450 (CYP) or other pathway that is immature early in life. Except for the third group, these conditions do not consider removal of the metabolite. As another example of identification of the rate-limiting step, if a chemical is cleared primarily by glucuronidation, the low activity at early ages suggests that particular attention should be paid to urinary metabolites to determine whether adequate clearance occurs via alternative conjugation pathway (e.g., sulfation).

### 4.2 Potential enhancements to the framework and data needs

The framework presented here focuses on dosimetry comparisons between adults and children for inhaled gases and vapors. It could be further enhanced to consider variability, as part of evaluation of the appropriate intraspecies uncertainty factor. Only limited investigations were identified that evaluated variability within the child population. Pelekis et al. (2003) conducted PBPK modeling for methylene chloride using ranges for estimates of age-related physiological and biochemical parameters to develop annual

average concentrations as population distributions. This approach could be used to evaluate total population variability. Consideration of first principles would suggest that children would vary less than adults in many physiological parameters. While some physiological parameters (e.g., body fat) tend to exhibit greater variability at later ages, child variability in dose appears to be comparable to or greater than in adults. Renwick et al. (2000) reported that the magnitude of inter-individual variability in drug clearance (expressed as a percentage) is not influenced by age. However, Hattis et al. (2003) found that the neonates had greater variability for some, but not all drugs and metabolic pathways. Common pathogenic processes, such as asthma, may also alter the respiratory tract dimensions, and thus the dosimetry, in ways not accounted for in the current analysis (Ginsberg et al. 2005).

The framework focused on inhaled gases, and did not address inhaled particles or exposure via other routes. Extensive analyses of particle dosimetry have been conducted by Jarabek et al. (2005) and Ginsberg et al. (2005). Jarabek et al. (2005) used the Multiple Path Particle Dosimetry Model (MPPD)[5] to calculate the ratio of the human equivalent concentration (HEC) to laboratory animal exposure concentration for people ranging from 3 months to adulthood for poorly soluble nonfibrous particles (PSP) with mass median aerodynamic diameters (MMAD) ranging from 0.3 to 6 μm. The authors used a dose metric of retained mass in the tracheobronchial region normalized to surface area, taking into account deposition and clearance (but not age-specific clearance). Ginsberg et al. (2005) used the ICRP (Smith 1994) model to model deposited dose per unit surface area for 3-month-old infants and adults as a function of particle size. Martonen et al. (2000) developed a particle deposition model that takes into account structural elements of the lungs and used the model to calculate deposited dose per unit surface area as a function of particle size for four age groups. These sorts of analyses, along with analyses built on more recent data, such as the deposition calculations of Oldham and Robinson (2006), based on asymmetrical growth geometries of the tracheobronchial region, can be used to develop a framework for exposure to particles and aerosols. Similarly, frameworks for the oral and dermal routes of exposure would be useful. For example, the oral route would need to consider the implications of first-pass metabolism. Interagency efforts (Jarabek 2000; Rigas et al. 2000) to develop dosimetric approach for the oral route (in addition to dermal dosimetry and improved inhalation dosimetry) are likely to provide additional guidance for this route.

The intent of the proposed framework is to provide a structure for consideration of the implications of age-related kinetic differences for internal dose and to focus future research in this area. The results of the initial application of this framework suggests a selected number of data gaps, where additional research may help to refine analyses of age-related differences in dosimetry. These areas include: (1) age-dependence of blood:air partition coefficients; (2) liver blood flow for children less than 4 years of age; (3) enhanced understanding of age-dependent changes in enzyme activities; and (4) characterization of extrahepatic metabolism.

[5]Version 1.0, © CIIT and RIVM, 2002. Obtained from B. Asgharian, CIIT.

**Table 1. Compilation of Partition Coefficients for Some Category 3 Gases**

| Chemical | Blood:Air Partition Coefficient[1] | Fat:Blood Partition Coefficient[2] |
|---|---|---|
| Methyl chloride | 2.5 | 5.4 |
| Dichloromethane | 8.9 | 13 |
| Chloroform | 6.9 | 29 |
| Carbon tetrachloride | 2.7 | 133 |
| Chlorodibromomethane | 53 | 36 |
| Chloroethane | 2.7 | 14 |
| Vinyl Chloride | 1.2 | 17 |
| 1,1-Dichloroethane | 4.9 | 33 |
| 1,1,2-Trichloroethane | 36 | 40 |
| Benzene | 8.2 | 24 |
| Chlorobenzene | 30 | 43 |
| o-Xylene | 35 | 43 |
| m-Xylene | 33 | 56 |
| p-Xylene | 45 | 39 |
| Styrene | 48[3] | 72[4] |

[1]Gargas et al. (1989)
[2]Estimated based on rat Fat:Air partition coefficients and human Blood:Air partition coefficients reported by Gargas et al. (1989).
[3]Csanady et al. (1994)
[4]Estimated based on rat Fat:Air partition coefficient reported by Gargas et al. (1989) and human Blood:Air partition coefficient reported by Csanady et al. (1994).

**Table 2. Age-dependent Lipid and Water Content of Whole Blood**

| Age (yr) | % Lipid[1] | % Water[2] |
|---|---|---|
| 0 | 0.11 | 84 |
| 1/2 to 2 | 0.22 | 87 |
| 2 to 6 | 0.21 | 87 |
| 6 to 12 | 0.22 | 86 |
| 12 to 18 | 0.21 | 86 |
| Over 18 | 0.22 | 85 |

[1](Berenson et al. 1982)
[2](Family Practice Notebook, 2005)

**Figure 1. Revised framework for evaluating the relative tissue dosimetry in adults and children for inhaled gases.**

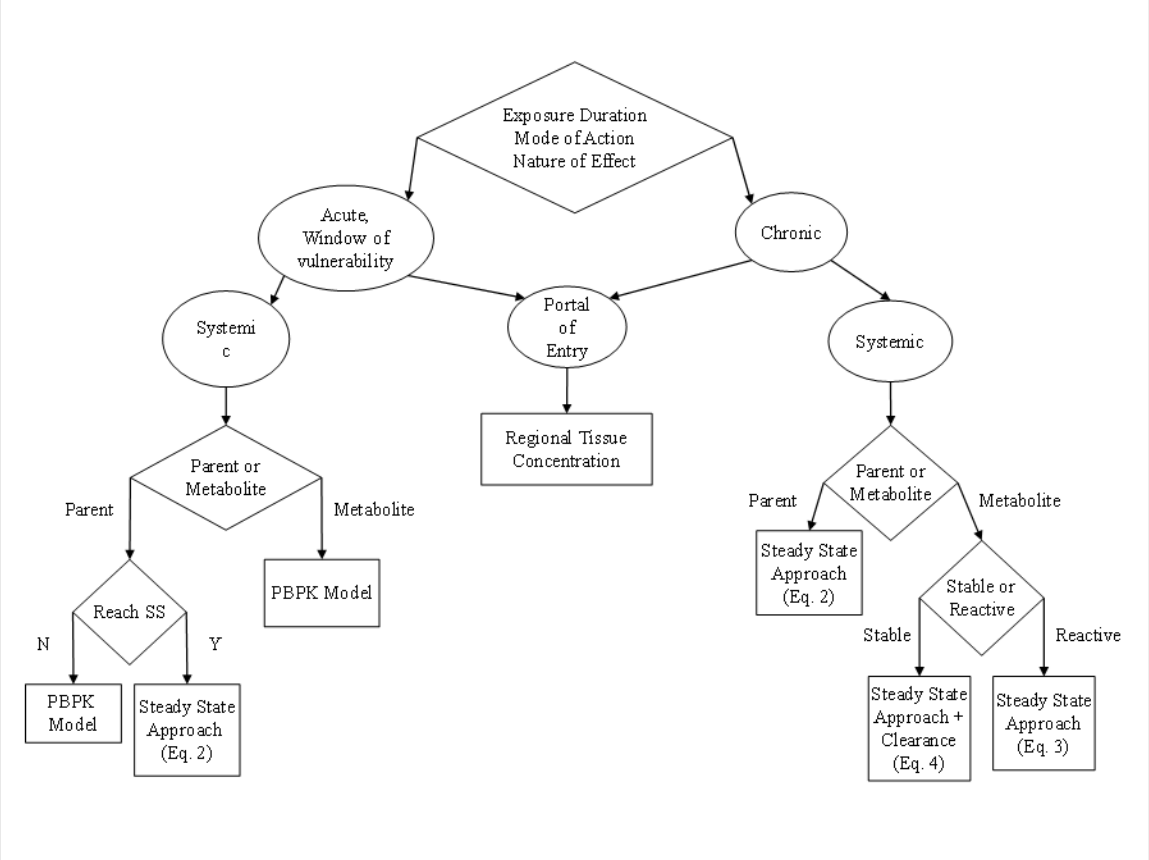


**Figure 2. Child/adult ratio of the steady-state concentration of inhaled parent chemical: A bounding case study. The hepatic clearance in children of all ages is set to zero, whereas that in adults is assumed to equal the maximal level (i.e., hepatic blood flow rate).**

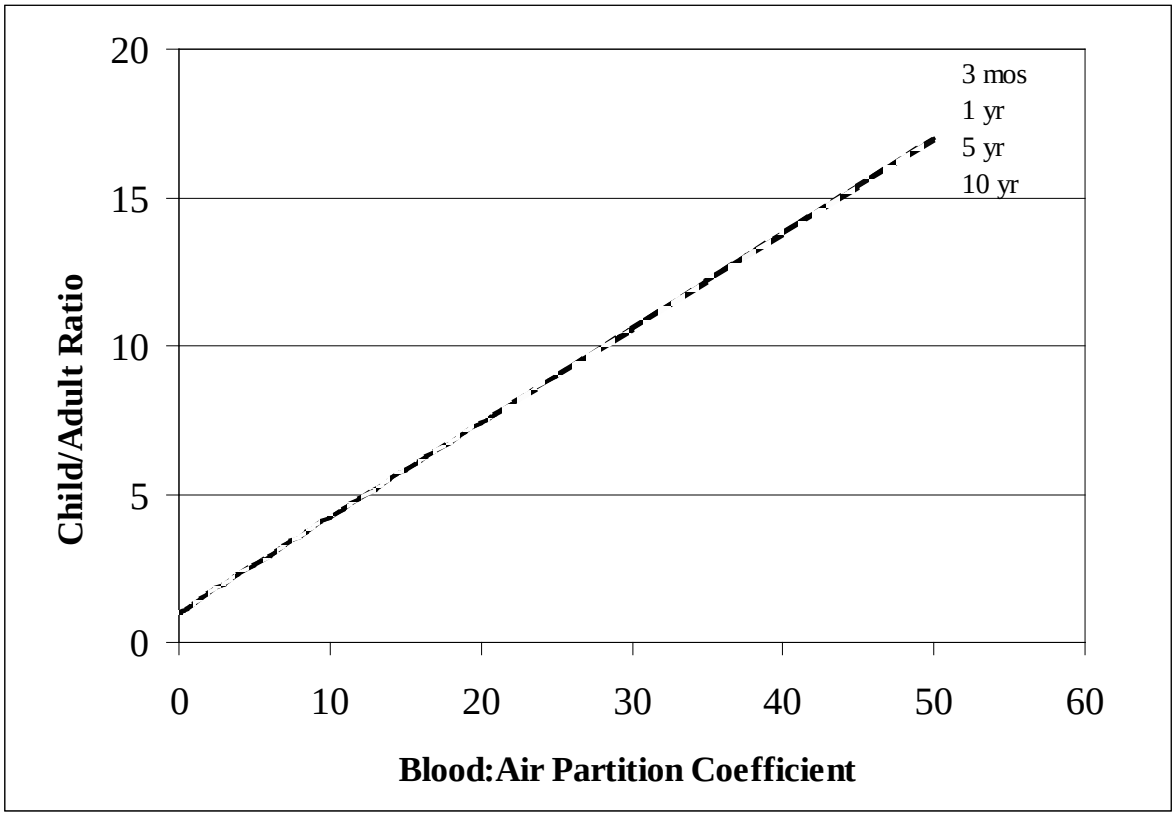


**Figure 3. Child/adult ratio of the parent chemical concentration at steady-state when metabolism is flow-limited in both adults and children.**

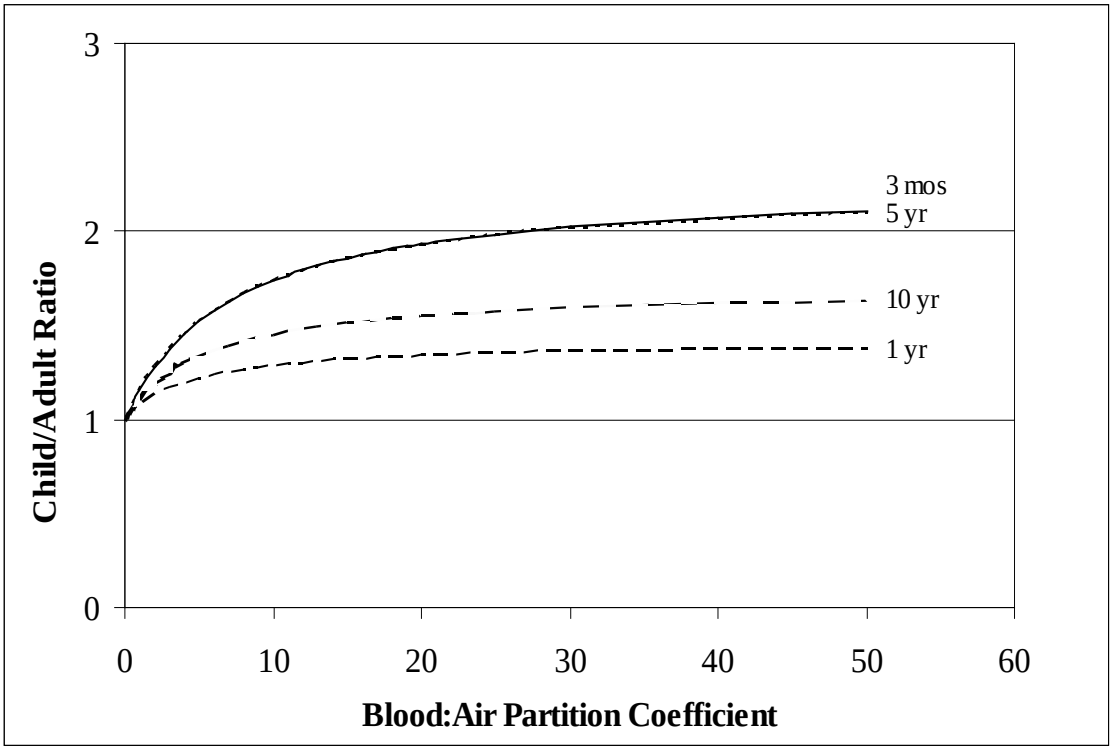



**Figure 4a. Child/adult ratio of the steady-state concentration of parent chemical for which the metabolism rate is proportional to the CYP2E1 content (intrinsic clearance is 1000 L/hr).**

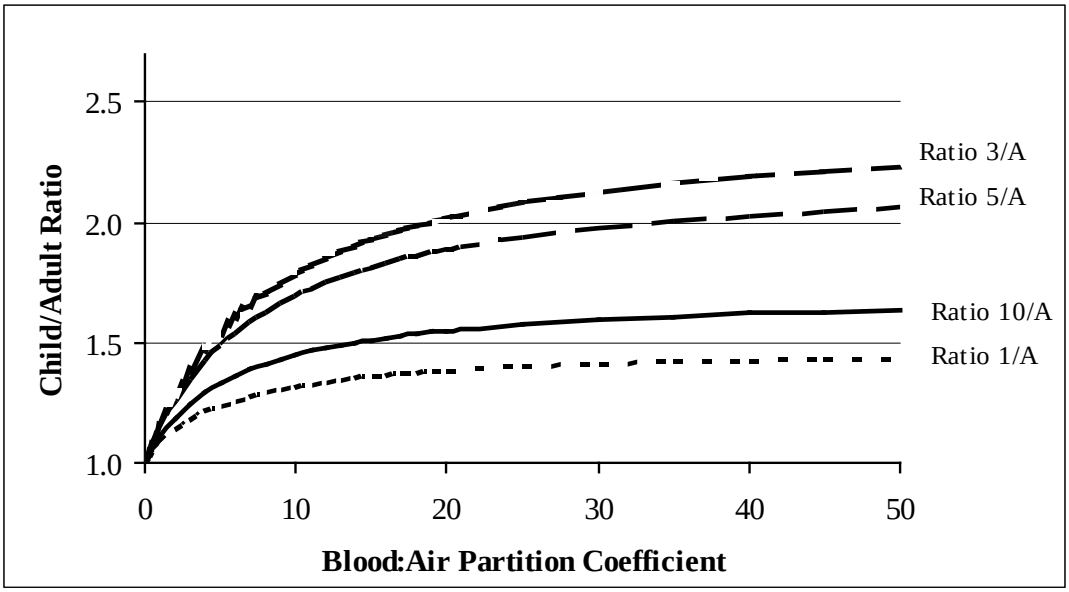
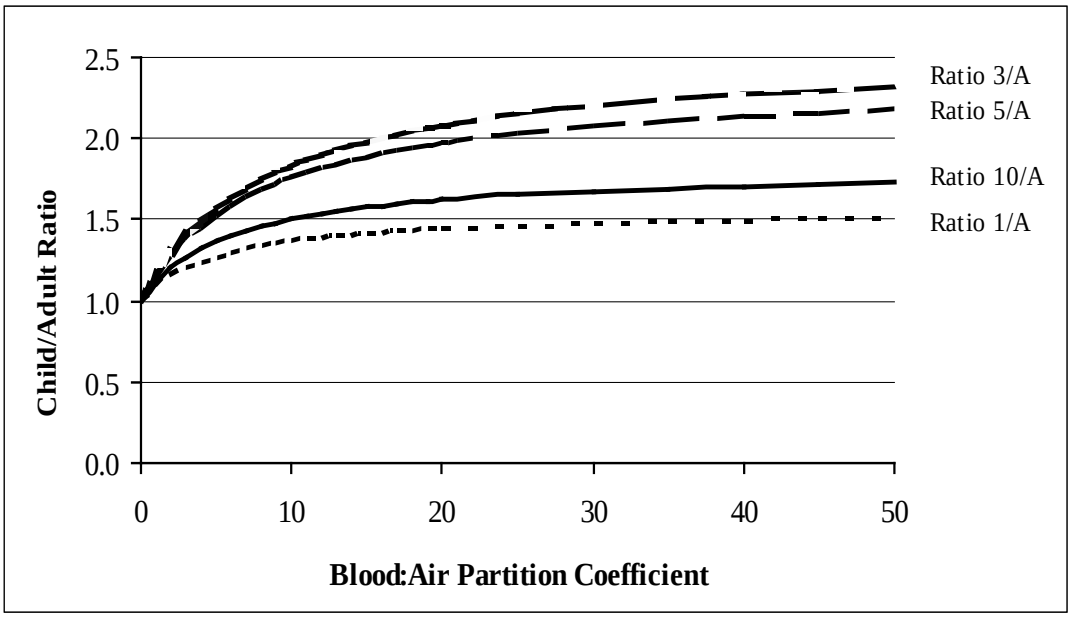


**Figure 4b. Child/adult ratio of the steady-state concentration of parent chemical for which the metabolism rate is proportional to the ADH content (CLint is 1000 L/hr).**




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

**Figure 5. Child/adult ratio of the concentration of reactive metabolite at steady-state when metabolism is flow-limited in both adults and children.**

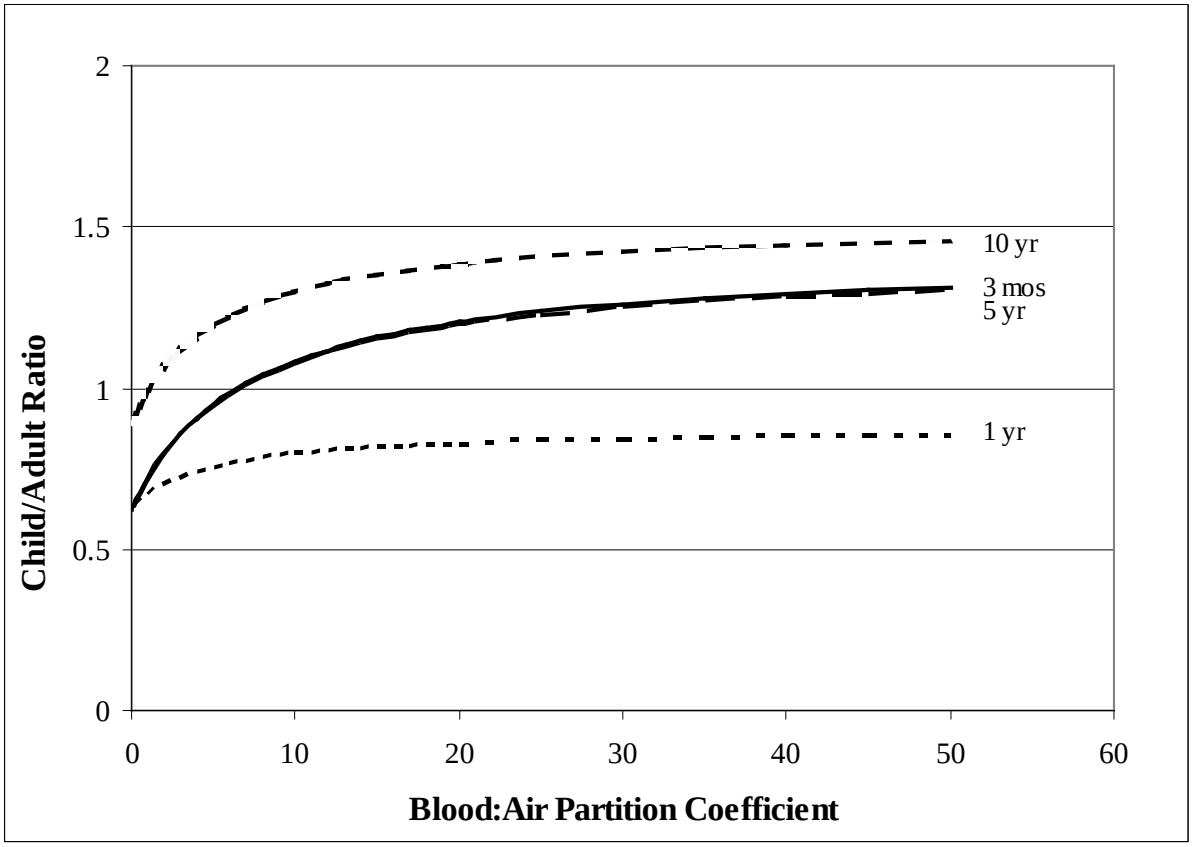
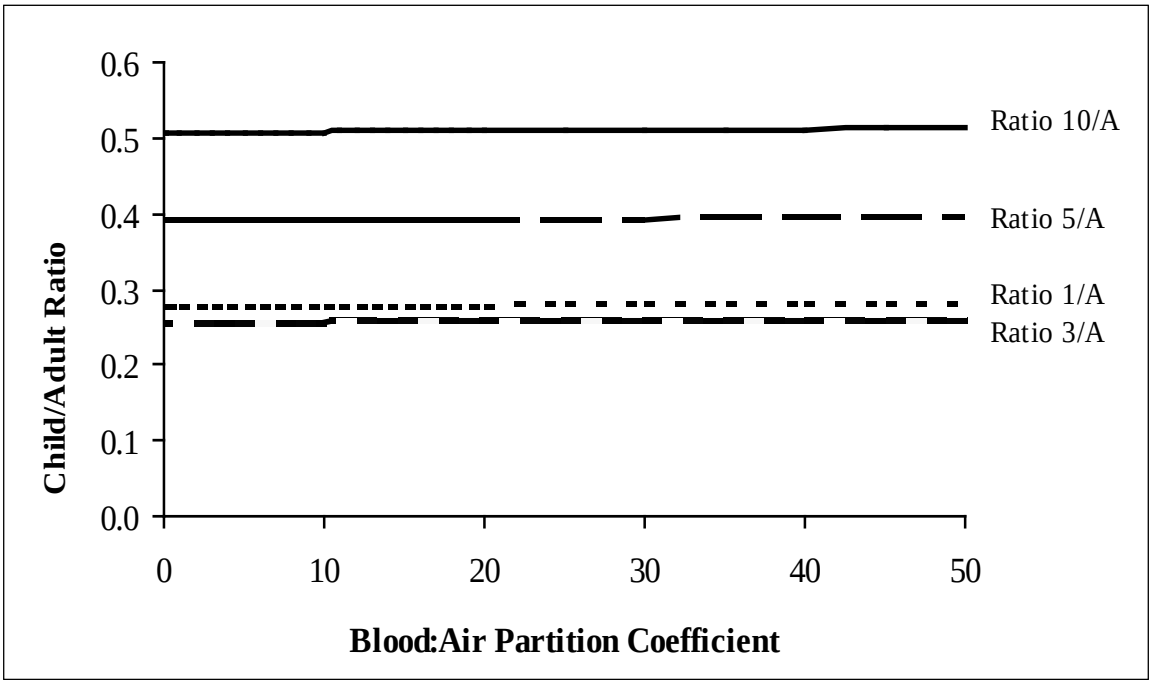
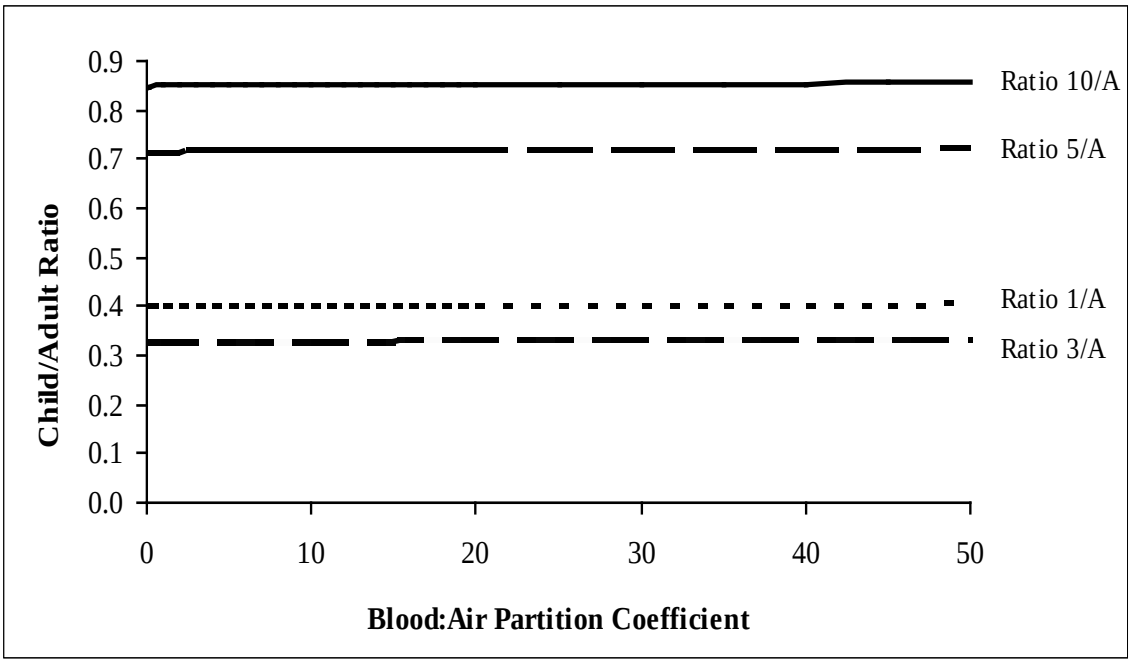


**Figure 6. Child/adult ratio of the steady state concentration of reactive metabolite formed from inhaled gases for which the metabolite clearance is proportional to the ADH content (intrinsic clearance is 0.1 L/hr).**



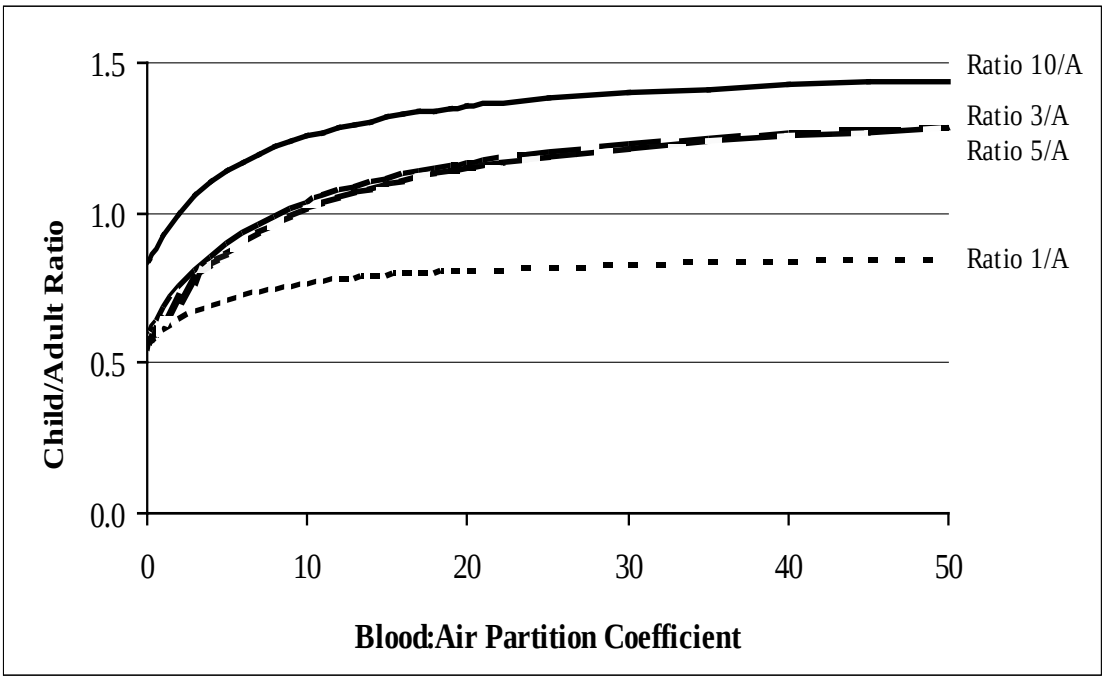

* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

**Figure 7. Child/adult ratio of the steady state concentration of reactive metabolite formed from inhaled gases for which the metabolite clearance is proportional to the CYP2E1 content (intrinsic clearance is 0.1 L/hr).**



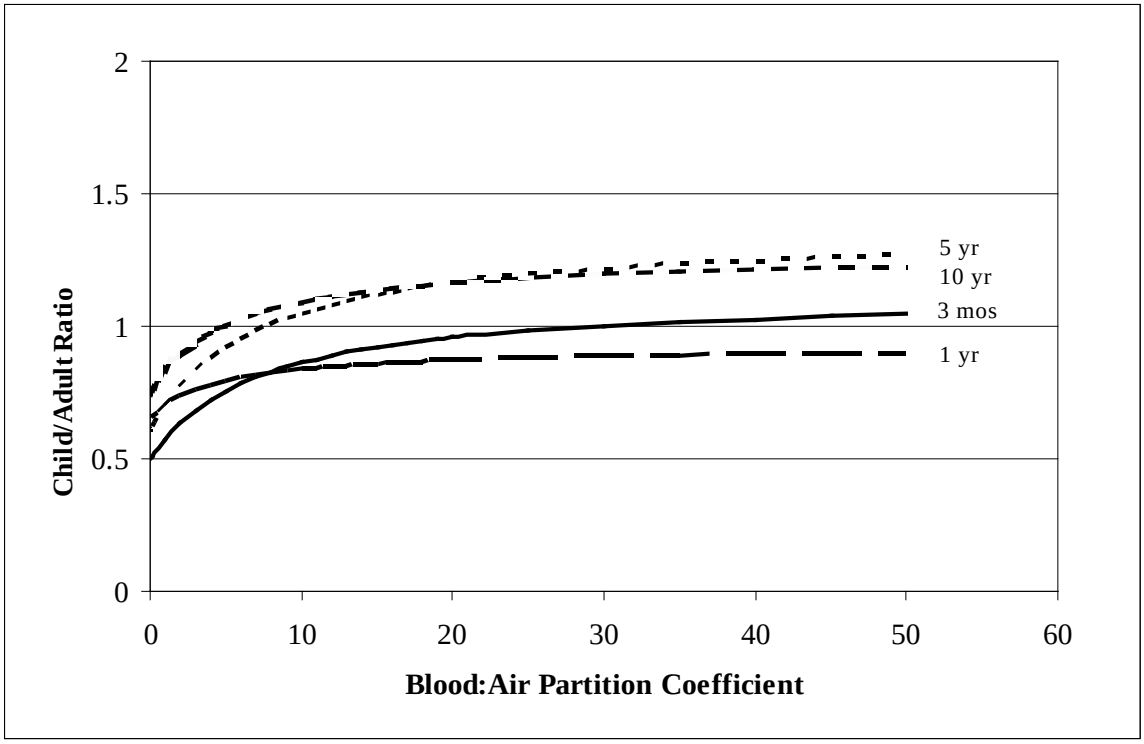

* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

**Figure 8. Child/adult ratio of the steady state concentration of reactive metabolite formed from inhaled gases for which the metabolite clearance is proportional to the ADH content (intrinsic clearance is 1000 L/hr).**




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

**Figure 9. Child/adult ratio of stable metabolite formed by flow-limited metabolism and cleared by renal excretion.**




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

**Figure 10a. Child/adult ratio of stable metabolite for which the formation rate is proportional to the ADH content and renal clearance is dependent upon the GFR (intrinsic clearance is 1000 L/hr).**

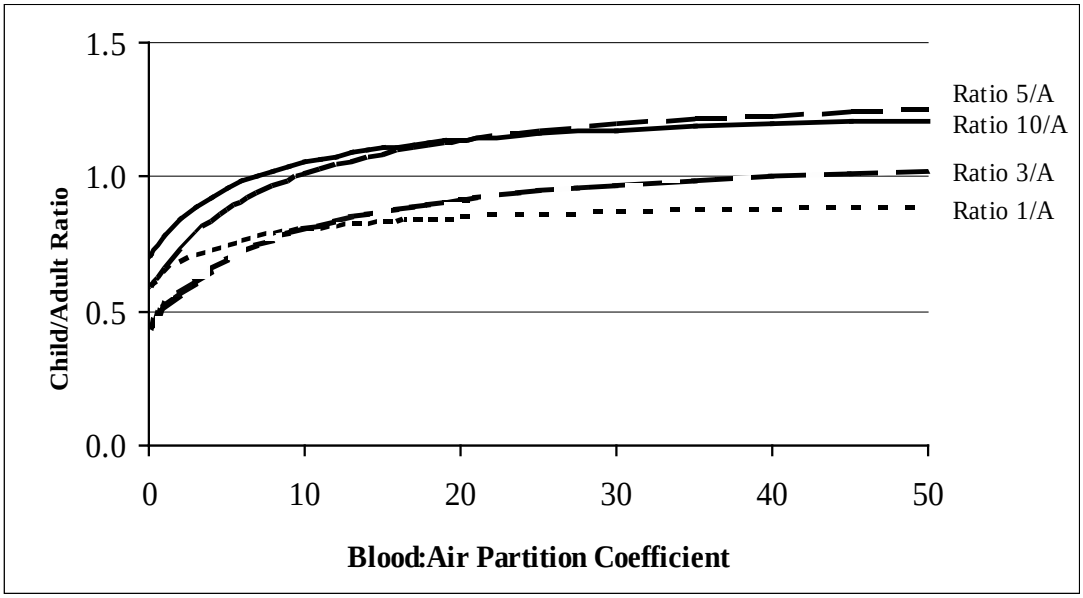
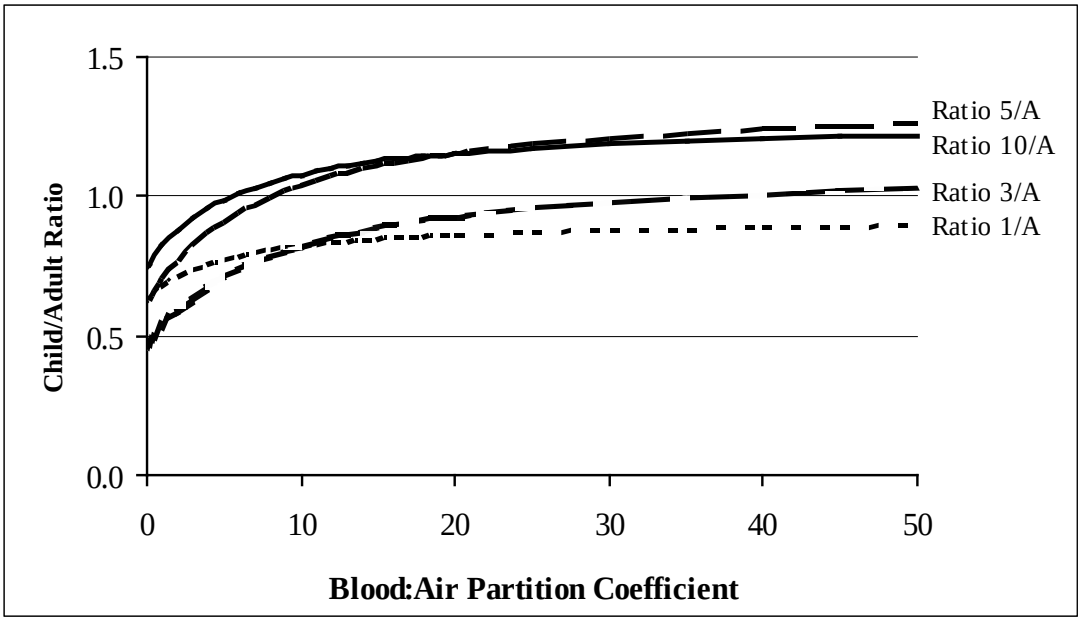



**Figure 10b. Child/adult ratio of stable metabolite for which the formation rate is proportional to the CYP2E1 content and renal clearance is dependent upon the GFR (intrinsic clearance is 1000 L/hr).**




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

**Figure 11a. Child/adult ratio of stable metabolite for which the formation rate is proportional to the ADH content and renal clearance is dependent upon the GFR (intrinsic clearance is 0.1 L/hr).**

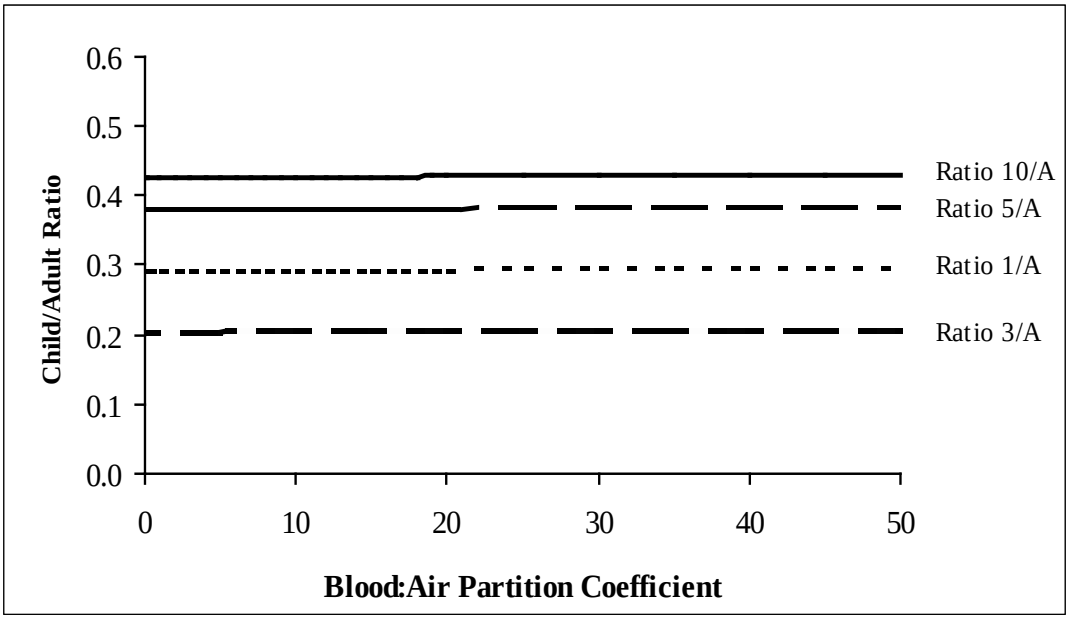
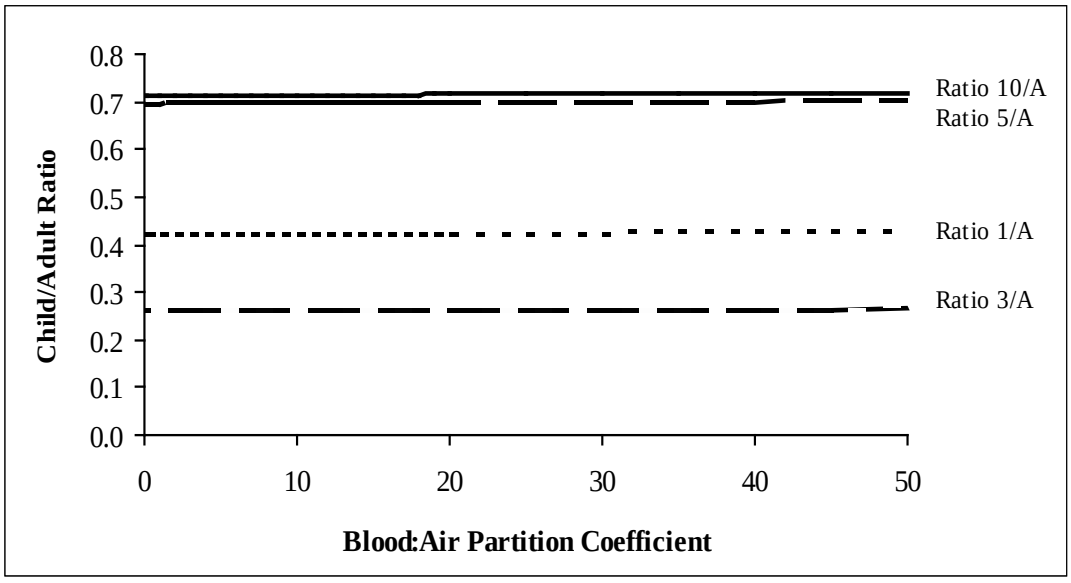
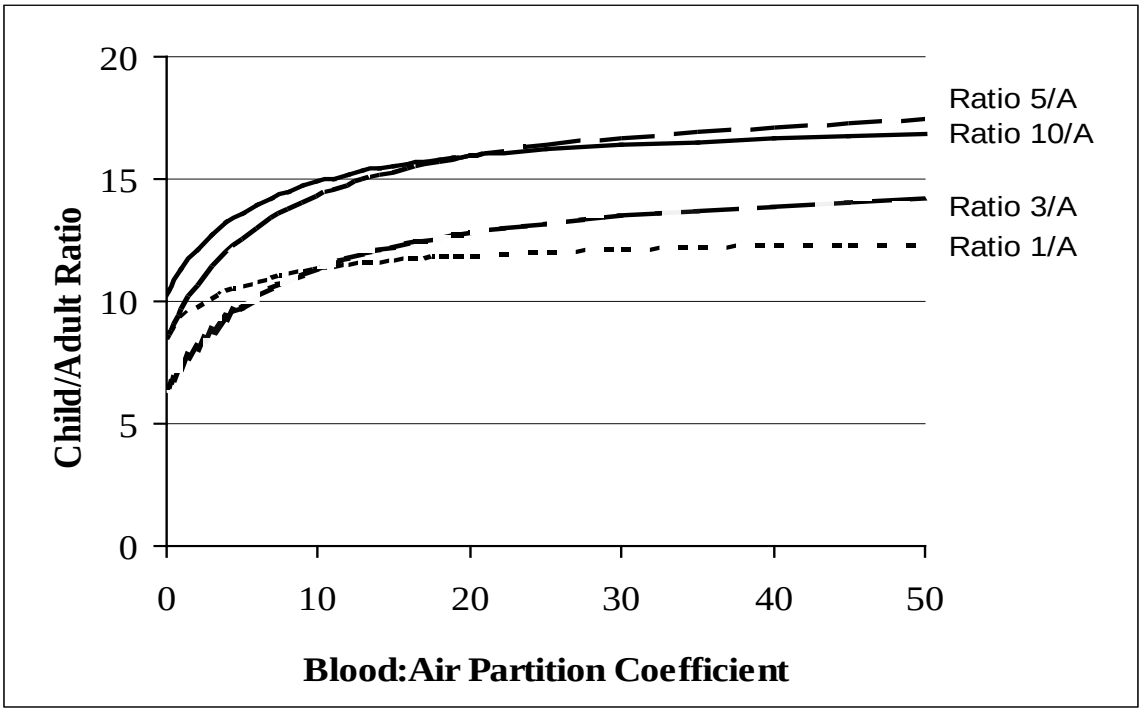



**Figure 11b. Child/adult ratio of stable metabolite for which the formation rate is proportional to the CYP2E1 content and renal clearance is dependent upon the GFR (intrinsic clearance is 0.1 L/hr).**



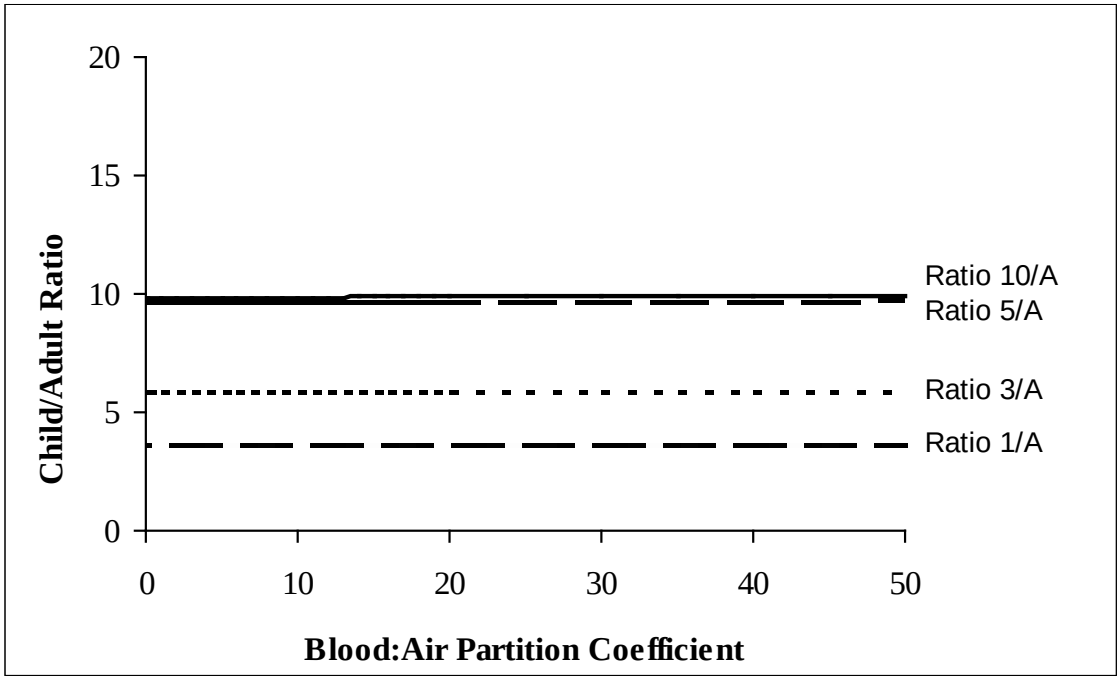

* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

**Figure 12. Child/adult ratio of steady state concentration of a stable metabolite with efficient metabolic clearance in adults (i.e., flow limited process) but only renal clearance in children (i.e., hepatic extraction ratio = 0) (intrinsic clearance of parent is 1000 L/hr).**




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

**Figure 13. Child/adult ratio of steady state concentration of a stable metabolite with efficient metabolic clearance of metabolite in adults (i.e., flow limited process) but only renal clearance in children (i.e., hepatic extraction ratio = 0) (intrinsic clearance of parent is 0.1 L/hr).**




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

## 5.0 REFERENCES

Andersen ME. (1981). A physiologically based toxicokinetic description of the metabolism of inhaled gases and vapors: analysis at steady state. Toxicol Appl Pharmacol 60, 509-526.

Arms AD; Travis CC. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. Washington, DC: Office of Health and Environmental Assessment.

Asgharian B; Wood R; Schlesinger RB. (1995). Empirical modeling of particle deposition in the alveolar region of the lungs: a basis for interspecies extrapolation. Fundam Appl Toxicol 27, 232-238.

Beliveau M; Lipscomb J; Tardif R; Krishnan K. (2005). Quantitative structure-property relationships for interspecies extrapolation of the inhalation pharmacokinetics of organic chemicals. Chem Res Toxicol 18, 475-485.

Beliveau M; Tardif R; Krishnan K. (2003). Quantitative structure-property relationships for physiologically based pharmacokinetic modeling of volatile organic chemicals in rats. Toxicol Appl Pharmacol 189, 221-232.

Berenson G; Frank G; Hunter S. (1982). Cardiovascular risk factors in children -- should they concern the pediatrician? Amer. J. Dis. Child. 136, 855-862.

Bogdanffy M; Plowchalk D; Sarangapani R; Starr T; Andersen M. (2001). Mode-of-action-based dosimeters for interspecies extrapolation of vinyl acetate inhalation risk. Inhal Toxicol 13, 377-396.

Bogdanffy MS; Sarangapani R. (2003). Physiologically-based kinetic modeling of vapours toxic to the respiratory tract. Toxicol Lett 138, 103-117.

Clewell HJ; Gentry PR; Covington TR; Sarangapani R; Teeguarden JG. (2004). Evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. Toxicol Sci 79, 381-393.

Clewell HJ; Teeguarden J; McDonald T; Sarangapani R; Lawrence G; Covington T; Gentry R; Shipp A. (2002). Review and Evaluation of the Potential Impact of Age and Gender-Specific Pharmacokinetic Differences on Tissue Dosimetry. Crit Rev Toxicol 32, 329-389.

Csanady GA; Filser JG. (2001). The relevance of physical activity for the kinetics of inhaled gaseous substances. Arch Toxicol 74, 663-672.

Csanady GA; Mendrala AL; Nolan RJ; Filser JG. (1994). A physiologic pharmacokinetic model for styrene and styrene-7,8-oxide in mouse, rat and man. Arch Toxicol 68, 143-157.

Daston G; Faustman E; Ginsberg G; Fenner-Crisp P; Olin S; Sonawane B; Bruckner J; Breslin W; McLaughlin TJ. (2004). A framework for assessing risks to children from exposure to environmental agents. Environ Health Perspect 112, 238-256.

de Zwart LL; Haenen HE; Versantvoort CH; Sips AJ. (2002). Pharmacokinetics of ingested xenobiotics in children: A comparison with adults. RIVM for Ministry of Health, Welfare and Sports.

de Zwart LL; Haenen HE; Versantvoort CH; Wolterink G; van Engelen JG; Sips AJ. (2004). Role of biokinetics in risk assessment of drugs and chemicals in children. Regul Toxicol Pharmacol 39, 282-309.

EEA (European Environmental Agency); WHO (World Health Organization). (2002). Children's Health and Environment: A Review of Evidence. Copenhagen: Environmental Issue Report. No. 29.

Family Practice Notebook. (2005). A Family Medicine Resource. Hematocrit: Hematocrit Cutoffs for Anemia. vol. 2005.

Gargas M; Burgess R; al. e. (1989). Partition coefficients of Low-Molecular-Weight Volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98, 87-99.

Gargas M; Burgess R; Voisard D; Cason G; Andersen M. (1989). Partition coefficients of Low-Molecular-Weight Volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98, 87-99.

Gentry PR; Covington TR; Andersen ME; Clewell HJ, 3rd. (2002). Application of a physiologically based pharmacokinetic model for isopropanol in the derivation of a reference dose and reference concentration. Regul Toxicol Pharmacol 36, 51-68.

Ginsberg G; Foos B; Firestone M. (2005). Review and analysis of inhalation dosimetry methods for application to children's risk assessment. In press.

Ginsberg G; Hattis D; Miller R; Sonawane B. (2004). Pediatric pharmacokinetic data: Implications for environmental risk assessment for children. Pediatrics 113, 973-983.

Ginsberg G; Hattis D; Russ A; Sonawane B. (2004). Physiologically based pharmacokinetic (PBPK) modeling of caffeine and theophylline in neonates and adults: Implications for assessing children's risks from environmental agents. J Toxicol Environ Health A 67, 297-329.

Ginsberg G; Hattis D; Sonawane B. (2004). Incorporating pharmacokinetic differences between children and adults in assessing children's risks to environmental toxicants. Toxicol Appl Pharmacol 198, 164-183.

Ginsberg G; Hattis D; Sonawane B; Russ A; Banati P; Kozlak M; Smolenski S; Goble R. (2002). Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 66, 185-200.

Ginsberg G; Slikker W, Jr.; Bruckner J; Sonawane B. (2004). Incorporating children's toxicokinetics into a risk framework. Environ Health Perspect 112, 272-283.

Haddad S; Restieri C; Krishnan K. (1999). Physiological modeling to characterize adult-children differences in pharmacokinetics. Toxicologist 48, 657.

Hanna LM; Lou SR; Su S; Jarabek AM. (2001). Mass transport analysis: Inhalation RfC methods framework for interspecies dosimetric adjustment. Inhal Toxicol 13, 437-463.

Hattis D; Ginsberg G; Sonawane B; Smolenski S; Russ A; Kozlak M; Goble R. (2003). Differences in pharmacokinetics between children and adults--II. Children's variability in drug elimination half-lives and in some parameters needed for physiologically-based pharmacokinetic modeling. Risk Anal 23, 117-142.

Health Canada. (2002). Children's Health Priorities within the Pest Management Regulatory Agency. Ottawa, Ontario, Canada: Pesticide Management Regulatory Agency.

Hofmann W. (1982). Mathematical model for the postnatal growth of the human lung. Respir Physiol 49, 115-129.

IPCS. (2006). Environmental Health Criteria 237: Principles for evaluating health risks in children associated with exposure to chemicals. Geneva: World Health Organization.

IPCS (International Programme for Chemical Safety). (2005). Harmonization Project Document No. 2. Chemical-Specific Adjustment Factors For Interspecies Differences And Human Variability: Guidance Document For Use Of Data In Dose/Concentration–Response Assessment. Geneva, Switzerland: World Health Organization.

Jarabek A. (2000). U.S. EPA mode of action: Framework for dosimetry model development. SRA.

Jarabek AM; Asgharian B; Miller FJ. (2005). Dosimetric Adjustments for Interspecies Extrapolation of Inhaled Poorly Soluble Particles (PSP). Inhal Toxicol.

Kimbell JS; Gross EA; Joyner DR; Godo MN; Morgan KT. (1993). Application of computational fluid dynamics to regional dosimetry of inhaled chemicals in the upper respiratory tract of the rat. Toxicol. Appl. Pharmacol. 121, 253-263.

Krishnan K. (2007). Chapter in Principles and Methods of Toxicology. In Hayes W. Boston, MA: CRC, pp. (Release date, September 12, 2007).

Krishnan K; Andersen M. (1991). Physiological Modeling and Cancer Risk Assessment. In Rescignio A; Thakur A, New Trends in Pharmacokinetics. NY: Plenum Press, pp. 335-354.

Lam G; Chen M; al. e. (1982). Determination of tissue to blood partition coefficients in physiologically-based pharmacokinetic studies. J Pharm Sci 71, 454-456.

Lees M; Way R; Ross B. (1967). Ventilation and respiration gas transfer of infants with increased pulmonary blood flow. Pediatrics 40, 262. (as cited by Price et al. 2003).

Lerman J; Gregory GA; Willis MM; Eger EI, 2nd. (1984). Age and solubility of volatile anesthetics in blood. Anesthesiology 61, 139-143.

Martonen TB; Graham RC; Hofmann W. (1989). Human subject age and activity level: factors addressed in a biomathematical deposition program for extrapolation modeling. Health Phys 57 Suppl 1, 49-59.

Martonen TB; Schroeter JD; Hwang D; Fleming JS; Conway JH. (2000). Human lung morphology models for particle deposition studies. Inhal Toxicol 12 Suppl 4, 109-121.

Nong A; McCarver DG; Hines RN; Krishnan K. (2006). Modeling interchild differences in pharmacokinetics on the basis of subject-specific data on physiology and hepatic CYP2E1 levels: a case study with toluene. Toxicol Appl Pharmacol 214, 78-87.

Oldham MJ; Robinson RJ. (2006). Calculated deposition in growing tracheobronchial airways: effect of growth-rate assumptions. Inhal Toxicol 18, 803-808.

Overton JH; Graham RC. (1989). Predictions of ozone absorption in human lungs from newborn to adult. Health Phys 57 Suppl 1, 29-36.

Pelekis M; Gephart LA; Lerman SE. (2001). Physiological-model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile organic compounds. Regul Toxicol Pharmacol 33, 12-20.

Pelekis M; Krewski D; Krishnan K. (1997). Physiologically based algebraic expressions for predicting steady-state toxicokinetics of inhaled vapors. Toxicol Methodol 7, 205-225.

Pelekis M; Nicolich MJ; Gauthier JS. (2003). Probabilistic framework for the estimation of the adult and child toxicokinetic intraspecies uncertainty factors. Risk Anal 23, 1239-1255.

Plunkett LM; Turnbull D; Rodricks JV. (1992). Differences Between Adults and Children Affecting Exposure Assessment. In Guzelian P;Henry C; Olin S,

Similarities and Differences Between Children and Adults: Implications for Risk Assessment. Washington, DC: ILSI Press, pp. 79-94.

Price K; Haddad S; Krishnan K. (2003). Physiological modeling of age-specific changes in the pharmacokinetics of organic chemicals in children. J Toxicol Environ Health A 66, 417-433.

Renwick AG. (1998). Toxicokinetics in infants and children in relation to the ADI and TDI. Food Addit Contam 15 Suppl, 17-35.

Renwick AG; Dorne JL; Walton K. (2000). An analysis of the need for an additional uncertainty factor for infants and children. Regul Toxicol Pharmacol 31, 286-296.

Rigas ML; Catlin SN; Ben-Jebria A; Ultman JS. (2000). Ozone uptake in the intact human respiratory tract: relationship between inhaled dose and actual dose. J Appl Physiol 88, 2015-2022.

Sarangapani R; Gentry PR; Covington TR; Teeguarden JG; Clewell HJ, 3rd. (2003). Evaluation of the potential impact of age- and gender-specific lung morphology and ventilation rate on the dosimetry of vapors. Inhal Toxicol 15, 987-1016.

Scheuplein R; Charnley G; Dourson M. (2002). Differential sensitivity of children and adults to chemical toxicity. I. Biological basis. Regul Toxicol Pharmacol 35, 429-447.

Smith H ed. (1994). Human respiratory tract model for radiological protection: A report of a Task Group of the International Commission on Radiological Protection. In: Annals of the ICRP: Published for the International Commission on Radiological Protection by Pergamon Press.

Snodgrass W. (1992). Physiological and Biochemical Differences Between Children and Adults as Determinants of Toxic Response to Environmental Pollutants. In Guzelian P;Henry C; Olin S, Similarities and Differences Between Children and Adults: Implications for Risk Assessment. Washington, DC: ILSI Press, pp. 35-42.

Szantay V; Tamas S; Marian L; Bochis G. (1974). [Changes of hepatic blood flow in children as a function of age]. Rev Roum Med Intern 11, 91-93 (as cited in Price et al. 2003).

US EPA (U.S. Environmental Protection Agency). (1994). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Washington DC: National Center for Environmental Assessment, Office of Research and Development.

US EPA (U.S. Environmental Protection Agency). (1997). Exposure Factors Handbook: Volume I. General Factors. Washington, DC: Office of Research and Development.

US EPA (U.S. Environmental Protection Agency). (2000). Benchmark Dose Technical Guidance Document (external review Draft). Washington, DC: Risk Assessment Forum.

US EPA (U.S. Environmental Protection Agency). (2006). Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment (Final Report). Washington, DC: National Center for Environmental Assessment, Office of Research and Development.

White D; Widdowson E; Woodard H; Dickerson J. (1991). The composition of body tissues (II): Fetus to young adult. Br J Radiol 64, 149-159 (as cited in Price et al 2003).

Wolterink G; Piersma AH; van Engelen JG. (2002). Risk Assessment of Chemicals: What About Children? : RIVM for Ministry of Health, Welfare and Sports.

Woodard HQ; White DR. (1986). The composition of body tissues. Br. J. Radiol 59, 1209-1219 (as cited in Price et al. 2003).

# Appendix D: Linear Multiplicative Relative Risk Models

## D.1 Overview of Poisson Regression Models

Poisson regression models assume that the number of observed events (e.g., number of cancer deaths) for a particular group of individuals or persons years follow a Poisson distribution. The Poisson distribution indicates that the probability of observing r events is given by the following function

$$p(R=r) = (\lambda n)^r \times e^{-\lambda n} / r!$$

where:

p(R=r) is the probability that r events are observed

r is the number of events occurring in the group

n is the number of individuals or person-years in the group

$\lambda$ is the unknown rate of occurrence of events per individual or person-year at risk (i.e., $\lambda n$ is the number of events occurring in the group)

The expected value (i.e., E[R]) of the Poisson distribution is given by $\lambda n$.

Tables of summary data from epidemiological studies are often presented in the form of observed and expected number of cancer deaths for different groups. The groups can correspond to combinations of different dose intervals, different sexes, different plants, etc. Poisson regression assumes that the rate of cancer death remains constant within each group defined by a combination of the dose interval, sex, plant, etc. The rate of cancer deaths in a specific group is in terms of the number of cancer deaths per person-year at risk. The number of person-years at risk is the total number of years that different individuals contribute to each different group. For example, consider the following table defining groups according to sex, age and cumulative exposure:

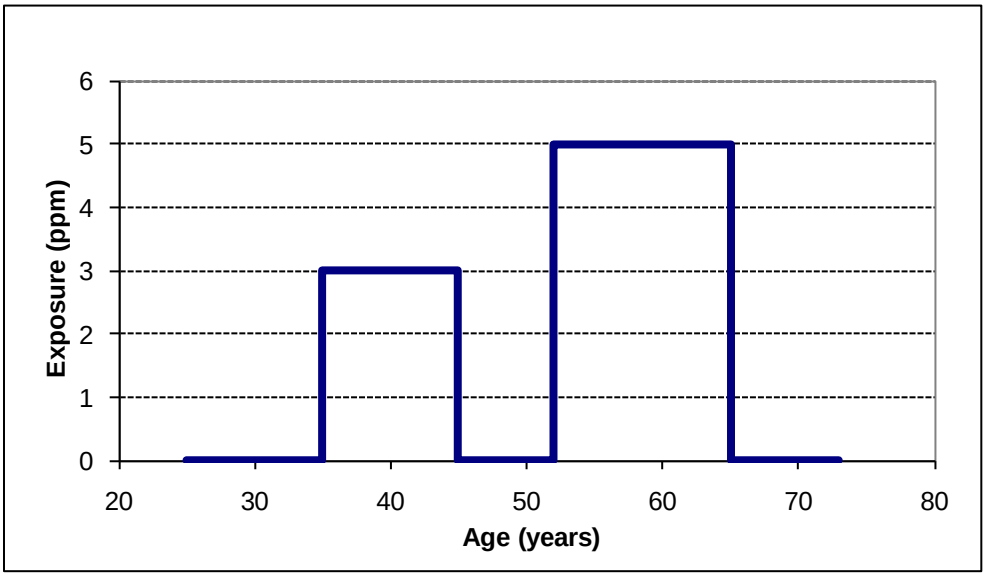
| Covariates | | Cumulative Exposure (ppm-years) | | | |
|---|---|---|---|---|---|
| Sex | Age | 0 | 0 to 10 | 10 to 100 | 100+ |
| Male | < 40 | | | | |
| | 40 to 60 | | | | |
| | 60 + | | | | |
| Female | < 40 | | | | |
| | 40 to 60 | | | | |
| | 60 + | | | | |

Now consider the following job exposure profile for one male worker who was followed up (i.e., was at risk because he was being observed) from age 25 through age 73 years. His job history indicates that:

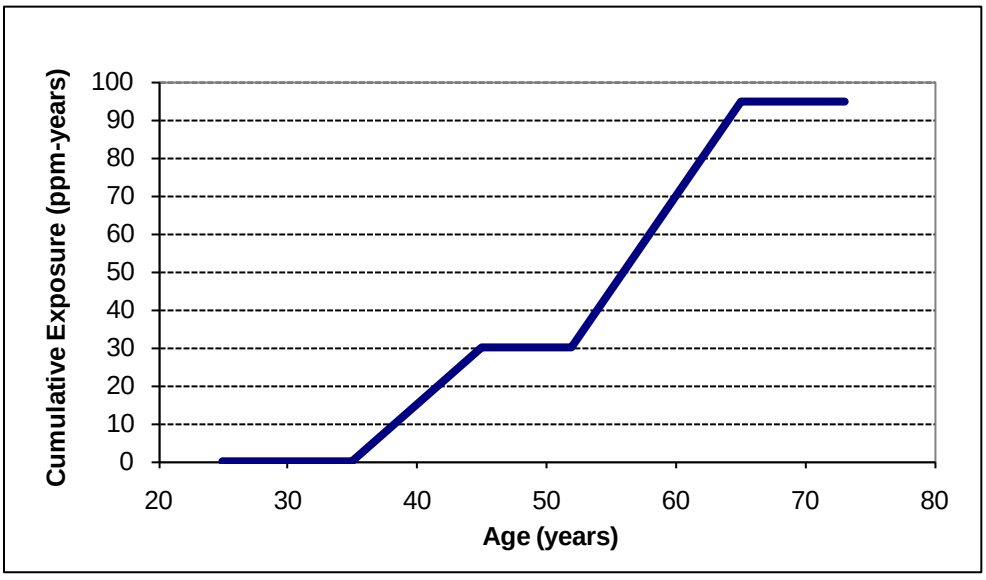
He started to be followed up when he was 25

Before age 25 he was not exposed
From age 25 to 35 he was not exposed
From age 35 to 45 he was exposed to 3 ppm on his job
From age 45 to 52 he was not exposed
From age 52 to 65 he was exposed to 5 ppm on his job
From age 65 to 73 he was not exposed
His follow-up ended when he was 73 and he was alive at that time
He was followed up for a total of 48 years (48 person-years)

This worker's aged changed over the period he was observed (i.e., he belonged for different periods of time to different age groups in the table above). The cumulative exposure also changed over the period the worker was observed (i.e., his cumulative exposure was in different exposure intervals at different times in the table above). The following graph shows the exposure profile for this worker.

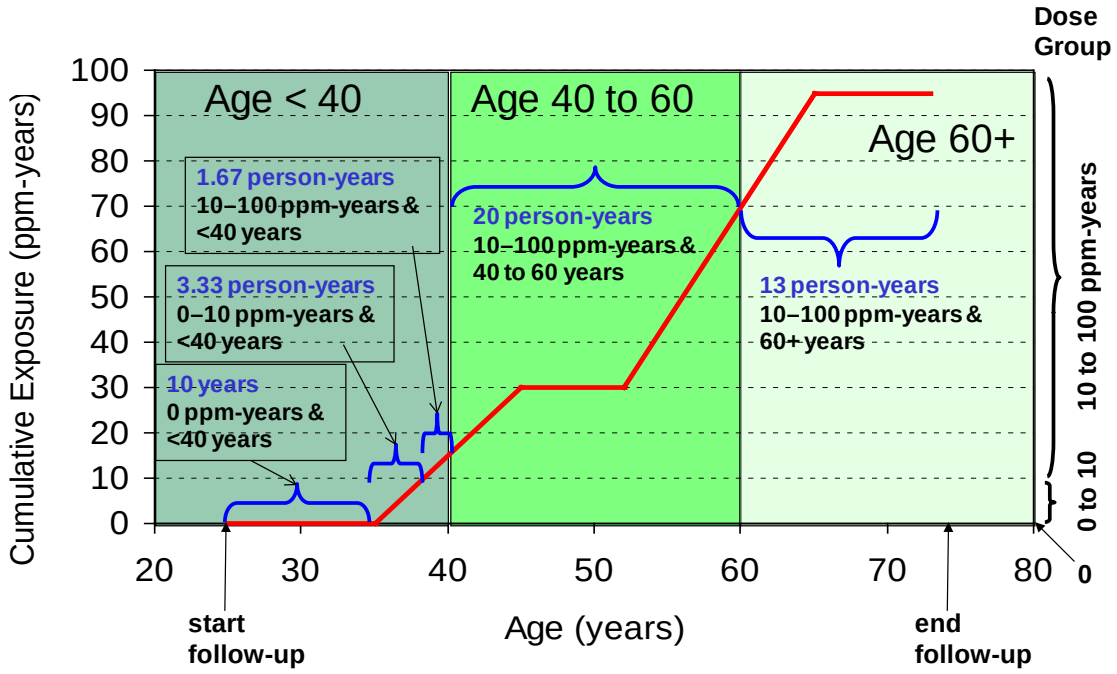



The corresponding cumulative exposure (ppm-years) is in the following graph.




It is clear that all the time this worker is at risk (i.e., being observed) he is male (i.e., all his person-years belong to the male group). It is also clear how many years of this

worker's time at risk he was younger than 40, between 40 and 60 and over 60 years (i.e., 15, 20 and 13 years, respectively). However, it is not so clear the length of time this worker spent in each of the age groups and each of the cumulative exposure intervals. The following graph overlaps the age groups and cumulative exposure intervals for this particular worker.




The above graph shows length of time in years that this worker belonged to each combination of age group and exposure interval. During the first 15 years of follow-up (age 25 to age 40) he was exposed to 0 ppm-years for 10 year, 3.33 years he was exposed to a cumulative exposure less than 10 ppm-years but more than 0 ppm-years, and for 1.67 years his exposure ranged between 10 and 100 ppm-years. The next 20 years of his life were spent between the ages of 40 and 60 years and his cumulative exposure was between 10 and 100 ppm-years. He was older than 60 during his last 13 years of observation and his cumulative exposure was between 10 and 100 ppm-years. The numbers of person-years for this worker in each group of sex, age and cumulative exposure are summarized in the following table

| Covariates | | Cumulative Exposure (ppm-years) | | | |
|---|---|---|---|---|---|
| Sex | Age | 0 | 0 to 10 | 10 to 100 | 100+ |
| Male | < 40 | 10 | 3.33 | 1.67 | |
| | 40 to 60 | | | 20 | |
| | 60 + | | | 13 | |
| Female | < 40 | | | | |
| | 40 to 60 | | | | |

| | |
|---|---|
| 60 + | |

A table similar to the above table tallies the number of events in each group. For example, if the worker of the example had died with the response (e.g., cancer) then the worker would contribute with one event to the cell of his last person-year of follow-up.

After following a large number of workers in an epidemiological study, the table may look like

| Covariates | | Cumulative Exposure (ppm-years) | | | |
|---|---|---|---|---|---|
| Sex | Age | 0 ($e_0$) | 0 to 10 ($e_1$) | 10 to 100 ($e_2$) | 100+ ($e_3$) |
| Male ($s_0$) | < 40 ($a_0$) | 0 / 1233.0 | 0 / 755.3 | 1 / 693.2 | 0 / 121.5 |
| | 40 to 60 ($a_1$) | 1 / 1433.0 | 1 / 957.8 | 1 / 893.7 | 2 / 357.9 |
| | 60 + ($a_2$) | 1 / 893.1 | 2 / 1055.0 | 1 / 752.1 | 0 / 523.8 |
| Female ($s_1$) | < 40 ($a_0$) | 1 / 1793.0 | 0 / 867.2 | 1 / 323.6 | |
| | 40 to 60 ($a_1$) | 0 / 899.0 | 0 / 739.5 | 1 / 651.8 | 0 / 225.3 |
| | 60 + ($a_2$) | 2 / 795.3 | 1 / 516.7 | 1 / 419.6 | 1 / 337.2 |

In the table above, the #1 of the entry #1 / #2 refers to the number of events (e.g., cancer deaths) and #2 refers to the number of person-years at risk. The labels $s_0$, $s_1$, $a_0$, $a_1$, $a_2$, $e_0$, $e_1$, $e_2$, and $e_3$ indicate different levels of the factors or covariates. A Poisson regression model for the above summary data would account for each of the factors (covariates). That is, the probability of observing the number of deaths in each cell follows a Poisson distribution given by

$$p(R=r_{ijk}) = (\lambda_{ijk} n_{ijk})^{r}_{ijk} \times e^{-\lambda}_{ijk}{}^{n}_{ijk} / r_{ijk}!$$

where:

the subscript refers to the i-th sex ($s_0$ or $s_1$)

j-the age group ($a_0$, $a_1$, or $a_2$)

k-th cumulative exposure interval ($e_0$, $e_1$, $e_2$, or $e_3$)

The unknown hazard rate $\lambda_{ijk}$ for the ijk-th cell in the table can be modeled using a multiplicative background model as follows,

$$\lambda_{ijk} = \lambda \times s_i \times a_j \times e_k$$

where:

$\lambda$ is the overall background hazard rate for the cohort

$s_i$ is the effect of sex

$a_j$ is the effect of age

$e_k$ is the effect of cumulative exposure

In this model the values of $s_0$, $a_0$ and $e_0$ are defined as 1 and $\lambda$ and the values of the variables with other subscripts are unknown parameters.

The purpose of dose-response modeling is to determine the relationship between a dose (e.g., cumulative exposure ppm-years) and the observed response (e.g., cancer deaths). In other words, the effect $e_k$ in the above equation is modeled as a function of dose rather than as a categorical effect. For example, the effect of cumulative exposure on the rate can be modeled as a linear function of the cumulative exposure as in the following

$$e_k = 1 + \beta \times d_k,$$

where:

$d_k$ is the cumulative exposure of the k-th dose interval (the average dose for the person years in the interval is the most appropriate value)

$\beta$ is an unknown parameter that needs to be estimated

After replacing the effect of cumulative exposure by the linear function, the multiplicative model is as follows:

$$\lambda_{ijk} = \lambda \times s_i \times a_j \times (1 + \beta \times d_k)$$

The parameters $\lambda$, $s_1$, $a_1$, $a_2$ and $\beta$ can then be estimated using maximum likelihood. The likelihood function is given by

$$\text{Likelihood} = \prod_{ijk} p(R=r_{ijk})$$

$$= \prod_{ijk} \exp\{-\lambda_{ijk} n_{ijk}\} \times (\lambda_{ijk} n_{ijk})^{r_{ijk}} \ / \ r_{ijk}!$$

where the product is over all cells in the table and $\lambda_{ijk} = \lambda \times s_i \times a_j \times (1 + \beta \times d_k)$. The values of $\lambda$, $s_1$, $a_1$, $a_2$ and $\beta$ that maximize the likelihood are the maximum likelihood estimates of those parameters.

The product $\lambda \times s_i \times a_j$ in the Poisson regression model is the estimate of background hazard rate for the ijk-th cell in the table when the cumulative exposure is equal to zero. The relation $(1 + \beta \times d_k)$ in the model is the relative risk and describes the effect of cumulative exposure on the background hazard rate. In the estimation of risks for a different population the effect of the cumulative exposure is used but the background hazard rate ($\lambda \times s_i \times a_j$) is replaced by the sex- and age-dependent target population's background rate.

## D.2 Summary Estimates of Standardized Mortality/Incidence Rates

Summary data presented in most published epidemiological studies are in the form of SMRs or SIRs. The SMRs are the ratio of the observed number of events in the cohort of the epidemiology study (e.g., number of cancer deaths) to the expected number of events

in a reference population. The summary data can be used to fit a dose-response model using Poisson regression if the observed and expected numbers of deaths are given for different dose intervals. For example, the following table was reported by Enterline et al. 1995 for workers exposed to arsenic.

| Cumulative Exposure (mg/m3-year) | Mean Cumulative Exposure (mg/m3-year) | Number of Deaths with Respiratory Cancer Observed in the Cohort | Number of Deaths with Respiratory Cancer Expected in the Reference Population* | SMR |
|---|---|---|---|---|
| [0, 0.75) | 0.405 | 22 | 14.29 | 154.0 |
| [0.75, 2) | 1.305 | 30 | 17.10 | 175.5 |
| [2, 4) | 2.925 | 36 | 17.17 | 209.7 |
| [4, 8) | 5.708 | 36 | 17.00 | 211.7 |
| [8, 20) | 12.334 | 39 | 15.48 | 252.0 |
| [20, 45) | 28.336 | 20 | 7.04 | 284.0 |
| 45+ | 58.957 | 5 | 1.58 | 315.7 |

*White men in the State of Washington were used as the reference population because the plant of the study is located in that state and because all 2,802 workers in the study were men and most of them where white.

The data in the summary table can be fit using Poisson regression and the multiplicative background hazards model. The model for the linear dose-response model was specified in the previous section as

$$\lambda_{ijk} = \lambda \times s_i \times a_j \times (1 + \beta \times d_k)$$

where the $s_i$ and $a_j$ reflected the effects of sex and age, respectively. However, if only the effect of cumulative exposure is to be modeled (because that is the only information available in the Enterline et al. 1995 paper), the dose-response model reduces to

$$\lambda_k = \lambda \times (1 + \beta \times d_k).$$

If both sides of the equation are multiplied by the number of person-years in the k-th cell, then the expression is as follows,

$$\lambda_k \times n_k = \lambda \times n_k \times (1 + \beta \times d_k).$$

This is equivalent to

$$Observed_k = \text{Expected}_k \times (1 + \beta \times d_k)$$

Where

$Observed_k$ is the number of deaths in the k-th exposure interval predicted by the model,

$Expected_k$ is the expected number of deaths in the reference population corresponding to the person-years in the k-th exposure interval.

The parameter β can then be estimated using maximum likelihood. The likelihood function is given by

$$\text{Likelihood} = \prod_k p(R=Observed_k)$$

$$= \prod_k \exp\{- Expected_k \times (1 + \beta \times d_k)\} \times$$

$$[ Expected_k \times (1 + \beta \times d_k)]^{Observed_k} / Observed_k!$$

where the product is over all exposure intervals in the table and $Observed_k$ is the actual number of respiratory cancer deaths observed in the k-th dose interval. (Note that $Observed_k$ is the actual number while $Observed_k$ is the number predicted by the model). The value of β that maximizes the likelihood is the maximum likelihood estimate of that parameter.

The relation $(1 + \beta \times d_k)$ in the model describes the effect of cumulative exposure on the background rate. In the estimation of risks for a different population, the effect of the cumulative exposure is used along with the background hazard rate of that population.

### D.3 Adjustments for Possible Differences Between the Population Background Cancer Rate and the Cohort's Cancer Rate in the Relative Risk Model

A multiplicative relative risk model that uses reference population background cancer rates to fit the cohort's observed cancer rates should adjust for possible discrepancies between the background cancer rates in the reference population and the background cancer rates in the cohort.

In the example given in Section A.2, the multiplicative background dose-response model relates the number of observed respiratory cancer deaths to the product of the number of respiratory cancers expected in a reference population and the effect of the dose. The underlying background respiratory cancer hazard rates of the workers in the cohort may be (and usually are) different than the underlying background respiratory hazard rates in the reference population. If no adjustment for this difference is made, the dose-dependent function (i.e., the term $1+\beta \times d_k$ in the model) is forced to explain not only the effect of the dose in the observed respiratory cancer mortalities but also any discrepancies between the study and reference population background rates. In other words, ignoring discrepancies between the cohort's background hazards rates and the reference population hazard rates may result in distorted (i.e., biased) dose-response relationships.

Crump and Allen (1985) discuss the relative risk model with a factor that accounts for the possibility of different background rates in an epidemiological cohort and its reference population. This factor may adjust for issues like the healthy worker effect, the difference between internally and externally derived background cancer rates, covariate effects not explicitly incorporated in the summary epidemiological data, etc. For example, the multiplicative background relative risk model with no adjustment for differences in background rates can be extended from

$$Observed_k = \text{Expected}_k \times (1 + \beta \times d_k)$$

to

$$Observed_k = \alpha \times \text{Expected}_k \times (1 + \beta \times d_k)$$

where the $\alpha$ term adjusts for any possible difference between the population's background cancer rates and the cohort's observed cancer rates in unexposed workers.

In the equations above the variables are:

$Observed_k$ = number of lung cancer deaths for exposure group k predicted by the model;

$\text{Expected}_k$ = expected number of background lung cancer deaths for exposure group k based on the reference population background cancer rates;

$\beta$ = multiplicative factor by which background risk increases with cumulative exposure;

$d_k$ = cumulative exposure for exposure group k;

$\alpha$ = multiplicative factor that accounts for differences in cancer mortality background rates between the study cohort and the reference population.

## D.4 Estimating the Slope Parameter, β, in the Relative Risk Model Adjusting for Differences in Background Rates

As discussed in Section A.1, Poisson regression is a standard modeling technique in epidemiological studies. Poisson regression relies on the assumption that the number of cancer deaths in a dose group follows a Poisson distribution with mean equal to the expected number of cancer deaths and uses the maximum likelihood estimation procedure for the estimation of the parameters $\alpha$ and $\beta$ in the model.

The Poisson distribution that describes probabilistically the number of cancers observed in a group is given by:

$$p(x) = \lambda^x \times e^{-\lambda} / x!$$

where p(x) is the probability of observing x cancers, x is the number of cancer deaths actually observed, x! = x ( x-1) (x-2) … 1, and $\lambda$ is the number of cancers in the group predicted by the model. Thus, for dose group k, $x_k = \text{Observed}_k$ and $\lambda_k = Observed_k = \alpha \times \text{Expected}_k \times (1 + \beta \times d_k)$. That is, for each group k of person-years with average dose $d_k$, the observed number of cancer deaths in the dose interval ($\text{Observed}_k$) follows a Poisson distribution with parameter $\lambda_k = Observed_k = \alpha \times \text{Expected}_k \times (1 + \beta \times d_k)$ and the likelihood of observing $\text{Observed}_k$ cancer deaths is given by,

$$p(\text{Observed}_k) = \exp\{-\alpha \times \text{Expected}_k \times (1 + \beta \times d_k)\} \times [\alpha \times \text{Expected}_k \times (1 + \beta \times d_k)]^{\text{Observed}_k} / \text{Observed}_k!.$$

The likelihood (L) is given by the product of the likelihoods of observing the number of cancer deaths in each dose group. That is,

$$L = p(Observed_1) \times p(Observed_2) \times \ldots.$$

or, equivalently,

$$L = \exp\{-\alpha\times Expected_1\times (1+\beta\times d_1)\}\times[\alpha\times Expected_1\times(1+\beta\times d_1)]^{Observed_1}/Observed_1!\times$$

$$\exp\{-\alpha\times Expected_2\times (1+\beta\times d_2)\}\times[\alpha\times Expected_2\times(1+\beta\times d_2)]^{Observed_2}/Observed_2!\times$$

$$\ldots..$$

where exp{.} is the base of the natural logarithm (e) raised to the power in the braces and $Observed_k$ is the number of cancer cases observed for the person-years with cumulative exposures equal to $d_k$. The likelihood equation can be written using mathematical notation as follows:

$$L = \prod \exp\{-\alpha\times Expected_k\times (1+\beta\times d_k)\}\times [\alpha\times Expected_k\times(1+\beta\times d_k)]^{Observed_k}/Observed_k!$$

where the symbol $\prod$ indicates that it is the product over all dose groups k=1,2,…

The maximum likelihood estimates of the unknown parameters $\alpha$ and $\beta$ can then be obtained by selecting the values of $\alpha$ and $\beta$ that maximize the value of L. Finding the values of $\alpha$ and $\beta$ that maximize the value of the likelihood L cannot be determined using a close-form solution because there are two variables. However, any routine that can maximize nonlinear functions of more than one variable can be used to calculate the maximum likelihood estimates of $\alpha$ and $\beta$.

The parameters $\alpha$ and $\beta$ that maximize the likelihood function given above also maximize the logarithm of the likelihood because the logarithm is a monotone function. The logarithm of the likelihood function (LL) for the model given above is

$$LL = \sum \{ -\alpha\times Expected_k\times (1+\beta\times d_k) + Observed_k \times \ln[\alpha\times Expected_k\times(1+\beta\times d_k)] - \ln(Observed_k!) \}$$

where the symbol $\sum$ indicates that it is the sum over all dose groups k=1,2,… and ln(x) is the natural logarithm of x. The LL function can also be written as

$$LL = \sum\{-\alpha\times Expected_k\times (1+\beta\times d_k) + Observed_k\times\ln(\alpha) + Observed_k \times \ln(Expected_k) + Observed_k \times \ln(1+\beta\times d_k)] - \ln(Observed_k!) \}$$

Note that the terms $Observed_k\times\ln(Expected_k)$ and $\ln(Observed_k!)$ in the LL equation above do not depend on the values of $\alpha$ and $\beta$, and hence, the values of $\alpha$ and $\beta$ that maximize the LL also maximize the following simplified LL function:

$$LL = \sum\{-\alpha\times Expected_k\times (1+\beta\times d_k) + Observed_k\times\ln(\alpha) + Observed_k \times \ln(1+\beta\times d_k)] \}$$

Finally, the maximum likelihood estimates of $\alpha$ and $\beta$ can also be obtained by solving for $\alpha$ and $\beta$ in the following system of equations:

$$\frac{\partial LL}{\partial \alpha} = \sum \{ -Expected_k \times (1+\beta \times d_k) + Observed_k/\alpha \} = 0$$

$$\frac{\partial LL}{\partial \beta} = \sum \{ -\alpha \times Expected_k \times d_k + (Observed_k \times d_k) / (1 + \beta \times d_k) \} = 0$$

where $\partial LL/\partial \alpha$ and $\partial LL/\partial \beta$ are the partial derivatives of the logarithm of the likelihood with respect to $\alpha$ and $\beta$, respectively.

## D.5 Estimating the Asymptotic Variance for the Slope Parameter in the Relative Risk Model

The system of equations of the partial derivatives of the logarithm of the likelihood given in the previous section can be used to estimate the asymptotic variance of the maximum likelihood estimates of $\alpha$ and $\beta$. The variance-covariance matrix of the parameters $\alpha$ and $\beta$ is approximated by

$$Cov(\alpha,\beta) = -\begin{pmatrix} \partial^2 LL/\partial \alpha^2 & \partial^2 LL/\partial \alpha \partial \beta \\ \partial^2 LL/\partial \alpha \partial \beta & \partial^2 LL/\partial \beta^2 \end{pmatrix}^{-1}$$

where $[.]^{-1}$ is the inverse of the matrix, $\partial^2 LL/\partial \alpha^2$ is the second partial derivative of the logarithm of the likelihood with respect to $\alpha$, $\partial^2 LL/\partial \beta^2$ is the second partial derivative of the logarithm of the likelihood with respect to $\beta$, and $\partial^2 LL/\partial \alpha \partial \beta$ is the partial derivative of the logarithm of the likelihood with respect to $\alpha$ and $\beta$. The approximation of the covariance is then given by

$$Cov(\alpha,\beta) = -\begin{pmatrix} \partial^2 LL/\partial \beta^2 & -\partial^2 LL/\partial \alpha \partial \beta \\ -\partial^2 LL/\partial \alpha \partial \beta & \partial^2 LL/\partial \alpha^2 \end{pmatrix} / \text{Determinant}$$

where

$$\text{Determinant} = 1 / [\, \partial^2 LL/\partial \alpha^2 \times \partial^2 LL/\partial \beta^2 - (\partial^2 LL/\partial \alpha \partial \beta)^2 \,]$$

The second-order derivatives used for the estimation of the variance-covariance matrix are:

$$\frac{\partial^2 LL}{\partial \alpha^2} = \sum -Observed_k/\alpha^2$$

$$\frac{\partial^2 LL}{\partial \alpha^2}$$

$$\frac{\partial^2 LL}{\partial \beta^2} = \sum -(Observed_k \times d_k^2) / (1 + \beta \times d_k)^2$$

$$\frac{\partial^2 LL}{\partial \alpha \partial \beta} = \sum -Expected_k \times d_k$$

A better asymptotic variance calls for substituting the variance-covariance matrix of $\alpha$ and $\beta$ by the expected value of the above matrix. That is, by replacing the observed number of cancer deaths in a dose group k ($Observed_k$) by its expected value (i.e., $E(Observed_k) = Observed_k = \alpha \times Expected_k \times (1 + \beta \times d_k)$). After substituting $Observed_k$ by $\alpha \times Expected_k \times (1 + \beta \times d_k)$ in the second-order derivatives and the variance-covariance matrix given above, and some simplification, the better approximation of $Cov(\alpha,\beta)$ is given by:

$$Cov(\alpha,\beta) = \begin{pmatrix} \sum Expected_k \times (1 + \beta \times d_k)/\alpha & \sum Expected_k \times d_k \\ \sum Expected_k \times d_k & \alpha \times \sum (Expected_k \times d_k^2) / (1 + \beta \times d_k) \end{pmatrix}^{-1}$$

The determinant for the matrix is

$$Determinant = [ \sum Expected_k \times (1 + \beta \times d_k) ] \times [ \sum (Expected_k \times d_k^2) / (1 + \beta \times d_k) ] - ( \sum Expected_k \times d_k )^2$$

and the variance of the maximum likelihood estimate of $\alpha$ is

$$var(\alpha) = [ \alpha \times \sum (Expected_k \times d_k^2) / (1 + \beta \times d_k) ] / Determinant,$$

while the variance of the maximum likelihood estimate of $\beta$ is

$$var(\beta) = [ \sum Expected_k \times (1 + \beta \times d_k)/\alpha ] / Determinant,$$

and the standard errors (SE) of the estimated parameters are the square root of their respective variances.

# Appendix E: Document Revision Record of Change

# 2015 Revision Record of Change

This section is intended to serve as a record of change for the 2015 revision to the Guidelines. This record of change contains the same information as was posted during the public comment period. It highlights, in general, where and what changes were made.

## Outline



## 1.0 New Additions to the Guidelines

This section summarizes the changes that are new additions to the Guidelines. Additions to the Guidelines are visible by red underlined text.

### 1.1 Methods to Derive 24-h AMCVs

#### *1.1.1 Background*

In the summer of 2011, the draft 2012 revision to the Guidelines underwent an expert panel letter peer review, which was organized by Toxicology Excellence for Risk Assessment. At the same time, public comments were also accepted. The final report from the peer review can be obtained from TERA Final Report[6]. Included in this draft were procedures to develop 24-h ReVs (Chapter 4), this chapter was also reviewed by the expert peer review panel.

Based on favorable peer review comments, the TCEQ revised the 24-h procedures. One of the suggestions was to include chemical-specific examples for developing 24-h ReVs.

[6] http://www.tera.org/peer/tceqesl/

In order for TCEQ staff to have the opportunity to derive chemical-specific 24-h ReVs, the section on deriving 24-h values was not included in the final RG-442 2012 revision.

In May 2012, the revised 24-h procedures and examples of 24-h ReVs for acrolein, 1,3-butadiene, and benzene were presented as a case study to the science panel for Beyond Science and Decisions: From Problem Formulation to Dose-Response Assessment (May 28-30, 2013), Workshop 6: Workshop 6 website[7]. After receiving comments from the science panel, the procedures to develop 24-h ReVs were revised again.

In March 2014, the TCEQ posted a White Paper: TCEQ Guidelines to Develop 24-Hour Inhalation Reference Values (hereafter referred to as the 24-h White Paper) for a 90-day public comment period. Proposed 24-h ReVs for benzene, 1,3 butadiene, and formaldehyde were posted at the same time using the 24-h White Paper methodology. On June 16, 2014, the 24-h White Paper was revised based on public comments and posted as final.

At this point, TCEQ would like to revise the Guidelines to include the 24-h White Paper. Since the methods in the 24-h White Paper have undergone two sets of peer review and two rounds of public comments, these methods are considered final.

### *1.1.2 Changes*

The following identifies where these methods were included in the Guidelines:

1) Section 4.6 24-Hour AMCVs

   a. The bulk of the 24-h White Paper was added into the Guidelines as Section 4.6 in Chapter 4, with little change from the 24-h White Paper.

      i. This section was titled: 24-Hour AMCVs

      ii. Document Description and Intended Use was put directly under the section header as background information.

      iii. The first paragraph and paragraphs three through seven under Document Description and Intended Use from the 24-h White Paper were not included. These paragraphs are redundant as they give background information that already exist in the Guidelines or not necessary for inclusion into the Guidelines.

      iv. Chapter and Section headings from the 24-h White Paper were adapted to fit the structure of Section 4.6 in the Guidelines, as well as the Figure and Equation.

      v. Citations were added, if not already present, to the Guidelines.

## 1.2 Derivation of Generic ReVs

### *1.2.1 Background*

[7] http://www.allianceforrisk.org/ARA_Dose-Response.htm

The Guidelines currently allow for the derivation of generic ESLs for chemicals with limited toxicity data. This addition also allows for the derivation of generic ReVs, where appropriate, for chemicals with limited toxicity data.

### *1.2.2 Changes*

1) Language to include generic ReV development was added to the following:
    a. Section 1.5.2
    b. Table 1-4
    c. Table 1-5
    d. Section 3.11
    e. Section 3.15
    f. Section 3.15.1
    g. Section 3.15.2.3
        i. Equation 3-13
    h. Section 4.5
        i. Figure 4-2
    i. Section 4.5.1
    j. Section 4.5.3
    k. Section 5.4

## 2.0 Updates to the Guidelines

This section summarizes the changes (updates) to the current Guidelines (RG-442, rev 2012). Additions to the Guidelines are visible by red underlined text.

## 2.1 Dosimetric Adjustment Update

### *2.1.1 Background*

TCEQ finalized the White Paper: Revisions to Animal-to-Human Inhalation Dosimetric Adjustments, in November 2013. This White Paper updated Section 3.9.1, Default Dosimetry Adjustments for Gases (RG-442, rev 2012), to include information recommended in the following USEPA documents on animal-to-human inhalation gas dosimetric adjustments:

- Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment (USEPA 2012).
- STATUS REPORT: Advances in Inhalation Dosimetry of Gases and Vapors with Portal of Entry Effects in the Upper Respiratory Tract (USEPA 2011).
- STATUS REPORT: Advances in Inhalation Dosimetry for Gases with Lower Respiratory Tract and Systemic Effects (USEPA 2009).

These three USEPA documents summarize new scientific developments and advancements in animal-to-human inhalation dosimetry for gases and vapors from those provided in USEPA's 1994 Reference Concentration (RfC) Methodology.

The intent of interspecies dosimetric extrapolation is to adjust an externally applied inhalation animal exposure to achieve the same internal concentration in humans. According to Section 3.9 of the Guidelines, when species-specific data for dosimetric adjustment from animal data to humans are not available, simplified mathematical models can be used as conservative default adjustments. The 2012 revision of the Guidelines directed readers to the 1994 USEPA's RfC Methodology for a thorough understanding of the default dosimetric adjustments for respiratory tract or systemic health effects.

Since default inhalation interspecies dosimetric adjustments have been reviewed and updated by USEPA (2012), a corresponding review of the updated information was undertaken by the TCEQ and the recommendations outlined in the White Paper were incorporated for animal-to-human dosimetric adjustments.

### *2.1.2 Changes*

1) Section 3.9.1
    a. Language was added to reflect the changes in animal-to-human dosimetric adjustments recommended by USEPA and adopted by TCEQ.

## 2.2 Methods to Derive Odor Values Update

### *2.2.1. Background*

On April 15, 2015, a 90-day public comment period began on a Position Paper: Approaches to Derive Odor-Based Values (hereafter referred to as the Odor Position Paper).

Texas is the only state in the United States that regulates odor nuisance based upon the use of odor-based values. The TCEQ is required by the Texas Clean Air Act (Chapter 382 of the Texas Health and Safety Code) to conduct air permit reviews and ensure that the construction of a facility or modification of an existing facility will use at least the best available control technology and be protective of human health and physical property.

The intent of an odor-based value is regulation of odor with the intention to prevent odor nuisance conditions, rather than prevention of odor detection. Odor nuisance generally occurs when short-term emissions from a source are of character, duration, intensity, and frequency to constitute a nuisance condition, as described in TCEQ guidance (Odor Complaint Investigation Procedures). Briefly, when the TCEQ investigates an odor complaint, evidence is gathered to evaluate four primary characteristics of odor (FIDO procedure):

- frequency (how often an odor is experienced);
- intensity (how strong is the odor);
- duration (the duration that the odor is experienced); and

- offensiveness (how unpleasant the odor is to most people).

Given that these characteristics are the primary basis upon which the TCEQ will evaluate odor complaints, it is important for odor-based values to be derived with the intention of preventing odor nuisance conditions. Therefore, TCEQ is revising Chapter 2 of the Guidelines; the odor Section in Chapter 2 will be replaced by the Odor Position Paper, when finalized.

### *2.2.2 Changes*

1) Section 2.2 Odor-Based ESLs

   b. All Sections under Section 2.2 in the Guidelines were removed.

   c. The text under Section 1.0 Air Quality and Protection of Welfare from Odor Nuisance from the Odor Position Paper was added, with unnecessary text removed.

   d. The Guidelines now refer detailed information on derivation of odor-based values to the Odor Position Paper.

   e. References and text in the Guidelines were amended with the removal of citations that are no longer in the Guidelines. Subsequently, changes were made to any affected citations throughout the document.

## 2.3 Uncertainty Factor Update

### *2.3.1 Background*

Although the Guidelines discuss short-term reproductive effects in the acute section, their importance is not reflected in Tables 4-2 and 5-2, or the acute UFD section. This disconnect in the Guidelines is being updated at this time. This update also includes route-to-route and sufficiently similar compounds or mixtures that are not represented in the tables and text in regards to uncertainty factors.

### *2.3.2 Changes*

1) Language was added to, or clarified in, the following:

   a. Section 4.2.4.1

   b. Table 4-2 Footnote

   c. Section 4.4.2.2

   d. Table 5-2 Footnote

   f. Section 5.5.2

## 2.4 Miscellaneous Updates

There are several miscellaneous updates, including some minor editorial updates to the Guidelines.

1) Section 3.11.1.2

a. Changed Draft USEPA (2011b) reference to finalized reference (USEPA 2014).

b. Change was made to reference list, and subsequently, any affected citations throughout the document.

2) Figure 4-2

a. "Route-to-Route Extrapolation, or" was added to the Tier III box

b. "ReV or" was added between "generic" and "ESL" in the Tier III box

3) Section 7.12

a. Added endogenous human breath statement to the reality check section.

4) Miscellaneous editorial updates throughout the document.