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Development of Effects Screening Levels, Reference Values, and Unit Risk Factors

April 2005

Texas Commission on Environmental Quality
Toxicology Section
Chief Engineer's Office

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The Toxicology Section also acknowledges the following Reviewers:

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Document Description and Intended Use

This is a technical guidance document that describes the process used by staff of the Toxicology Section (TS) to develop Effects Screening Levels (ESLs), Inhalation Reference Values (ReVs), and Unit Risk Factors (URFs). Although this document is primarily written as guidance for the TS staff, it also documents the ESL, ReV, and URF development methodology for any interested person with training in inhalation toxicology and risk assessment.

ESLs are chemical-specific air concentrations set to protect human health and welfare. Short-term ESLs are based on data concerning acute health effects, odor nuisance potential, and vegetative effects, while long-term ESLs are generally based on data concerning chronic noncarcinogenic and/or carcinogenic health effects. Before a health-based screening level can be calculated, a toxicity assessment involving hazard identification and dose-response assessment is conducted and toxicity factors are derived. These toxicity factors are referred to as inhalation ReVs and URFs. ReVs are based on the most sensitive, relevant, noncarcinogenic health effects reported in the literature. Acute ReVs are health-based exposure concentrations used in assessing health risks of short relatively high chemical exposures. Chronic ReVs are health-based exposure concentrations that specify safe levels of exposure over a lifetime. Health-based URFs are used for the evaluation of chronic exposure to carcinogens. ReVs and URFs are used to calculate screening levels (i.e., ESLs) that correspond to specific risk and hazard levels.

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ACRONYMS AND ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Level
AIHA	American Industrial Hygiene Association
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 level
BMDS	Benchmark Dose Software
BMR	Benchmark response
C	Concentration
Cal EPA	California Environmental Protection Agency
CCRIS	Chemical Carcinogenesis Research Information System
COC	Chemical of concern
CSAF	Chemical-specific adjustment factor
DAF	Dosimetric adjustment factor
DART	Developmental and Reproductive Toxicology
DSD	Development support document
DTIC	Defense Technical Information Center
E	Exposure level
ERPG	Emergency Response Planning Guideline
ESL	Effects Screening Level
ESL_{Odor}	Odor-based Effects Screening Level
ESL_{Veg}	Vegetation-based Effects Screening Level
$^{Acute}ESL_{Noncarc}$	Acute Effects Screening Level for Noncarcinogens
$^{Acute}ESL_{Odor}$	Acute Odor-based Effects Screening Level
$^{Acute}ESL_{Veg}$	Acute Vegetation-based Effects Screening Level
$^{Chronic}ESL_{Carc}$	Chronic Effects Screening Level for Carcinogens
$^{Chronic}ESL_{Noncarc}$	Chronic Effects Screening Level for Noncarcinogens
ETIC	Environmental Teratology Information Center
FEDRIP	Federal Research in Progress

1	GLC	Ground level concentration
2	HEAST	Health Effects Assessment Summary Tables
3	HEC	Human equivalent concentration
4	HED	Human equivalent dose
5	HQ	Hazard quotient
6	HSDB	Hazardous Substances Data Bank
7	IARC	International Agency for Research on Cancer
8	IDLH	Immediately Dangerous to Life or Health
9	IPCS	International Programme on Chemical Safety
10	IRIS	Integrated Risk Information System
11	K	Constant level or severity of response
12	LC_{50}	Concentration producing lethality in 50% of experimental animals
13	LC_{Lo}	Lowest concentration producing lethality
14	LD_{50}	Dose producing lethality in 50% of experimental animals
15	LOAEL	Lowest-observed-adverse-effect-level
16	MAK	Federal Republic of Germany Maximum Concentration Values in the Workplace
17	MF	Modifying factor
18	MOE	Margin of exposure
19	MRL	Minimal Risk Level
20	NAAQS	National Ambient Air Quality Standards
21	NCI	National Cancer Institute
22	NIOSH	National Institute for Occupational Safety and Health
23	NLM	National Library of Medicine
24	NOAEL	No-observed-adverse-effect-level
25	NOEL	No-observed-effect-level
26	NRC	National Research Council
27	NTIS	National Technical Information Service
28	NTP	National Toxicology Program
29	OEHHA	Office of Environmental Health Hazard Assessment
30	OEL	Occupational Exposure Limit
31	OSHA	Occupational Safety and Health Administration
32	PBPK	Physiologically-based pharmacokinetic model

PCBs	Polychlorinated biphenyls
PEL	Permissible Exposure Limit
POD	Point of departure
POE	Portal of entry
ppbv	parts per billion by volume
PPRTV	Provisional Peer-Reviewed Toxicity Value
PUBMED	Public Medicine
RDDR	Regional deposited dose ratio
REL	Reference Exposure Level
ReV	Reference Value
RfC	Reference concentration
RfD	Reference dose
RGDR	Regional gas dose ratio
R_{GM}	Geometric mean ratio
RPF	Relative potency factor
RTECS	Registry of Toxic Effects of Chemical Substances
RtR	Route-to-route
SCAPA	Subcommittee on Consequence Assessment and Protective Action
STEL	Short-term Exposure Level
T	Time or exposure duration
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
THSC	Texas Health and Safety Code
TLV	Threshold Limit Value
TS	Toxicology Section
TWA	Time-Weighted Average
TWA-TLV	Time-Weighted Average Threshold Limit Value
UF	Uncertainty factor
URF	Unit risk factor
USEPA	United States Environmental Protection Agency

1	WEEL	Workplace Environmental Exposure Level
2	WOE	Weight of evidence

Chapter 1 Introduction to Effects Screening Levels, Reference Values, and Unit Risk Factors

I. Legal Authority and Regulatory Use

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.

The TCEQ also relies upon this authority to evaluate air monitoring data. Texas has the largest air toxics monitoring network in the country, receiving monitoring data for up to 186 chemicals at approximately 57 different locations throughout the state. The Toxicology Section (TS) is responsible for evaluating this air toxics monitoring data for potential health and welfare effects, as well as to help the agency prioritize its resources in the areas of Permitting, Compliance, & Enforcement.

The 1993 Risk Reduction Rule (Subchapters A and S of 30 Texas Administrative Code (TAC) Chapter 335) and the 1999 Texas Risk Reduction Program Rule (30 TAC 350) require the calculation of health-protective media cleanup levels for the TCEQ's remediation program. Inhalation toxicity factors are used, in accordance with rule requirements and guidance, to calculate source media (*i.e.*, soil, groundwater) cleanup levels that are health-protective of exposure to contaminants through the inhalation of vapors and/or particulate emanating from source media.

Sections II through IV of this chapter will introduce and define health- and welfare-based ESLs as well as health-based reference values (ReVs) for the evaluation of exposure to noncarcinogens and health-based

unit risk factors (URFs) for the evaluation of chronic exposure to carcinogens. Since the TS provides toxicological support to multiple program areas within the TCEQ, Section V of this chapter will discuss the uses of health- and welfare-based ESLs, health-based ReVs, and health-based URFs in different TCEQ program areas (i.e., air permitting, air monitoring, and remediation programs).

II. Definition of ESLs

ESLs are chemical-specific air concentrations set to protect human health and welfare. Exposure to air concentrations at or below the ESL is not likely to cause adverse health effects 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 screening levels, not ambient air standards. If predicted airborne levels of a contaminant exceed the ESL, adverse health or welfare effects would not necessarily be expected to result, but rather triggers a more in-depth review, as described in *Modeling and Effects Review Applicability: How to Determine the Scope of Modeling and Effects Review for Air Permits* (TCEQ 2001) (http://www.tnrcc.state.tx.us/permitting/airperm/nsr_permits/files/mera.pdf).

The focus of short-term ESLs is generally 1-h exposure duration, although exposure may occur on an intermittent basis. This duration is consistent with the TCEQ air permits modeling. Short-term ESLs for exposure durations other than 1 h may be needed based on reproductive/developmental endpoints. Long-term ESLs represent air concentrations to which a lifetime of exposure is expected to be free of adverse health effects for the general public.

Short-term ESLs are based on data concerning acute health effects, odor potential, and vegetative effects (Figure 1). Long-term ESLs are generally based on data concerning chronic noncarcinogenic and/or carcinogenic health effects (Figure 2). Therefore, before a short-term or long-term ESL can be developed, available information on each of these health and welfare effects is obtained as described in the following sections.

Figure 1. Procedure for Developing a Short-Term ESL

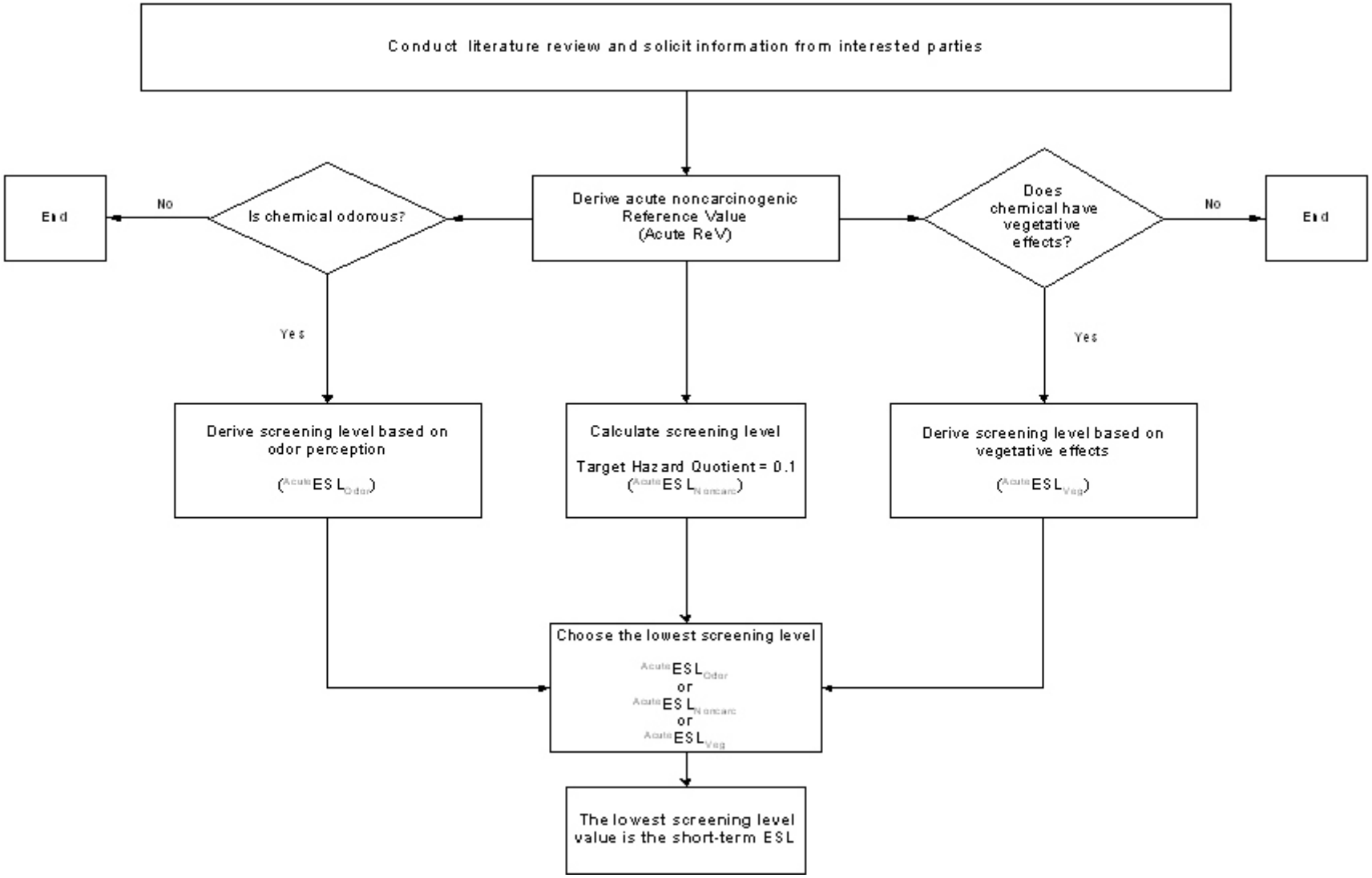
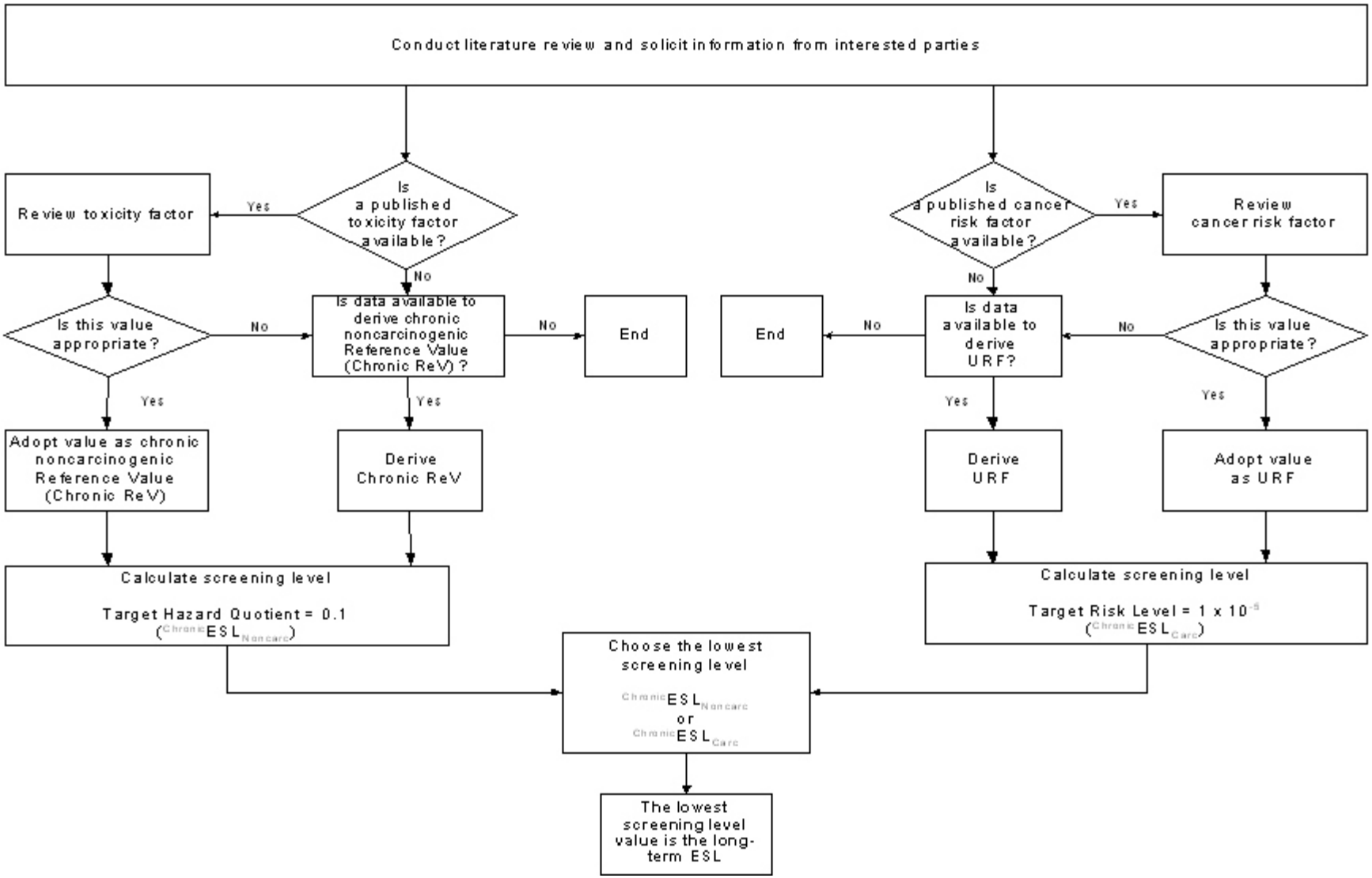


Figure 2. Procedure for Developing a Long-Term ESL



III. Definitions of Other Health- and Welfare-Based Screening Levels

A. Health-Based Screening Levels

Before a health-based screening level can be calculated, a toxicity assessment involving hazard identification and dose-response assessment is conducted and a toxicity factor is determined. The TS derives or adopts inhalation ReVs for both acute and chronic exposures to evaluate noncarcinogens (Chapters 2, 3, and 4), and inhalation URFs to evaluate carcinogens (Chapter 4).

A.1 Reference Values

An inhalation ReV for noncarcinogens is defined as an estimation of an inhalation exposure concentration for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse effects. It is derived from an appropriate point of departure (POD) (e.g., benchmark concentration lower confidence limit (BMCL), no-observed-adverse-effect-level (NOAEL), lowest-observed-adverse-effect-level (LOAEL)) with uncertainty/variability factors applied to reflect data limitations. The focus of an acute ReV is generally a 1-h exposure duration whereas a chronic ReV is for lifetime inhalation exposure. Acute ReVs based on reproductive/developmental effects may be derived for exposure durations other than 1 h. The acute ReV can be adjusted to other acute exposure durations using guidelines in Chapter 3 since averaging times other than 1 h may be needed to evaluate monitoring data.

ReVs are based on the most sensitive, relevant, adverse health effect reported in the literature. Acute ReVs are health-based exposure concentrations used in assessing health risks of short-term chemical exposures. Acute ReVs are derived from acute human studies, animal studies of less than four weeks duration, or from developmental toxicity studies conducted on animals. Chronic ReVs are health-based exposure concentrations used in assessing health risks of long-term (i.e. lifetime) chemical exposures. The chronic ReVs are derived from chronic human epidemiology studies, chronic animal studies, or well-conducted subchronic animal studies. ReVs are designed to protect the most sensitive individuals in a population by inclusion of uncertainty factors (UFs). UFs account for differences in sensitivity within human populations and uncertainties related to the applicability and completeness of the available data. Since UFs are incorporated to address data gaps and other uncertainties, exceeding the ReV does not automatically indicate an adverse health impact.

A.2 Unit Risk Factors

The dose-response assessment for linear carcinogens diverges from that conducted for noncarcinogens due to differences in the underlying dose-response concepts. Noncarcinogens are characterized by a threshold dose-response relationship, implying a concentration below which exposures are not expected to cause adverse effects in the general public. But for linear carcinogens, it is assumed that there exists no dose-response threshold (USEPA 2005a). Therefore, a linear extrapolation from the POD to the origin of the inhalation dose-response curve is performed to estimate excess lifetime cancer risk at lower doses. The slope of the line from this linear extrapolation is the inhalation URF, which is defined as the upper-bound excess cancer 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 $\mu g/m^3$). For nonlinear carcinogens that exhibit a threshold, a chronic ReV is developed using procedures that are similar to chronic noncarcinogenic ReVs, as discussed in Chapter 4.

A.3 Target Risk and Hazard Levels

Toxicity factors are used to calculate screening levels that correspond to specific risk and hazard levels. The risk/hazard level serves as a starting point in the development of scientifically defensible risk-based air concentrations or ESLs. In developing ESLs, it is important to establish a single acceptable risk/hazard level to ensure the same level of protection of human health and also taking into account cumulative exposure. In accordance with this approach, the TS uses a target hazard quotient (HQ) of 0.1 to calculate short-term and long-term screening levels for individual noncarcinogenic constituents and a risk management goal of 1×10^{-5} excess lifetime theoretical cancer risk in calculating screening levels for individual carcinogens (or a 1 in 100,000 excess theoretical cancer risk). These target risk and hazard levels account for cumulative exposure to multiple chemicals of concern (COCs) from different sources or environmental media, and in the case of acute exposure, cumulative effects of intermittent exposure to the chemical of concern.

A.3.1 Consideration of Cumulative Risk

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 addition to this provision in the Texas Water Code, other lines of evidence support consideration of cumulative exposure to chemicals. Monitoring data provide actual measured concentrations of chemicals in a given area. Multiple chemicals have been detected in air samples and therefore, exposure to multiple chemicals can occur. Monitoring data also indicate that intermittent exposure to a single chemical can occur. There are circumstances where exposure to multiple chemicals or multiple exposures to a single chemical are likely to exist. It is possible that the same chemical could be emitted from other sources (facilities) other than the permitted facility within an area. Furthermore, the permit review process may not account for every emission source that may be present at the permitted site. For example, emission sources authorized by standard permits or permit-by-rule emission sources may not be included in site-wide modeling for a given facility. When all these factors are considered, it is apparent that cumulative risk must be addressed in the development of health-based screening levels.

A.3.1.1 Noncarcinogens

For noncarcinogens, the HQ is defined as the ratio of the exposure concentration (E) to the reference toxicity factor (ReV). Both E and ReV are expressed in the same units ($\mu g/m^3$) and represent the same exposure period (i.e., acute or chronic exposure):

$$HQ = E / ReV$$

This equation can be rearranged to solve for the exposure concentration ($\mu g/m^3$) for a specified exposure period that corresponds to a specified target hazard quotient:

$$E = HQ \times ReV$$

For noncarcinogens, the screening level of a chemical that corresponds to a target HQ of 0.1 for an acute exposure period ($^{Acute}ESL_{Noncarc}$) or a chronic exposure period ($^{Chronic}ESL_{Noncarc}$) is calculated as follows:

$$^{Acute}ESL_{Noncarc} = HQ \times \text{acute ReV}$$
$$= 0.1 \times \text{acute ReV}$$

$$^{Chronic}ESL_{Noncarc} = HQ \times \text{chronic ReV}$$
$$= 0.1 \times \text{chronic ReV}$$

A.3.1.2 Carcinogens

For carcinogens, the risk level is defined as the product of E and the URF. Both E and URF are expressed in the same units (i.e., $\mu g/m^3$ and $(\mu g/m^3)^{-1}$, respectively) and represent a chronic exposure:

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

This equation can be rearranged to solve for E concentration ($\mu g/m^3$) for a chronic exposure period that corresponds to a specified target risk level:

$$E = \text{Risk Level} \,/\, URF$$

For carcinogens, the screening level of a chemical that corresponds to a target risk level of 1×10^{-5} for a chronic exposure period ($^{Chronic}ESL_{Carc}$) is calculated as follows:

$$^{Chronic}ESL_{Carc} = (1 \times 10^{-5}) \,/\, URF$$

Please refer to Chapter 5, Section III.C for procedures for calculating the screening level of a mutagenic carcinogen that accounts for increased cancer risk due to early-life exposure (USEPA 2005b).

B. Welfare-Based Screening Levels

B.1 Derivation of Odor-Based ESLs

The odor-based ESLs (ESL_{Odor}) are set at a chemical's odor threshold. Types of odor thresholds include the detection threshold and the recognition threshold. The definitions of odor threshold values are as follows:

1. Detection Threshold (Absolute Threshold): the concentration at which 50% of the odor panel detected the odor.
2. 50% Recognition Threshold: the concentration at which 50% of the odor panel defined the odor as being representative of the odorant being studied.
3. 100% Recognition Threshold: the concentration at which 100% of the odor panel defined the odor as being representative of the odorant being studied.

In order to identify and interpret the odor threshold values of chemicals that are odorous, the TS staff conducts a comprehensive literature search of published odor thresholds for a variety of air contaminants. Some of these thresholds are derived from original research and some are from literature reviews. Sources of information for odor thresholds are listed in Appendix B *Source of Information for Odor Thresholds*. It should be noted that the reported odor threshold data differ considerably. It is not uncommon for reported odor threshold values to range over several orders of magnitude for the same chemical. For example, 26 values were reported for hydrogen sulfide, ranging from 0.072 - 1,400 parts per billion by volume (ppbv), a factor of 10,000. Major sources of variability include: different types of data sources; differences in experimental methodology; and human olfactory response characteristics, which exhibit a great deal of inter-individual variability.

In a report: "Odor Threshold for Chemicals with Established Occupational Health Standards", the American Industrial Hygiene Association (AIHA 1989) reviewed and critiqued odor threshold data for 182 chemicals which have a threshold limit value (TLV). The project developed a set of criteria for acceptability of odor threshold measurement techniques to evaluate the experimental odor threshold determinations reported in the literature. The criteria are briefly summarized below.

- Panel size of at least six people per group
- Panelist selection based on odor sensitivity
- Panel calibration
- Consideration of vapor modality (air or water)
- Diluent in accord with compound
- Presentation mode that minimizes additional dilution (ambient) air intake
- Analytical measurement of odorant concentration
- Calibration of flow rate and face velocity for (olfactometers)

- Concentration presentation series that reduces olfactory fatigue
- Repeated trials
- Forced-choice procedure
- Concentration steps increasing by a factor of two or three

Of the 182 odorants with a TLV, the AIHA review resulted in 110 compounds, from 36 reference sources, that had odor threshold values that met evaluation criteria (AIHA 1989). The AIHA approach was then used by the United States Environmental Protection Agency (USEPA 1992) to conduct critical reviews of published odor threshold values for the chemicals listed as hazardous air pollutants (HAPs) in the 1990 Clean Air Act Amendments of 1990. The review resulted in 57 odorous HAPs, from 16 reference sources, that had acceptable odor threshold values (USEPA 1992).

To set appropriate ESL_{Odor} for odorous air contaminants, the odor threshold values for chemicals that have been critiqued and accepted by AIHA and USEPA are used by TS. The primary experimental odor threshold references for these acceptable values that met the AIHA and/or USEPA's evaluation criteria are listed in Appendix C *List of Accepted Odor References Based on the AIHA and USEPA's Evaluation Criteria.* In addition, odor thresholds reported in these accepted odor references for chemicals that were not evaluated by AIHA and USEPA are also used in setting $ESL_{Odor.}$ In general, the ESL_{Odor} is set at the lowest acceptable 50% detection threshold. However, when only recognition thresholds are available, the ESL_{Odor} is set at the lowest acceptable 50% recognition threshold. When only 100% recognition thresholds are available, the ESL_{Odor} is set at the lowest acceptable 100% recognition threshold.

The accepted odor references listed in Appendix C, which were reported prior to 1989, can be superceded by new research. Therefore, any experimental threshold values reported after 1989 are assessed based on the same criteria established by AIHA and USEPA.

The ESL_{Odor} is generally set at the lowest 50% detection threshold concentration based on exposure of humans to chemicals for periods significantly less than 1 h. These short duration exposure periods are not adjusted to reflect a 1-h exposure duration because the perception of odor is concentration dependent but not duration dependent (i.e., an enhanced response is not produced by prolonged exposure) (NRC 2001). It should be noted that if the general public were exposed to an air concentration at the ESL_{Odor}, it would not be expected to cause direct health effects, but exposure to these levels would be expected to contribute to an odorous condition and possibly indirect health effects. Persistent or recurrent exposure to strong odors could cause indirect short-term adverse health effects, which may include: mild irritation, nausea, vomiting, loss of coordination, or headache in some individuals.

B.2 Consideration of Vegetation Effects

If a chemical's adverse effect levels in plants are substantially higher than its odor threshold or adverse effect levels in humans, available plant toxicity information is presented in the Development Support Document (DSD; see Section VII), but a vegetation-based ESL ($^{Acute}ESL_{Veg}$) is not developed. This approach is taken in such situations for the following reasons: development of an $^{Acute}ESL_{Veg}$ is not critical for the protection of health and welfare; the amount and quality of plant toxicity information is likely to be low; and, the provision of any available information in the DSD will assist staff in evaluating questions about the potential for adverse vegetative effects.

If adverse effects in plants are expected to occur at concentrations close to or below levels of odor or human health concern, the following guidance is applied if data are available. The $^{Acute}ESL_{Veg}$ is generally

set to protect sensitive plant species from serious adverse effects. Hazard identification focuses on: (1) plant species that are native to Texas or known to be grown in the state; and (2) relatively more serious adverse effects such as defoliation, abscission of flower buds, epinasty, and disproportionate leaf growth, rather than milder effects such as slight dry sepal injury. Relevant toxicity information is obtained from published scientific literature and plant experts as necessary. Several publications which provide general information about air pollution and plant damage and are available in the TCEQ State Library Collection (Air Pollution Control Association 1970; Air Pollution and Plant Life 2002; University of California, Irvine 1977; U.S. Department of Agriculture 1974; American Chemical Society 1974).

IV. Determination of Short-Term and Long-Term ESLs

Figure 1 (page 3) illustrates the process whereby health- and welfare-based ESLs are used to determine the short-term ESL. The lowest value of the following health- and welfare-based ESLs is the short-term ESL:

$$^{\text{Acute}}\text{ESL}_{\text{Noncarc}}$$

$$^{\text{Acute}}\text{ESL}_{\text{Odor}}$$

$$^{\text{Acute}}\text{ESL}_{\text{Veg}}$$

Figure 2 (page 4) illustrates the process whereby health-based ESLs are used to determine the long-term ESL. The lowest value of the following health-based ESLs is the long-term ESL:

$$^{\text{Chronic}}\text{ESL}_{\text{Noncarc}}$$

$$^{\text{Chronic}}\text{ESL}_{\text{Carc}}$$

V. The Use of ESLs, ReVs, and URFs in TCEQ Program Areas

The TS develops ESLs, ReVs, and URFs to provide toxicological support to multiple program areas within the TCEQ (Table 1). In the air permitting review process, the TS utilizes short- and long-term ESLs to evaluate proposed emissions by facilities to protect human health and welfare. For evaluation of ambient air monitoring results, acute and chronic ReVs and URFs are used to assess human health. To assess potential short-term welfare effects for monitoring results, the TS uses odor- and vegetative-based ESLs. Lastly, in accordance with rule requirements and guidance, the TS uses chronic ReVs and URFs as toxicity factors for both the 1993 Risk Reduction Rule (Subchapters A and S of 30 Texas Administrative Code (TAC) Chapter 335) and the 1999 Texas Risk Reduction Program Rule (30 TAC 350) to derive health-protective media cleanup levels for the TCEQ's remediation program. More specifically, chronic ReVs and URFs are used to calculate source media (*i.e.*, soil, groundwater) cleanup levels that are health-protective of exposure to contaminants through the inhalation of vapors and/or particulate emanating from source media. These cleanup levels, which are protective of the inhalation route of exposure, are incorporated into cleanup values which are protective of all applicable routes of exposure (*e.g.*,

inhalation, incidental ingestion, dermal contact, consumption of vegetables grown in affected soil) for the receptor of concern (*e.g.*, resident, commercial/industrial worker).

Table 1
ESLs, ReVs, and URFs in Different TCEQ Program Areas

Acute Exposure		
Air Permitting	Air Monitoring	1993 Risk Reduction Rule and 1999 Texas Risk Reduction Program
Short-Term ESL[1]	Acute ReV	NA
	$^{Acute}ESL_{Odor}$	NA
	$^{Acute}ESL_{Veg}$	NA
Chronic Exposure		
Air Permitting	Air Monitoring	1993 Risk Reduction Rule and 1999 Texas Risk Reduction Program
Long-Term ESL[2]	Chronic ReV	Chronic ReV
	URF	URF

[1] Lowest value of $^{Acute}ESL_{Noncarc}$, $^{Acute}ESL_{Odor}$, or $^{Acute}ESL_{Veg}$ (Figure 1)

[2] Lowest value of $^{Chronic}ESL_{Carc}$ or $^{Chronic}ESL_{Noncarc}$ (Figure 2)

NA - Not applicable

VI. Exemption of Substances from ESL Development

ESLs are developed for all substances determined by the TS to be airborne toxicants. Substances not considered to be airborne toxicants are exempt from ESL development. A substance is accorded exemption status by the TS if the scientific evidence or prior regulatory experience indicates that the substance should not be classified as an airborne toxicant. In addition, ESLs are not developed for constituents that must meet National Ambient Air Quality Standards (NAAQS) or state rules and regulations (see Appendix D) unless directed to do so by a change in state law. For an updated list of exempt substances, please visit the TCEQ website (add website URL). The categorization of substances as exempt from ESL development is a dynamic process. Substances may be added or removed from exemption status if scientific evidence or regulatory experience dictates a change in status. The TS

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. An example of substances currently exempt from ESL development is included in Appendix E *Example of Substances Exempt from ESL Development.*

VII. ESL Development Support Document (DSD)

The purpose of the DSD is to provide a summary of information on the ESL development process and the key toxicity studies/information used to derive toxicity factors. First, several summary tables of key information are provided. Then, a brief summary of occurrence and use of the chemical followed by a review of the key acute and chronic toxicity studies used to derive reference values is included. Finally, a section entitled "Other Relevant Information" may be included, if additional information pertinent to an understanding of the toxicity of the compound needs to be included. At the end of the document, 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 TS staff but were not discussed in the DSD.

VIII. ESL Peer-Review and Public Comment Process

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

Data evaluation, data selection, and the development of ESLs are all performed as a collaborative effort among staff toxicologists. An ESL Development Team composed of 2-3 TCEQ toxicologists is formed for each chemical under review. The product of this effort is a draft DSD. The draft DSD is subsequently circulated to other TCEQ toxicologists for review and comment. Suggested changes/revisions are incorporated, and the DSD is considered a proposed document.

The proposed DSD is published on the TCEQ website for a 30-day review and comment period. Following publication of the proposed ESLs on the TCEQ website, the ESL Development Team reviews the public comments, addresses and resolves relevant issues, and seeks a consensus on the original or modified ESL values and the accompanying scientific rationale. The responses of the TS to public comments are available on the TCEQ website. Following resolution of relevant issues raised through public review and comment, the ESL values are classified as final and the final DSD is posted on the TCEQ website. The ESL may be reviewed if compelling new data becomes available.

Chapter 2 Common Procedures Used to Derive Acute and Chronic Toxicity Factors

I. Federal and State Guidance Documents

The procedures used to develop acute and chronic ReVs and inhalation URFs 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. 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 ReVs and inhalation URFs. Chapter 3 addresses the procedures that are unique to the derivation of acute ReVs, and Chapter 4 addresses the procedures that are unique to the derivation of chronic ReVs and URFs.

The procedures for developing chronic toxicity values are fairly well established (i.e., RfCs for the evaluation of systemic toxicants and URFs for the evaluation of carcinogens). 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 are still being formalized. The TS reviewed numerous federal and state guidance documents and scientific articles, but used the following documents as main sources of information: USEPA 1994; USEPA 2002; NRC 2001; OEHHA 1999; USEPA 1998; OEHHA 2000; USEPA 2005a; and USEPA 2005b.

The TS closely follows procedures provided in the above mentioned guidance documents so a detailed discussion of procedures that are well established is not included. 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 TS employed different procedures than those recommended in the guidance documents, then a detailed discussion is included to clarify the approaches that the TS used in deriving ReVs or URFs.

II. Overview

Acute ReVs, chronic ReVs, and URFs (hereafter referred to as toxicity factors) are derived from dose-response assessments of 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 relationship exists. Notwithstanding the use of valid references and guidelines, the final determination of an acceptable toxicity factor for each chemical is based on professional scientific judgement.

The toxicity factor development process includes the following steps:

- Conduct literature search
- Identify and evaluate existing toxicity values and, if appropriate, adopt as the toxicity factor
- If appropriate toxicity values do not exist, choose a key study, emphasizing human data

- Identify critical biological endpoint
- Estimate threshold for effect (BMCL, NOAEL, or other appropriate POD)
- Perform temporal/dosimetric adjustments
- Account for uncertainties in data.

A. Data Sources

The TS uses scientifically defensible studies, identified through reviewing literature from reputable sources, to develop toxicity factors. 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 data from private industry or other private organizations.

Databases

TOXNET (http://toxnet.nlm.nih.gov), which is supported by the National Library of Medicine (NLM) and includes searchable databases from

TOXLINE

Developmental and Reproductive Toxicology and Environmental Teratology Information Center (DART/ETIC)

EPA's database containing peer reviewed mutagenicity test data (GENE-TOX).

Chemical Carcinogenesis Research Information System (CCRIS)

National Cancer Institute (NCI)

Hazardous Substances Data Bank (HSDB)

ChemIDplus

Public Medicine (PUBMED) (http://www.ncbi.nlm.nih.gov/PubMed)

Registry of Toxic Effects of Chemical Substances (RTECS) (http://www.cdc.gov/niosh/rtecs.html)

National Technical Information Service (NTIS) (http://www.ntis.gov)

Integrated Risk Information System (IRIS) (http://www.epa.gov/iris)

Federal Research in Progress (FEDRIP) (http://grc.ntis.gov/fedrip.htm)

Defense Technical Information Center (DTIC) (http://www.dtic.mil)

Chemfinder (http://chemfinder.cambridgesoft.com)

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 (http://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) (http://www.iarc.fr)

Merck Index

National Toxicology Program (NTP) (http://ntp-server.niehs.nih.gov)

Patty's Industrial Hygiene and Toxicology

General References for Regulatory Information and Standards

American Industrial Hygiene Association (AIHA) (http://www.aiha.org)

American Conference of Government and Industrial Hygienists (ACGIH) (http://www.acgih.org/home.htm)

National Ambient Air Quality Standards (NAAQS) (http://www.epa.gov/ttn/naaqs)

National Institute for Occupational Safety and Health (NIOSH) (http://www.cdc.gov/niosh/homepage.html)

Occupational Safety and Health Administration (OSHA) (http://www.osha.gov)

Federal Republic of Germany Maximum Concentration Values in the Workplace (MAK)

EPA Health Effects Documents

California Environmental Protection Agency (Cal EPA) (http://www.calepa.ca.gov)

B. Identification of the Critical Adverse Effect

The first step in toxicity factor development is the identification of the relevant, adverse health effect observed at the lowest concentration in the most appropriate, sensitive species (i.e., critical adverse effect) reported in the literature. Several factors are considered in this process, such as evidence of a dose-response relationship, reproducibility of findings, mechanism or mode of action, and consistency with other studies. The strength, consistency, and specificity of the association between chemical exposure and adverse effect is assessed. Finally, a temporal association between exposure to the compound and the adverse health effect is verified.

C. Selection of Key Studies

Evaluation and selection of key studies follows the guidelines detailed by USEPA (1994; 2005a) and NRC (2001). Studies that contribute most significantly to the weight of evidence are selected as key studies. Key studies are used in estimating a threshold for adverse effects and in identifying the critical adverse

effect. These studies may involve a human population studied in an epidemiological, clinical or experimental exposure setting, or they may involve experimental studies with animals.

C.1 Human Studies

Human data are preferred as the source on which to base toxicity factors. Three study types are relied upon for human exposure data (i.e., epidemiology, controlled human inhalation experiments, and case reports). Each of the three study types has limitations and advantages. One advantage that is common to each is the potential verification that adverse effects demonstrated in animal studies are also observed in the human population (i.e., the data may be useful in hazard assessment).

C.1.1 Epidemiology

Epidemiology provides data about potential cause-effect relationships that are useful in hazard identification, and if accompanied by accurate exposure data, may be useful in the dose-response assessment for a toxicant. Use of epidemiological studies can be limited by such issues as confounding factors (e.g., predisposing lifestyles, preexisting health problems) and reliability of the exposure data. Data from epidemiological studies have been used by various organizations to establish health ReVs. The TS evaluates the supportive data for each value, and if acceptable, those data are used to derive a toxicity factor.

C.1.2 Controlled Exposure Studies

Human exposure studies involve well-controlled environments in which short-term effects of exposure to a toxicant may be documented. Moreover, they can provide data about the disposition of the toxicant and may identify biomarkers of early exposure that may be used for toxicity factor derivation. 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.

C.1.3 Case Reports

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

C.2 Animal Data

When relevant human studies are not available, animal data are used to develop toxicity factors. Several factors are considered when selecting key animal studies. 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 studies.

D. Point of Departure

Table 1 lists the definitions of terms relevant to a discussion of Point of Departure (POD). The POD is the dose-response point that marks the beginning of a low-dose extrapolation for an adverse effect. When choosing the critical adverse effect, it should be noted that all effects reported for a substance are not necessarily considered adverse. The USEPA defines adverse effects as "any effects 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 1994).

As mentioned in Chapter 1, a POD may be a BMCL, NOAEL, or LOAEL. The quality of the experimental study as well as the nature of the data collected during the study will determine whether the dose-response data can be modeled using benchmark concentration (BMC) modeling (USEPA 1995; USEPA 2000b) or whether a NOAEL/LOAEL approach is used.

Table 2

Definitions of POD Terms (IRIS 2003)

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 (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 in response rate of an adverse effect (called the benchmark response or BMR) compared to background.
BMDL OR BMCL	A statistical lower confidence limit on the dose or concentration at the BMD or BMC, respectively. The TS uses a 95 % confidence level.
Benchmark Response (BMR)	An adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. The change in response rate over background of 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 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.
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.

When possible, the TS performs BMC modeling following established guidelines (USEPA 1995; USEPA 2000b) because of the advantages of this approach over the NOAEL/LOAEL approach. The level of the Benchmark Response (BMR) chosen for BMC modeling will be the lowest dose level that can be

supported for modeling 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). BMR_{01} may be chosen if available epidemiological studies are of sufficient quality to model such a dose-response. Unless information about the mode of action 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) are not appropriate. The quality and nature of the experimental data will determine whether the dose-response data can be modeled at the BMR_{01}, BMR_{05} or BMR_{10}. The software used is USEPA's Benchmark Dose Software (BMDS) Version 1.3.2 or updates, available from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167.

When BMC modeling cannot be performed, acceptable exposure concentrations are determined using the NOAEL or LOAEL as the POD. If experimental data are not available from an inhalation study but data from a non-inhalation exposure route are available, then route-to-route extrapolation is considered, as discussed in the following section (Section E). Since ESLs are developed for as many air contaminants as possible, acute toxicity factors may need to be developed for substances with only limited data, such as LC_{50} or LD_{50} data. For these substances, toxicity information from surrogate compounds is also considered. Generally, the following hierarchy is used to determine the POD when deriving inhalation toxicity factors:

- Inhalation BMCL
- Inhalation NOAEL
- Inhalation LOAEL
- Oral BMDL
- Oral NOAEL
- Oral LOAEL
- LC_{50} and/or surrogate compound
- LD_{50} and/or surrogate compound.

E. Route-to-Route Extrapolation

In the absence of human and animal dose-response data for the inhalation of a given agent, it may be necessary for the TS to derive toxicity factors based on data from non-inhalation exposure routes. 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 (RtR) extrapolation include: (1) the presence of portal-of-entry (POE) effects in the lung and via the referenced exposure route; (2) first-pass effects in the respiratory system or in the liver, if oral ingestion is the referenced exposure route; and (3) accurate dosimetry to normalize the internal dose and biologically effective dose achieved by the compared exposure routes. USEPA states that if either a first-pass effect or POE effect is present, RtR extrapolation is not recommended for derivation of chronic health reference values such as the RfC (USEPA 1994).

Oral ingestion is the most common exposure route from which toxicity is estimated for other routes, including inhalation. Given the aforementioned uncertainties associated with RtR extrapolation, USEPA (USEPA 1994) discourages the use of oral data in any of the following circumstances:

- Different critical adverse effects are expected to result from the compared exposure routes
- Respiratory or hepatic first-pass effects are expected
- A respiratory effect is known to occur, but accurate dosimetry between the two routes is not established
- Referenced oral studies do not include adequate assessment of respiratory tract effects
- Referenced studies are not of adequate quality to establish a toxicity factor for the referenced route
- POE effects.

Data from parenteral exposure routes may also be used by the TS for RtR extrapolation. Intravenous administration provides the best data, due to the absence of POE effects and first-pass effects. However, accurate dosimetry is still required to normalize internal and effective doses to those expected from inhalation.

The preferred method for RtR extrapolation is the use of physiologically-based pharmacokinetic (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 validated 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 RtR extrapolation with fewer uncertainties than other methods, and the TS utilizes this method whenever possible to derive the ReV for a constituent.

TCEQ's mandate to develop ESLs for as many airborne contaminants as practical requires that, when necessary, the TS derives toxicity factors by RtR extrapolation. Therefore, when the available data are inadequate for PBPK modeling, the TS relies on toxicity factors or PODs from other exposure routes (following the hierarchy listed in Section I.(D) of this chapter), scientifically-defensible absorption factors, if available, and the procedures based on established guidelines to perform RtR adjustments (USEPA 1994; USEPA 1996).

The adjustment of a toxicity factor determined from the oral route of exposure to the inhalation route of exposure is as follows:

$$extrapolated\ URF\ (ug/m^3)^{-1} = SFo\ (mg/kg/day)^{-1}\ x\ \frac{1}{70\ kg}\ x\ 20\frac{m^3}{day}\ x\ 10^{-3}\frac{mg}{ug}$$

$$extrapolated\ ReV\ (mg/m^3) = RfD\ (mg/kg/day)\ x\ \frac{70\ kg}{20\ (m^3/day)}$$

F. Assignment of Confidence Levels

Confidence levels are assigned to each $^{Acute}ESL_{odor}$, $^{Acute}ESL_{Noncarc}$, $^{Acute}ESL_{Veg}$, $^{Chronic}ESL_{Noncarc}$, and $^{Chronic}ESL_{Carc}$ based on guidance in the Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (USEPA 1994), hereafter referred to as the RfC Methodology. A confidence level of high, medium, or low is assigned to the key study used in the ESL, the overall database, and to the ESL itself. A key study of excellent quality will likely receive a high confidence rating, even if its duration is not ideal (e.g., a subchronic study for a chronic ESL). The duration of the key study, relevance/quality/quantity of the supporting studies, and spectrum of investigated endpoints are considered in assigning a confidence level to the overall database. The confidence rating then assigned to the ESL is a function of both the confidence in the quality of the key study and confidence in the completeness of the supporting database, with more weight given to the database confidence. An ESL will have a higher confidence rating if it is based on human data and supported by animal data. The level of confidence in an animal study is evaluated through consideration of adequacy of study design, demonstration of dose-response relationships, species differences, and other factors. These factors will be evaluated using the questions posed in the RfC Methodology (USEPA 1994) and listed in Appendix F *Factors to Use in Evaluating Confidence in Animal Studies*.

G. Issues Relating to Particulate Matter Size

There are a number of chemical compounds that are present as particulate matter (PM) in the atmosphere. Often the key study upon which a PM ReV and ESL is based has a PM size fraction that differs from the monitored or modeled PM size fraction, so the applicability of comparing different PM size fractions must be evaluated. The level of confidence in the use of ReVs and ESLs is greatest where the monitored or modeled PM size are similar to those noted in the key study. However, the TS recognizes that this situation is often not achievable.

To address this issue, the TS preferentially derives PM ReVs and ESLs from key studies that evaluate the respirable PM fraction, when data are available. The TS defines the respirable fraction as PM that is less than or equal to 10 micrometers in aerodynamic diameter and capable of depositing in the tracheobronchial and alveolar regions of the respiratory system. ReVs and ESLs derived from key studies evaluating respirable PM may be considered applicable to the entire respirable PM size fraction and larger.

If the only data is from a key study that evaluates a PM size fraction larger than the respirable fraction, then the ReVs and ESLs based on these studies should only be applied to comparable PM size fractions and not respirable fractions. If information on the PM size is not provided in the key studies, ReVs and ESLs will be derived based on procedures described in Chapters 3 and 4. In such instances, professional judgement will be exercised in determining the appropriate PM size fraction to which the ReVs and ESLs are applicable. For select PM species, it may be advisable to derive separate ReVs and ESLs for respirable PM and PM sizes greater than the respirable fraction, if data are available and suggest the need for separate values.

The TS acknowledges that significant differences in PM size distributions can occur between monitored and modeled PM levels and the PM size fraction evaluated in the key study. This in turn confounds public health assessment of PM levels. However, the TS views the approaches described above as conservative and justified from a public health standpoint. In the event that an exceedance of a ReV or ESL occurs for monitored or modeled PM levels and significant differences in PM size and size distribution exist, further evaluation will be necessary to better assess the public health risk. The RfC Methodology (1994) discusses procedures that may be followed to evaluate differences between experimental and ambient exposures.

Chapter 3 Derivation of Acute Toxicity Factors

I. Published Toxicity Factors or Guideline Levels

When acute toxicity factors or guideline levels are identified in the scientific literature or databases, they are reviewed with attention to the critical adverse effect, quality of the supporting toxicological database and the key study, and the application of factors reflecting associated uncertainties. 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 TS considers the key studies used by federal and state agencies or other parties to derive their peer-reviewed toxicity factors or guideline levels. However, because the toxicity factors or guideline levels may be outdated, the TS 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 TS will consider adoption of a published acute toxicity factor or guideline level when it is based on a well-conducted scientific study, evaluation of the body of scientific literature (including studies made available after the date of publication) indicates that the published toxicity factor or guideline level is sufficiently health-protective of the general public (including sensitive subpopulations), and the risk assessment procedures used are similar to those described in this guidance. The following is the generally preferred hierarchy of database sources (A-D) to which the TS refers during its search for published acute values and/or data.

A. Federal and State Guideline Levels

- The ATSDR publishes acute (1-14 days) inhalation minimal risk levels (MRLs) for noncancer health effects for several chemicals (http://www.atsdr.cdc.gov/mrls.html).
- Cal EPA Office of Environmental Health Hazard Assessment (OEHHA) publishes acute reference exposure levels (RELs) for chemicals in the Air Toxics "Hot Spots" Act (http://www.oehha.ca.gov/air/acute_rels/index.html). The RELs are no-effect levels used to evaluate exposures for 1 h, except for reproductive/developmental toxicants (OEHHA 1999).

B. Guideline Levels for 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 (e.g., mild, transient irritation for AEGL-1 to life threatening for AEGL-3):

- Acute Exposure Guideline Levels (AEGL-1, AEGL-2, AEGL-3), National Advisory Committee (NRC 2001);
- Emergency Response Planning Guidelines (ERPG-1, ERPG-2, ERPG-3), American Industrial Hygiene Association;

- Temporary Emergency Exposure Limits (TEEL-0, TEEL-1, TEEL-2, TEEL-3), Department of Energy Emergency Management Advisory Committee's Subcommittee on Consequence Assessment and Protective Action (SCAPA) (Craig et al. 1995; Craig and Lux, 1998).

C. Short-Term Occupational Exposure Limits (OELs)

Data used in the establishment of the following short-term OELs (i.e., immediately dangerous to life or health concentrations (IDLHs), ceiling limits, and short-term exposure limits (STELs)) may also be considered:

- 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 (http://www.cdc.gov/niosh/idlh/idlh-1.html);

- Ceiling Limits - published by ACGIH, NIOSH and OSHA. 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.

D. Toxicity Factors Available in the Future

USEPA is conducting a pilot program to evaluate the feasibility of adding health effects information for acute and/or other less-than-lifetime durations to IRIS (Federal Register 2004). If USEPA develops acute reference exposure factors (USEPA 1998), they would be appropriate factors for consideration.

II. Determining an Acute Toxicity Factor for Chemicals with Limited Toxicological Information

The TS frequently evaluates chemicals with limited toxicological information during the air permit review process. 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 is under review. The following procedures are followed when a short-term ESL must be developed for compounds with limited toxicological information:

1. If there are limited toxicity data or the confidence in the experimental data is low, the TS derives an acute toxicity factor for the chemical of interest based on a comparison to a chemical (that has an acute toxicity factor) that is similar in molecular structure, relative potency, and/or toxicity. Ratios of LC_{50} and/or LD_{50} values for the chemical of interest to the LC_{50} and/or LD_{50} values of the similar chemical obtained under the same testing conditions are calculated. A geometric mean ratio (R_{GM}) of all calculated ratios is then obtained. The acute toxicity factor for the new chemical can then be derived by applying the R_{GM} to the acute toxicity factor of the similar chemical. This process may be repeated if more than one chemical similar to the chemical of interest is identified.

2. If a structurally-similar chemical cannot be easily identified, and the only toxicity information for the chemical of interest is the LC_{50} and/or LD_{50}, uncertainty factors that account for differences in severity of effects are applied to the LC_{50} and/or LD_{50} to calculate a short-term ESL (Section III.C.4, *UF to Convert Lethal-Effects Level to an ESL)*.

3. If there is little or no toxicity information for a specific chemical, but adequate information is available for a structurally-similar chemical, the TS uses the toxicity information for the structurally-similar chemical as a surrogate.

A weight of evidence approach as well as scientific judgement is used to determine whether the aforementioned development procedures results in a realistic assessment. This approach assumes that shared structural characteristics imply shared physicochemical properties, which imply similar patterns of absorption, distribution, metabolism, and excretion, as well as similar target organs and critical effects. In all cases, when additional toxicity data become available, the ESL will be updated.

III. Procedures Employed after the Point of Departure Has Been Identified

A. Exposure Duration Adjustments

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 1 h. Therefore, it may be necessary to adjust data from experiments conducted at different exposure durations to a 1-h exposure duration. In addition, when reviewing monitoring data representative of average concentrations other than a 1-h time period, an adjustment to other exposure durations may be needed.

A.1 Procedures When Chemical-Specific Data Are Available

If a validated PBPK model is available for a given chemical, it is used to adjust exposure concentrations from one exposure duration to another. In the absence of a PBPK model, duration adjustments are based on the relationship of the product of concentration and time generally referred to as Haber's Law. Briefly, 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 Law 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):

$$C \times T = K$$

Exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (K), and 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. Appendix G *Haber's Law* provides additional information.

If a chemical-specific empirically derived value for "n" for the health effect endpoint is available from the scientific literature, then this value is used for exposure duration adjustment. However, values for "n" for specific health endpoints are available for relatively few chemicals, and mostly for lethality as an endpoint (ten Berge et al. 1986). If an acceptable "n" value is not available, the TS derives a chemical- and endpoint-specific "n" value via extrapolation based on the procedures for curve fitting and statistical testing of the generated curve recommended by the NRC (2001) if adequate experimental data at different exposure durations are available. The experimental data will be 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).

A.2 Default Procedures

In the absence of chemical-specific data to perform duration adjustment, the following default procedures are used to perform exposure duration adjustments, except for odor or mild sensory effects and reproductive/developmental effects, which are discussed in the following sections. When performing exposure duration adjustments to longer durations (e.g., 30-minute exposure to 1-h exposure), "n" is assigned a value of 1. This is a conservative procedure since it results in a rapid decrease in concentration (Figures G-1 and G-2, Appendix G).

For adjustment from an experimental study of less than or equal to 8 hours to shorter durations (e.g., 4- to 1-h exposure), the TS conservatively assumes there is no change in concentration (USEPA 1998; USEPA 2002). However, when the exposure duration of the key study is greater than 8 hours and less than 4 weeks, "n" is assigned a value of 3. In all cases, the TS uses scientific judgement to evaluate whether the default exposure duration adjustment for a chemical is supported by the relevant supporting experimental data.

A.3 Adjustments for Reproductive/Developmental Effects

Reproductive/developmental studies are usually conducted by exposing experimental animals to repeated doses over several days (e.g., 6 h per day for 5 days). The TS uses a single day of exposure from the experimental study for each chemical as the exposure duration and does not perform exposure duration extrapolation to 1 h (OEHHA 1999).

A.4 Adjustments for Odor and Mild Sensory Effects

The perception of odor as well as effects of mild sensory irritants may be concentration dependent but not duration dependent (i.e., an enhanced response is not produced by prolonged exposure) (NRC 2001). Therefore, the TS 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.

A.5 Adjustments for Subacute, Intermittent Studies

In some cases, the only toxicity information available for a chemical is from a subacute, intermittent study lasting more than one day to several weeks (e.g., 6 h per day for 2 weeks). The initial procedure will be to use a single day of exposure from the experimental study as the exposure duration, in which case the default procedures in Section A.2 apply. However, if information on the chemical's toxicity and recovery is available, then the exposure duration may be adjusted based on the following procedures. If the chemical produces an effect during one day's worth of exposure but full recovery occurs before another exposure period, then a single day of exposure from the experimental study is used as the exposure duration. If the chemical produces an effect during one day's worth of exposure and full recovery does not occur, such that each subsequent exposure contributes to the toxicity of the chemical over time, then the total number of hours of actual exposure over the entire period are summed, "n", for use in the Haber's Law equation, is assigned a value of 3, and the exposure concentration is adjusted to a 1-h exposure duration.

B. Dosimetry Adjustments from Animal to Human Exposure

The TS uses a validated PBPK model, if available, to perform dosimetry adjustments from animal data to a human equivalent concentration (HEC). If a validated PBPK model is not available and the experimental animal species is the rat, the Multiple Pass Particle Dosimetry Model (version 1.0, released 2002; Anjilvel and Asgharian 1995; Asgharian et al.1999) is used to calculate an HEC for particulates (Jarabek 2004). For other animal species, the TS uses the Regional Deposited Dose Ratio software for particulates and procedures recommended in the RfC Methodology (USEPA 1994).

The TS does not perform dosimetry adjustments for gases using the RfC Methodology (USEPA 1994) for acute exposure to high concentrations of chemicals since the underlying assumptions for such dosimetric adjustments were for chronic, low-concentration exposures (USEPA 1994). Dosimetric adjustments may be considered for reproductive/developmental studies or lower-dose sub-acute studies if the concentration that the animal is exposed to is low and does not produce any signs of overt-toxicity or distress. The final determination on whether to perform dosimetry adjustments in these situations depends on whether metabolic reactions can still be treated as pseudo-first-order or whether biological coreactants and/or protective mechanisms have been depleted. If this information is not available, then dosimetric adjustments will not be attempted. Animal to human dosimetric adjustments are discussed in greater detail in Chapter 4.

C. Selection of Uncertainty Factors (UFs)

C.1 Interspecies and Intraspecies UFs

Toxicological responses may vary across species (interspecies variation) and among individuals within the same species (intraspecies variation) (USEPA 1994). Therefore, the POD derived from experimental data is adjusted by interspecies and intraspecies UFs to account for known and unknown variability in response. In the past, default factors of 10 have been applied to account for each of these sources of variability. However, if toxicokinetic and toxicodynamic data are available, they may be used to support the selection of UFs other than the default value of 10. Other approaches to derive interspecies and intraspecies UFs include data-based UFs (Renwick 1993; Renwick and Lazarus 1998; Dourson 1996; Dourson et al. 1996) and chemical-specific adjustment factors (IPCS 2001). In addition, when BMC

modeling is conducted and a BMCL is used as the POD, Barnes *et al.* (1995) provides guidance on using data-based UFs rather than default UFs of 10. Appendix H provides a discussion of data considered by the TS staff when selecting interspecies and intraspecies UFs.

C.2 LOAEL to NOAEL UF

C.2.1 LOAEL/NOAEL Approach

In some cases, only a LOAEL is available from an experimental study and the uncertainty in converting a LOAEL into a NOAEL must be addressed:

$$\text{NOAEL} = \text{LOAEL} \,/\, \text{UF}$$

Typically, a default UF of 10 is used to adjust the LOAEL to a NOAEL. However, a UF less than 10 may be justified. Dourson et al. (1996) state the choice of UF should generally depend on the steepness of the dose-response curve. If the dose-response curve is steep, a larger UF may be needed because the expected NOAEL is further away from the LOAEL. If the dose-response curve is relatively shallow, then these effects would not require a large UF because, presumably, the LOAEL is closer to the unknown NOAEL. Generally, the dose-response curve for mild effects is not as steep as the dose-response curve for severe effects (Dourson et al. 1996). Alexeeff et al. (1997) analyzed 215 data sets from acute inhalation studies demonstrating the mild effects of 36 hazardous air pollutants in order to evaluate the distribution of the LOAEL to NOAEL ratios. This study showed that for mild adverse effects, LOAEL to NOAEL UFs of 2.0, 5.0, 6.3, and 10.0 corresponded to 50^{th}, 90^{th}, 95^{th}, and 99^{th} percentiles, respectively. Based on the Alexeeff et al. (1997) study and guidance in OEHHA (1999), the TS uses a LOAEL to NOAEL UF of 6.3 if the health effect is judged to be mild (Appendix I), uses a default UF of 10 if the effect is judged to be more severe (Appendix I), or uses a chemical-specific LOAEL to NOAEL UF if data is sufficient. The TS uses professional judgement in determining the most scientifically-defensible LOAEL to NOAEL UF for a given chemical.

C.2.2 Benchmark Concentration Modeling Approach

When BMC modeling is performed, the TS uses the following guidelines to determine whether a LOAEL to NOAEL UF should be applied to the BMCL. This factor is used to decrease risk to below the benchmark response level.

For continuous data, if the dose-response data support the calculation of a $BMCL_{05}$, then it is assumed to be equivalent to a NOAEL (Faustman 1996; Fowles et al. 1999; Filipsson et al. 2003). If the data does not support the estimation of a $BMCL_{05}$ but a $BMCL_{10}$ can be determined, then the $BMCL_{10}$ is considered equivalent to a LOAEL (Faustman 1996; Fowles et al. 1999) and the uncertainty in converting a $BMCL_{10}$ into a NOAEL is addressed by applying a UF of up to 10.

For quantal or discontinuous data sets, whereas the $BMCL_{05}$ is considered equivalent to a NOAEL, it is possible that the $BMCL_{10}$ may be equivalent to the NOAEL (Faustman 1996) or the LOAEL (Farland and Dourson 1992; Fowles et al. 1999). In such cases, the TS staff uses scientific judgement to determine whether to apply a LOAEL to NOAEL UF of up to 10 to the $BMCL_{10}$.

C.3 Incomplete Database UF

Uncertainty introduced by database deficiencies such as a limited number of experimental studies, animal species, or bioassays, or deficiencies in the study design can be addressed by the use of a UF (Dourson et al. 1996). The TS uses a database UF up to 10 to address database deficiencies, especially uncertainties due to the lack of acute exposure studies during sensitive life stages (e.g., reproductive/developmental toxicants).

C.4 UF to Convert Lethal-Effects Level to an ESL

If a short-term ESL must be developed for a chemical, an appropriate surrogate chemical cannot be identified, and the only experimental datum available is an LC_{50}, LC_{Lo}, or LD_{50} value, then the TS uses a conservative UF of 100 to convert the LC_{50}, LC_{Lo}, or LD_{50} to a NOAEL. A short-term ESL based on LC_{50} or LD_{50} data would have the following UFs applied:

100 - LC_{50} / LD_{50} to NOAEL

10 - Interspecies

10 - Intraspecies

1 to 10 - Incomplete database

Therefore, the short-term ESL would equal:

LC_{50} or LD_{50} ⁄ 10,000 to 100,000

C.5 Rationale for Not Using a Modifying Factor

In the past, the USEPA (1994) recommended using a modifying factor (MF) to account for scientific uncertainties that were not explicitly addressed by other UFs. However, based on recent USEPA (2002) guidance, the TS does not use a MF to develop toxicity factors.

C.6 Multiple UFs

When default factors of 10 are used to account for each area of uncertainty (e.g., interspecies, intraspecies, LOAEL to NOAEL, incomplete database), the product of the UFs can be as high as 10,000-100,000, which may result in an overly conservative value for the acute ReV. Therefore, the TS uses criteria from the latest risk assessment guidance to evaluate the individual UFs (USEPA 1994; USEPA 2002), information on the differential toxicity of chemical classes or isomers, as well as scientific judgement to determine whether the product of the UFs is overly conservative. 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 will discuss the basis for each component UF and the conservatism of the resulting product.

Chapter 4 Derivation of Chronic Toxicity Factors

I. Published Toxicity Factors

Because of time and resource constraints, the TS frequently adopts toxicity factors developed by federal and state agencies or other parties in a manner similar to the USEPA's recommended tiered approach (USEPA 2003). When toxicity factors are identified in the available databases, they are reviewed with attention to the critical effect, quality of the supporting toxicological database and the key study, and the application of factors reflecting associated uncertainties. However, because the toxicity factors published in those databases may be outdated, the TS 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 toxicity factor. The following is a brief description of the databases to which the TS refers during its search for published values and/or data.

The TS will consider adoption of a published chronic toxicity factor when it is based on a well-conducted scientific study, evaluation of the body of scientific literature (including studies made available after the date of publication) indicates that the published toxicity factor is sufficiently health-protective of the general public (including sensitive subpopulations), and the risk assessment procedures used are similar to those described in this guidance. The following is the generally preferred hierarchy of database sources (A-F) to which the TS refers during its search for published chronic values and/or data.

A. IRIS Toxicity Factors

USEPA's IRIS (http://www.epa.gov/iris) is the preferred database from which to obtain existing toxicity factors (e.g., RfCs, URFs). The data 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.

B. NCEA Provisional Peer-Reviewed Toxicity Values (PPRTVs)

The USEPA Office of Research and Development/National Center for Environmental Assessment/Superfund Health Risk Technical Support Center (STSC) develops PPRTVs in response to requests from regional USEPA offices (USEPA 2003), and is conducting a batch review of values listed in HEAST (USEPA 1997).

C. Cal EPA RELs and Cancer Potency Factors

The Cal EPA Office of Environmental Health Hazard Assessment (OEHHA) maintains a database of peer-reviewed inhalation RELs, which address noncarcinogenic endpoints, and cancer potency factors (http://www.oehha.ca.gov/air/hot_spots/index.html).

D. ATSDR MRLs

ATSDR publishes chronic 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" (http://www.atsdr.cdc.gov/mrls.html).

E. HEAST Toxicity Factors

USEPA's Environmental Criteria and Assessment Office (ECAO) last updated HEAST in 1997 (USEPA 1997). The values in HEAST are provisional, not having undergone intra-agency peer review, but references are provided, allowing for critical evaluation of study quality.

F. 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; and maximum concentration values in the workplace (MAKs) published by Germany's Commission for the Investigation of Hazards of Chemical Compounds in the Work Area. Worker exposure data used in the development of these OELs may be evaluated.

II. Procedures Employed after the Point of Departure Has Been Identified

A. Dosimetry

Human and animal studies usually involve discontinuous exposure regimens. The data are adjusted to reflect continuous chronic exposure for the general human population. Further dosimetric adjustment is required for animal data to account for anatomical and physiological differences between the test species and humans. The TS uses a validated PBPK model if available to perform dosimetric adjustments. Otherwise, the following published default guidelines (USEPA 1994) are used.

A.1 Adjustment of Human Data

Data obtained from human occupational or controlled studies are adjusted to reflect ventilation rates and exposure durations in the general human population. This adjustment yields the HEC, as a $NOAEL_{HEC}$, $LOAEL_{HEC}$, or other relevant POD. The example that follows concerns an occupational study; however, application to data from controlled human studies may differ regarding the ventilation factors and exposure regimen.

$$POD_{HEC} = POD_{OC} \times \frac{VE_{ho}}{VE_{h}} \times \frac{days/week_{oc}}{days/week_{res}}$$

where:

POD_{HEC} = human equivalent concentration point of departure applicable to the general public

POD_{OC} = occupational time-weighted average POD

VE_{ho} = default occupational ventilation rate for an eight-hour day (10 m^3/day)

VE_h = default non-occupational ventilation rate for a 24-hour day (20 m^3/day)

$days/week_{oc}$ = occupational exposure frequency, usually 5 days/week

$days/week_{res}$ = residential exposure frequency; usually 7 days/week

A.2 Adjustment of Animal Data

Dosimetric adjustments of animal data account for differences in both exposure and the anatomy and physiology between the test species and humans.

A.2.1 Temporal Exposure Parameters

The adjustment of a discontinuous animal exposure regimen to continuous exposure is similar to that used for data from human studies.

$$POD_{ADJ} = POD \times \frac{D}{24\,hours} \times \frac{F}{7\,days}$$

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

A.2.2 Anatomical and Physiological Parameters

Adjustments for differences in anatomy and physiology between the respiratory systems of experimental animals and humans are necessary. These adjustments account for differences in the regional deposition and absorption within the respiratory tract and take into account the physicochemical properties of each toxicant. The Multiple Pass Particle Dosimetry Model (version 1.0, released 2002; Anjilvel and Asgharian 1995; Asgharian et al.1999) is used to calculate an HEC for particulates if the experimental animal species is the rat (Jarabek 2004). For other animal species, the TS uses the Regional Deposited Dose Ratio software for particulates and procedures recommended in the RfC Methodology (USEPA 1994). Dosimetry for gases is briefly described in Section A.2.2.2 below; however, the reader is referred to USEPA (1994) for a more detailed explanation.

A.2.2.1 Particulates

A dosimetric adjustment factor for a given respiratory region (DAF_r) is used to adjust for the effective dose in a particular region of the respiratory tract. The DAF_r normalizes the exposure concentration in an experimental animal species to the effective concentration in humans. $DAFs_r$ for particulates consider deposition in the several regions of the respiratory tract (i.e., the Regional Deposited Dose Ratio ($RDDR_r$)). 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.

The POD_{HEC} is calculated for particulates as follows:

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

where:

POD_{HEC} = human equivalent concentration POD

POD_{ADJ} = POD from animal studies, adjusted to a continuous exposure scenario

DAF = Dosimetric adjustment factor

A.2.2.2 Gases

The physicochemical properties of a chemical such as reactivity and lipid and water solubility influence whether gaseous toxicants affect the respiratory system (portal of entry effects) or more distal organ systems. These properties also determine the effective dose achieved in each respiratory region (i.e., extrathoracic, tracheobronchial, or pulmonary). Three categories of gases exist for purposes of inhalation dosimetry (USEPA 1994):

- 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 portal of entry 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.

The DAF_r for inhaled gases is the regional gas dose ratio ($RGDR_r$) for Category 1 gases or the ratio of the blood:gas partition coefficient in experimental species to the blood:gas partition coefficient in humans for

Category 3 gases. The DAF_r is used to adjust the dose in an experimental species to that in humans exposed to the same concentration. The equations used to calculate the $DAFs_r$ are found in the RfC Methodology (USEPA 1994). While the dosimetric factors for gases differ from those for particulates, the default equation for calculating the POD_{HEC} is the same as for particulates. Dosimetry for Category 2 gases is under review by USEPA. Until new findings suggest otherwise, the TS will conduct 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.

B. Uncertainty Factors (UFs)

B.1 Selection of UFs

UFs are discussed in Chapter 3 and Appendix H of this document. The numeric value of each factor ranges from 1 to 10. Typically, a toxicity factor is not derived if supporting data require application of more than four UFs. If four UFs are used and the cumulative UF exceeds 3,000, the TS uses a default of 3,000 to account for the interrelationships of uncertainty categories (USEPA 2002). Uncertainty factors and the values assigned to each are listed below:

- Up to 10 for extrapolation from a LOAEL to a NOAEL
- Up to 10 for variation in sensitivity within the human population
- Up to 10 for extrapolation from animal studies to humans
- Up to 10 for extrapolation from a subchronic exposure to a chronic exposure
- Up to 10 to account for an incomplete database.

B.2 Rationale for Not Using a Modifying Factor

The RfC Methodology(USEPA 1994) describes the use of an MF to address the quality of the underlying database used to derive RfCs. However, consistent with recent guidance (USEPA 2002), the TS does not utilize an MF.

III. Inhalation Unit Risk Factors (URFs)

While noncarcinogenic and carcinogenic risk assessment paradigms have similarities, they also exhibit some conceptual differences. This section describes the approach used by the TS to determine whether a toxicant warrants consideration for possible carcinogenic endpoints, and if so, the procedures used to derive inhalation URFs. The *Guidelines for Carcinogen Risk Assessment* (USEPA 1986a), hereafter referred to as the 1986 Cancer Guidelines, provided guidance to assess potential health risks from exposure to carcinogens. 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; Federal Register 2005a), as well as a supplemental guidance document entitled *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (USEPA 2005b; Federal Register 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 TS uses these guidance documents as the main source of information to derive URFs. However, if new information, scientific understanding, or science policy judgment become available, the TS 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: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283

A. Hazard Identification

Hazard identification for carcinogens is typically approached using a weight-of-evidence (WOE) approach (USEPA 2005a). 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 structure-activity relationships are examined in order "to construct a total analysis examining what the biological data reveal as a whole about carcinogenic effects and mode of action 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 some routes of exposure but not others, or whether sensitive life-stages of development may increase the carcinogenic potential of a chemical. 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 weight-of-evidence (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 TS uses all of the aforementioned sources as well as other peer-reviewed research when considering the carcinogenic potential of a toxicant.

Those toxicants lacking a WOE classification are evaluated by the TS regarding their chemical class/structure, toxicokinetics, metabolism, etc. A literature review determines if data are available from which URFs may be calculated.

B. Mode of Action and Dose-Response Assessment

B.1 Mode of Action

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. The use of mode-of-action information is a main focus of the guidelines. Mode-of-action 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 mode of action for a specific tumor response, or to decide whether other modes of action are plausible. The TS evaluates cancer risks in the absence of mode-of-action information through the use of health-protective default options designed to address uncertainty (i.e., linear approach). The 2005 Cancer Guidelines provide a discussion of circumstances where the use of default options may be adopted.

An initial process in the cancer dose-response assessment is to examine the mode of action 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 mode-of-action 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, the mode of action and other information may support one of the following dose-response extrapolations: 1) linear; 2) nonlinear approach; or (3) both linear and nonlinear analyses. In a few cases, detailed mode-of-action information may be available which allows the formulation of a toxicodynamic or biologically-based model (USEPA 2005a; Moolgavkar and Knudson 1981; Chen and Farland 1991; Portier 1987). Examples of factors supporting a linear approach, nonlinear approach, or both linear and nonlinear approaches are discussed in the 2005 Cancer Guidelines.

The TS uses health-protective and scientifically-defensible defaults to address uncertainty (e.g. the absence of critical information). When information on the underlying scientific process and chemical-specific data are available, the 2005 Cancer Guidelines allow flexibility to depart from conservative default assumptions.

B.2 Dose-Response Assessment

Generally, dose-response assessments are completed for chemicals considered "Carcinogenic to Humans" and "Likely to Be Carcinogenic to Humans." The following dosimetry adjustments discussed in Section II of this chapter for linear and nonlinear carcinogens are similar to those used for noncarcinogenic toxicants:

- Adjustment from discontinuous to continuous exposure scenario

- Adjustment from occupational exposures to residential exposures
- Dosimetric adjustments of animal experimental data to the HEC.

Dose-response assessment for each tumor type is performed in two steps: derivation of a POD based on observed data followed by extrapolation to lower exposures to the extent required.

B.2.1 Derivation of a POD Based on Observed Data

The first step of dose-response assessment is to model the observed data to derive a POD. 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. If adequate human data are not available, then animal data are generally used. If a detailed mode of action is available, a toxicodynamic or biologically-based model may be used to relate dose and response data. If the mode of action is not well characterized, a standard model can be used to curve-fit the data as discussed in the 2005 Cancer Guidelines. The software used is USEPA's Benchmark Dose Software (BMDS) Version 1.3.2 or updates, available from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167.

Typically, the lower 95% confidence limit on the lowest concentration that can be supported for modeling by the data is used as the POD. Typically, this lowest dose level is at a 10% response level (LEC_{10}) since the limit of detection of studies of tumor effect is about 10%. Using the lower 95% confidence limit as the POD accounts for experimental variability and is generally assumed to be health protective. Other PODs may be more appropriate for certain data sets (USEPA 2005a).

B.2.2 Extrapolation to Lower Exposures

After a POD has been determined, an extrapolation to lower dose levels is conducted as required. If substantial mode-of-action information is available, the extrapolation is based on an extension of a biologically-based model. If not, any information on the proposed mode(s) of action of the chemical can be used to decide whether the extrapolations should assume linearity or nonlinearity of the dose-response relationship, or both.

B.2.2.1 Linear Approach

When the mode-of-action information supports linearity, as is the case for a mutagenic carcinogen, or when mode of action is not understood for a chemical, the default is to use a linear approach. The linear approach is to draw a straight line 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:

$$URF = 0.10 \,/\, LEC_{10}$$

B.2.2.2 Nonlinear Approach

If sufficient evidence is available to support a nonlinear mode of action for the general population and any subpopulations of concern, the default approach changes to a determination of a POD and application of UFs, similar to procedures to derive a ReV. The POD is generally the BMCL, NOAEL, or LOAEL depending on the quality and nature of the data as discussed in Chapter 2, Section II.D. The POD for nonlinear carcinogens can be based on precursor responses if mode-of-action 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). Thus the POD would represent an actual "no effect level." The 2005 Cancer Guidelines discusses several key factors to consider when selecting a POD for nonlinear carcinogens such as 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 (USEPA 2005a). UFs are applied to the POD to account for variability and uncertainties to derive a chronic ReV as discussed in Section II.B of this chapter.

B.2.2.3 Linear and Nonlinear Approaches

If the dose-response can be adequately described by both a linear and a nonlinear approach, then the default is to present both the linear and nonlinear analyses. The results of both analyses are considered by the TS. This is important when the modes of action or responses appear to be very different at high and low doses (e.g. chloroform). The TS uses the following procedures to compare and combine multiple extrapolations so a judgement can be made on how best to derive a single ESL that represents the human cancer risk (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 mode of action
- 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, or
- A combination of these options.

C. Evaluating Susceptibility from Early-Life Exposure to Carcinogens

USEPA issued a 2005 Supplemental Guidance document (USEPA 2005b; Federal Register 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 TS 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 mode of action, the 2005 Supplemental Guidance provides specific guidance on potency adjustment. In order to determine whether a carcinogen operates by a mutagenic mode of action, the following information must be present:

- Evidence that the carcinogen or a metabolite is DNA-reactive and/or has the ability to bind to DNA as demonstrated with *in vivo* or *in vitro* short-term testing results for genetic endpoints
- The carcinogen produces positive effects in multiple test systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations
- Data from tests performed *in vivo* support positive tests *in vitro*
- The carcinogen has similar properties and SAR to mutagenic carcinogens.

USEPA (1986a) and Dearfield et al. (1991) discuss testing guidelines for detecting the ability of an agent to damage DNA and produce mutations and chromosomal alterations and also provide a weight-of-evidence approach to evaluate the possible mutagenicity of a chemical.

C.1 Carcinogens Acting Through a Mutagenic Mode of Action

As mentioned previously, the 2005 Supplemental Guidance provides specific guidance on potency adjustment for early-life exposure for carcinogens which act through a mutagenic mode of action. When data are available for a sensitive lifestage, they should be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. 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 mutagenic carcinogen. The following ADAFs are recommended for such chemicals, using estimates from chronic studies (i.e., URFs) 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.

C.2 Calculation of an ESL for Carcinogens Acting Through a Mutagenic Mode of Action

For mutagenic carcinogens, the risks associated with each of the three relevant time periods are as follows, where both E and URF are expressed in the same units (i.e., $\mu g/m^3$ and $(\mu g/m^3)^{-1}$, respectively):

Risk for birth through < 2 yr = E x URF x 10 x 2yr/70yr

Risk for ages 2 yr and < 16 yr = E x URF x 3 x 13yr/70yr

Risk for ages 16 until 70 yr = E x URF x 55yr/70yr

The 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:

Lifetime Risk Level = (Risk for birth through < 2 yr) +
(Risk for ages 2 yr and < 16 yr) +
(Risk for ages 16 yr until 70 yr)

Lifetime Risk Level = (E x URF x 10 x 2yr/70yr) +
(E x URF x 3 x 13 yr/70yr) +
(E x URF x 55yr/70yr)

This equation can be simplified as follows:

Risk Level = E x URF x [(10 x 2yr) + (3 x 13yr) + 55yr]/ 70yr

This equation can be rearranged to solve for the exposure concentration ($\mu g/m^3$) for a chronic exposure period that corresponds to a specified target risk level:

$$E = [\text{Risk Level} / \text{URF}] \times 0.6$$

For mutagenic carcinogens, the screening level of a chemical that corresponds to a target risk level of 1 x 10^{-5} for a chronic exposure period ($^{\text{Chronic}}ESL_{Carc}$) is calculated as follows:

$$^{\text{Chronic}}ESL_{Carc} = (6.0 \times 10^{-6}) / \text{URF}$$

C.3 Carcinogens Not Acting Through a Mutagenic Mode of Action

USEPA (2005b) concluded that the data for non-mutagenic carcinogens or for carcinogens where the mode of action is unknown were too limited and the modes of action too diverse to apply a general default adjustment factor approach. In this situation, 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 other modes of action, as data from new research and toxicity testing become available.

Chapter 5 Assessment of Chemical Groups and Mixtures

I. Overview

Guidelines for the Health Risk Assessment of Chemical Mixtures (USEPA 1986b) and *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA 2000a) provide procedural guides for evaluating data on the health risks from exposures to chemical mixtures. Briefly, if a dose-response assessment is developed for a mixture of compounds or a mixture that is judged similar, the TS uses this data to develop an ESL for that mixture. Examples of pollutant mixtures for which a dose-response has been evaluated are gasoline, coke oven emissions, and diesel exhaust. 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 in Section IV. *Product Formulations.* Specific approaches are used for carcinogenic polycyclic aromatic hydrocarbons, laterally-substituted dioxins/furans, and dioxin-like polychlorinated biphenyls.

II. Carcinogenic Polycyclic Aromatic Hydrocarbons (PAHs)

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. The National Center for Environmental Assessment (NCEA) has calculated an inhalation URF for benzo(a)pyrene, the index chemical for carcinogenic PAHs, from which a long-term ESL can be developed. Applicable RPFs can be used to derive long-term ESLs for specific PAH compounds. RPFs for seven carcinogenic PAHs have been published in *Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons* (USEPA 1993). Additional RPFs for other potential carcinogenic PAHs have been published by Collins et al. (1998).

III. Dioxins/Furans and Dioxin-Like Polychlorinated Biphenyls (PCBs)

The USEPA has developed an inhalation URF for 2,3,7,8- tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) from which a long-term ESL can be developed. Toxicity equivalence factors (TEFs) have been developed for other laterally-substituted dioxins/furans and the dioxin-like PCBs since these classes of chemicals have toxicologically similar properties. TEFs relate the toxicity of these compounds to the toxicity of 2,3,7,8-TCDD. The TS uses the congener-specific TEFs from Van den Berg et al. (1998).

IV. Product Formulations

If a chemical product contains two or more components and the ESLs for all components are known, the TS 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 TS 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':

ESL for Chemical Product $X = \dfrac{1}{f_a / ESL_a + f_b / ESL_b + f_c / ESL_c + \ldots\ldots\ldots\ldots + f_n / ESL_n}$

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).

$$\text{ESL for Product X} = \frac{1}{0.2/100 + 0.3/60 + 0.5/200} = \frac{1}{0.0095} = 105\mu/\text{m}^3$$

APPENDIX A

GLOSSARY

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.

Benchmark Dose (BMD) or Concentration (BMC): A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) 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): An adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. The change in response rate over background of 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.

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 laboratory animal species.

Chronic Toxicity: The capacity of a substance to cause adverse human health effects as a result of chronic exposure.

Critical Effect: The first adverse effect, or its known precursor, that occurs in the most sensitive species as the dose rate of an agent increases.

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.

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).

Effective Dose (ED10): The dose corresponding to a 10% increase in an adverse effect, relative to the control response.

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).

Guidelines (human health risk assessment): Official, peer-reviewed documentation stating current USEPA methodology in assessing risk of harm from environmental pollutants to populations.

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.

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.

Incidence: The number of new cases of a 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.

Linear Dose Response: A pattern of frequency or severity of biological response that varies directly with

the amount of dose of an agent.

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 LED10 or other point of departure 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.

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; model parameters may or may not have real world interpretation. When data quality is otherwise equivalent, extrapolation from mechanistic models (e.g., biologically based dose-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 TS does not utilize an MF.

Multistage Model: A mathematical function used to extrapolate the probability of cancer from animal bioassay data, using the form

where: P(d) = probability of cancer from a continuous, lifetime exposure rate d;

qi = fitted dose coefficients of model; I=0, 1, . . ., k; and

k = number of stages selected through best fit of the model, no greater than one less than the number of available dose groups.

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.

Non-Linear Dose Response: A pattern of frequency or severity of biological response that does not vary directly with the amount of dose of an agent.

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.

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: 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.

ppb: A unit of measure expressed as parts per billion. Equivalent to 1×10^{-9}.

ppm: A unit of measure expressed as parts per million. Equivalent to 1×10^{-6}.

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 point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. [Durations include acute, short-term, longer-term, and chronic and are defined individually in this glossary].

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: 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.

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: 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.

Subchronic Exposure: Exposure to a substance spanning approximately 10% of the lifetime of an organism.

Subchronic Study: A toxicity study designed to measure effects from subchronic exposure to a chemical.

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.

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

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.

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 = 1.5×10^{-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

SOURCES OF INFORMATION FOR ODOR THRESHOLDS

Sources of Information for Odor Thresholds

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APPENDIX C

LIST OF ACCEPTED ODOR REFERENCES BASED ON THE AIHA AND USEPA'S EVALUATION CRITERIA

List of Accepted Odor References Based on the AIHA and USEPA's Evaluation Criteria

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APPENDIX D

CURRENT LIST OF CHEMICALS THAT MUST MEET NAAQS OR STATE RULES AND REGULATIONS

Current List of Chemicals that Must Meet NAAQS or State Rules and Regulations

- Sulfur dioxide
- Hydrogen sulfide
- Sulfuric acid
- Total reduced sulfur
- Reduced sulfur compounds
- Particulate matter
- Inhalable particulate matter
- Fine particulate matter
- Nitrogen dioxide
- Carbon monoxide
- Lead (elemental)
- Ozone

APPENDIX E

EXAMPLES OF SUBSTANCES EXEMPT FROM ESL DEVELOPMENT

Examples of Substances Exempt from ESL Development

- Argon
- Carbon dioxide
- Ethane
- Helium
- Hydrogen
- Methane
- Neon
- Nitrogen
- Propane
- Propylene
- Fruit juices (apple, orange, lemon, etc.)
- Sweeteners (sugar, molasses, corn syrup, etc.)
- Cooking oils (corn oil, olive oil, etc.)
- Food seasonings (soy sauce, salt, pepper, etc.)
- Water (bottled, tap, etc.)

APPENDIX F

FACTORS TO USE IN EVALUATING CONFIDENCE IN ANIMAL STUDIES

Factors to Use in Evaluating Confidence in Animal Studies

Source: USEPA 1994, page 4-79.

Adequacy of study design

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

Demonstration of dose-response relationships

- Were sufficient exposure levels used to demonstrate the highest NOAEL for the endpoint of concern?
- Is the shape of the dose-response curve consistent with the known pharmacokinetics of the test substance?
- Has the dose-response curve been replicated by or is it consistent with data from other laboratories and other laboratory animal species?

Species differences

- Are the metabolism and pharmacokinetics in the animal species similar to those for humans?
- Is the species response consistent with that in other species?
- Is the species from which the threshold value was derived the most sensitive species?

Other factors

- The number of biological endpoints evaluated and associated with dose-response relationships.
- Sufficient description of exposure protocol, statistical tests, and results to make an evaluation.
- Condition of animals used in the study.

APPENDIX G

HABER'S LAW

Haber's Law

The following section, which provides a brief discussion of Haber's Law, was obtained from NRC (2001).

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. For a chemical where concentration and duration both play a role in producing an adverse effect, Haber's Law 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):

$$C \times T = K$$

Exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (K), and 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. ten Berge et al. (1986) examined the airborne concentration and short-term exposure duration relationship relative to death for approximately 20 structurally diverse chemicals and found that the empirically derived value of "n" ranged from 0.8 to 3.5 among this group of chemicals. The relationship between exposure concentration and exposure duration for a given chemical and for a specific health-effect endpoint is quantitatively defined by the value of the exponent (n) in the equation $C^n \times T = K$.

Figure G-1 illustrates the relationship of $C^n \times T = K$ for a 1-, 4-, 6-, 8-, and 24-hour exposure duration, for different values of "n" for a hypothetical case where experimental data are available for a two hour exposure duration to an air concentration of 200 ppm. Figure G-2 illustrates the linear relationship between log concentration versus log time for the data from Figure G-1. Haber's Law is the special case where n = 1 and both concentration and duration play an equal role in the specific health endpoint. 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.

Adjustments using Haber's Law when n = 1

When adjusting from one concentration (C_1) at a specific exposure duration (T_1) to another concentration (C_2) at a different exposure duration (T_2), Haber's Law can be expressed as follows:

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

When adjusting from a short exposure duration (T_1) to a longer exposure duration (T_2), the TS assumes that n = 1:

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

Simplifying:

$$C_2 = C_1 \times (T_1 / T_2)$$

Therefore, in order to adjust from a short exposure duration to a longer exposure duration, multiply the initial concentration (C_1) by the ratio of the initial exposure duration to the desired exposure duration (T_1 / T_2).

Figure G-1. C^n x T = K for Different Values of "n"

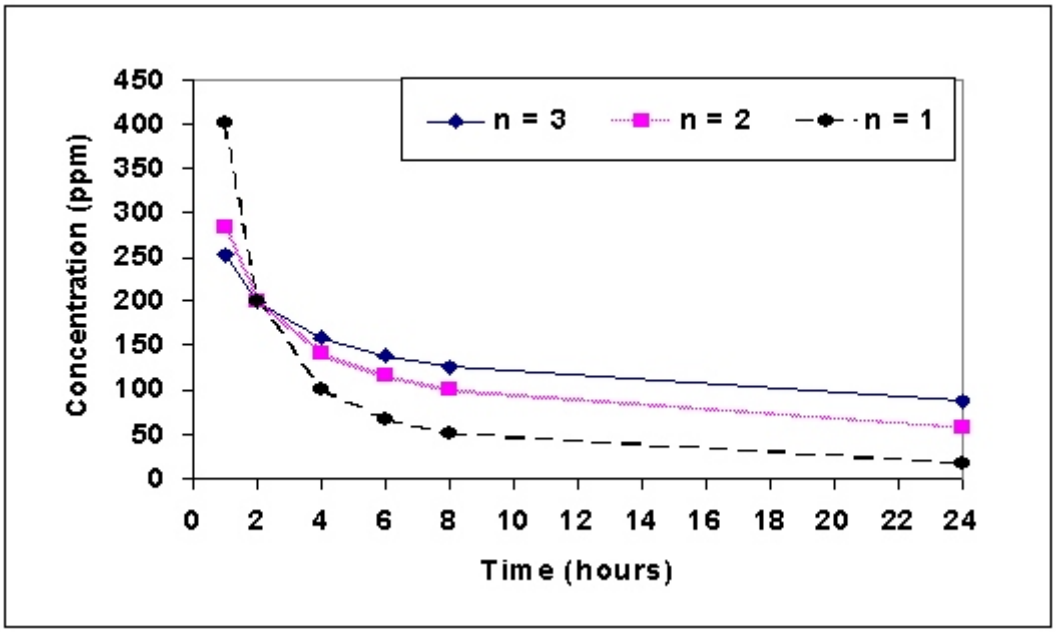
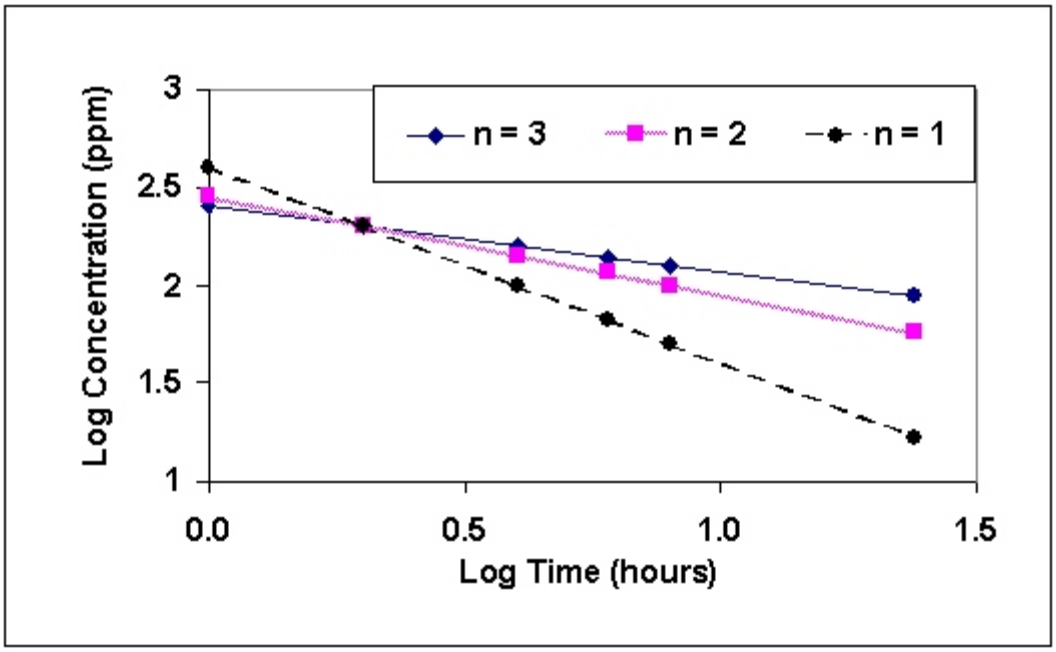


Figure G-2. Log C^n x Log T = K for Different Values of "n"



APPENDIX H

SELECTION OF INTERSPECIES AND INTRASPECIES UFS

Selection of Interspecies and Intraspecies UFs

Data-Based UFs

Factors of 10 are applied by default to account for interspecies and intraspecies sources of variability. Renwick (1993) proposed that each of these UFs can be described in terms of differences in toxicokinetics and toxicodynamics. Renwick 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 (Renwick 1993). Mode of action is the series of events leading to induction of the critical toxic endpoint, whereas mechanism of action implies a detailed molecular description of causality (IPCS 2001). The interspecies UF or the intraspecies UF of 10 can be divided into toxicokinetic and toxicodynamic components. If credible information on toxicokinetics or toxicodynamics is available, a data-based UF of 3, or even 1, may be used. A UF of 3 represents a geometric half of 10, rounded to one significant figure (i.e., $10^{0.5}$). For example, if a dosimetry adjustment from animal to human exposure has been performed, then the full interspecies toxicokinetic and toxicodynamic UF of 10 may be reduced to an interspecies toxicodynamic UF of 3 (USEPA 1994; Anjilvel and Asgharian 1995; Asgharian et al.1999).

A discussion of interspecies and intraspecies variability of response as well as research and case studies from USEPA and Health Canada risk assessments that support the use of lower UFs are presented in Dourson et al. (1996). In addition, when BMC modeling is conducted and a BMCL is used as the POD, Barnes et al. (1995) provides guidance on using data-based UFs rather than the default UF of 10. The factors considered when deciding on a specific value for an interspecies UF include: (1) the type, appropriateness, and range of animal species used in experimental studies; (2) the likely mode/mechanism of action; (3) the severity of the toxicological endpoint observed; (4) the range of response in the animal species tested; (5) the variability of response among the species tested; and (6) pharmacokinetic differences among the species tested. For the intraspecies UF, the factors considered include: (1) the mode/mechanism of action, (2) the toxicological endpoint observed, (3) pharmacokinetic differences among individuals, and (3) the range of response among humans and subpopulations.

An example of the types of data that are considered to justify UFs other than 10 and/or circumstances that would dictate use of the default UF of 10 are in Table H-1 for interspecies variation and Table H-2 for intraspecies variation. Dourson et al. (1996), Barnes et al. (1995), and NRC (2001) have discussions of data that should be considered to develop data-based UFs. NRC (2001) provides a list of questions that should be addressed to support the rationale for the UF used. The TS determines data-based UFs to account for interspecies and intraspecies variation for each chemical on a case-by-case basis.

Chemical-Specific Adjustment Factors

For a few chemicals, data are available to derive a chemical-specific adjustment factor (CSAF) to replace the default UF, thereby reducing the overall uncertainty. IPCS (2001) published a guidance document that details the data needed to develop CSAFs to account for interspecies and intraspecies uncertainty. The TS uses CSAFs to account for interspecies and intraspecies variation if published in the scientific literature.

Table H-1

Data-Based Interspecies Uncertainty Factor

Justification for a UF = 1	Justification for a UF = 3	Justification for a UF = 10
Well-conducted human studies are used	Small interspecies variability or most appropriate species used in experimental studies	Large interspecies variability or most susceptible species not used in experimental studies
The NOAEL selected is substantially below the NOAELs reported for other species	Mechanism or mode of action is unlikely to differ among species	Mechanism of action or mode of action is unknown
There is a high degree of confidence that the animal model tested is a sensitive surrogate for humans or is more sensitive than humans	A dosimetry adjustment from animal to human exposure data (HEC) was performed	Humans more susceptible than animals
		Inadequate data

Table H-2
Data-Based Intraspecies Uncertainty Factor

Justification for a UF = 1	Justification for a UF = 3	Justification for a UF = 10
Studies of sensitive human populations are used	Most sensitive toxic effect is based on a mild endpoint.	When data are insufficient to determine the relative susceptibility of individuals in a human population
	Susceptible animal species is used	When data indicate that certain groups based on age, life stage or physical condition may be uniquely susceptible in contrast to the general population
	Response of normal and susceptible individuals to chemical exposure is unlikely to differ for mechanistic reasons	Mechanism of Action or Mode of Action is unknown
	A BMCL based on a human study is used as the point of departure (Barnes et al. 1995)	When a broad range of response is observed
		When metabolic factors play an important role

APPENDIX I

OEHHA'S (1999) CLASSIFICATION OF SEVERITY LEVELS

OEHHA's Classification of Severity Levels

Table I-1

USEPA Effect Severity Levels (USEPA 1994) and Corresponding OEHHA Levels (OEHHA 1999)

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 effects.	< 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 I-2

OEHHA (1999) 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: Mild mucous membrane (eye, nose, throat) irritation Mild skin irritation Mild headache, dizziness, nausea	Statistically significant findings of preclinical significance: Mild conjunctivitis Mild lung function changes[2] Abnormal immunotoxicity test results Mild decreases in hemoglobin concentration
Severe Adverse	Potentially disabling effects that affect one's judgement and ability to take protective actions; prolonged exposure may result in irreversible effects: Severe mucous membrane irritation Blurry vision Shortness of breath, wheezing Severe nausea Severe headache In coordination Drowsiness Panic, confusion	Clinically significant findings: Findings consistent with central or peripheral nervous system toxicity Loss of consciousness Hemolysis Asthma exacerbation "Mild" pulmonary edema Clinically significant lung function changes[2] Cardiac ischemia Some cardiac arrhythmias (e.g., atrial fibrillation) Renal insufficiency Hepatitis Reproductive/developmental endpoints (e.g., infertility, spontaneous abortion, congenital anomalies)
Life-threatening		Potentially lethal effects: Severe pulmonary edema Respiratory arrest Ventricular arrhythmias 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 I-3 for detailed categorization of lung function tests.

Table I-3

System for Categorization of Pulmonary Function into Effect Severity Levels (OEHHA 1999)

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 resistence (SR_{aw}) or ≥50% decrease in airway conductance (SG_{aw}) no symptoms of bronchoconstriction < 20% decrement in FEV_1	100% increase in specific airway resistence (SR_{aw}) or 50% decrease in airway conductance (SG_{aw}) 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 Wheeze detected by examination Hypoxia or decreased oxygen saturation	Status asthmaticus 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

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